Therapeutic Class Overview
Benign Prostatic Hyperplasia Treatments

Therapeutic Class

- **Overview/Summary:** The agents approved for the treatment of signs and symptoms of benign prostatic hyperplasia will be the focus of this review. The α-adrenergic blockers including, alfuzosin, doxazosin, silodosin, tamsulosin, and terazosin, reduce smooth-muscle tone in the prostate and bladder neck decreasing lower urinary tract symptoms (LUTS) secondary to BPH. Alfuzosin, silodosin and tamsulosin are selective to the α-adrenergic receptors located in the prostate and therefore are only Food and Drug Administration (FDA) approved for BPH, whereas doxazosin and terazosin additionally inhibit α-adrenergic receptors found in the vascular smooth muscle and are additionally indicated for hypertension.[1-6] The 5-α reductase inhibitors, dutasteride and finasteride, are appropriate treatment options for LUTS associated with overall prostatic enlargement. They act by blocking the conversion of testosterone to dihydrotestosterone and in turn suppress the growth of the prostate.[7,8] Jalyn® (dutasteride/tamsulosin) is a combination of both an α-adrenergic blocker and a 5-α reductase inhibitors.[9] The final drug approved for use in BPH is the phosphodiesterase-5 inhibitor, tadalafil. The exact mechanism for reducing BPH symptoms is unknown.[10] Note that even though doxazosin and terazosin are FDA-approved for use in the treatment of hypertension, tadalafil is FDA-approved for use in the treatment of erectile dysfunction and pulmonary arterial hypertension, and finasteride is FDA-approved for alopecia, they are not included in this review. Jalyn® (dutasteride/tamsulosin) is a combination of both an α-adrenergic blocker and a 5-α reductase inhibitors.[9] The final drug approved for use in BPH is the phosphodiesterase-5 inhibitor, tadalafil. The exact mechanism for reducing BPH symptoms is unknown.[10] Note that even though doxazosin and terazosin are FDA-approved for use in the treatment of hypertension, tadalafil is FDA-approved for use in the treatment of erectile dysfunction and pulmonary arterial hypertension and finasteride is FDA-approved for alopecia, they are not included in this review.

  Clinical manifestations of BPH include LUTS (frequency of urination, nocturia, hesitancy, urgency, and weak urinary stream). The appearance and progression of symptoms is usually slow, over a couple of years, with a poor correlation between symptoms and the presence of an enlarged prostate on rectal exam.[11] Disease prevalence and the occurrence of symptoms are age dependent, with an initial onset of disease occurring patients greater than 50 years of age.[11] The American Urological Association (AUA) acknowledges that not all men with histological evidence of BPH will develop bothersome LUTS and not all patients with BPH and LUTS actually have prostate enlargement, one of the main features of symptomatic disease. Additionally, prostate enlargement may exist in the absence of LUTS.[12]

Table 1. Current Medications Available in the Therapeutic Class[1-10]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Alfuzosin hydrochloride (Uroxatral®)	Treatment of signs and symptoms of benign prostatic hyperplasia	Tablet, extended release: 10 mg	✔
Doxazosin mesylate (Cardura®,¶, Cardura XL®)	Treatment of signs and symptoms of benign prostatic hyperplasia#; treatment of hypertension*	Tablet, extended release: 4 mg 8 mg Tablet: 1 mg 2 mg 4 mg	✔

		8 mg	
Dutasteride (Avodart®)	Treatment of signs and symptoms of benign prostatic hyperplasia†,‡	Capsule: 0.5 mg	-
Finasteride (Proscar®)	Treatment of signs and symptoms of benign prostatic hyperplasia†,§	Tablet: 5 mg	✔
Silodosin (Rapaflo®)	Treatment of signs and symptoms of benign prostatic hyperplasia	Capsule: 4 mg 8 mg	-
Tadalafil (Cialis®, Adcirca®)	Treatment of signs and symptoms of benign prostatic hyperplasia, treatment of erectile dysfunction	Tablet: 2.5 5 10¶ 20¶	-
Tamsulosin hydrochloride (Flomax®)	Treatment of signs and symptoms of benign prostatic hyperplasia†	Capsule: 0.4 mg	-
Terazosin hydrochloride	Treatment of signs and symptoms of benign prostatic hyperplasia,	Capsule: 1 mg 2 mg 5 mg 10 mg	✔
Combination Products			
Dutasteride/tamsulosin hydrochloride (Jalyn®)	Treatment of signs and symptoms of benign prostatic hyperplasia†, treatment of hypertension	Capsule: 0.5 mg/0.4 mg	-

*Instant release formulation only.
†In men with an enlarged prostate, to improve symptoms, reduce the risk of acute urinary retention and reduce the risk of the need for BPH-related surgery.
‡To treat symptomatic BPH in men with an enlarged prostate in combination with tamsulosin.
§To reduce the risk of symptomatic progression of BPH in combination with doxazosin.
#Doxazosin indicated for both the urinary outflow obstruction and obstructive and irritative symptoms associated with BPH.
¶Generic available in at least one dosage form or strength.

Evidence-based Medicine

- FDA-approval of silodosin was based on two clinical trials where it was compared to placebo and demonstrated its efficacy in decreasing the International Prostate Symptom Score (IPSS) and improving general quality of life scores. In a pooled analysis of these two clinical trials, the mean change in total IPSS at baseline was -6.40 (±6.63) and -3.50 (±5.84) for the silodosin and placebo groups, respectively with an adjusted mean difference reported as -2.8 (P<0.0001). The maximum urinary flow rate (Q_{max}) at endpoint was 2.6 mL/second (standard deviation [SD]±4.43) in the silodosin group and 1.5 mL/ second (SD±4.36) in the placebo group; corresponding to an adjusted mean group difference of 1.0 mL/ second (P=0.0007).[16]
- The safety and efficacy of tadalafil for BPH has been evaluated in multiple studies. These studies. Tadalafil consistently showed significantly better improvement in IPSS compared to placebo.[18-25] One study evaluated men with BPH who had comorbid erectile dysfunction. Tadalafil was associated with statistically significant improvements in both internation index of erectile function (IIEF) scores and total IPSS (P<0.001 for both).[25]
- Studies comparing the α-adrenergic blocking agents to each. Although some trials have suggested superiority one agent over another, most studies, have tended toward non-inferiority within the α-blockers related to reducing IPSS.[26-46]
    - A Cochrane review has evaluated tamsulosin in comparison to other α-adrenergic blocking agents. It was concluded that tamsulosin was as effective as other α-adrenergic blockers in improving LUTS and urinary flow rates. Dizziness, rhinitis and abnormal ejaculation occurred

significantly more frequently than placebo and withdrawal was reported more often with higher doses of tamsulosin. Additionally, terazosin use was associated with a higher rate of discontinuation than low dose tamsulosin.[37]
    - A second Cochrane review evaluated terazosin to other α blockers, finasteride alone or in combination with terazosin and placebo. Terazosin was comparable to tamsulosin in improving IPSS (40% vs 43%), and more effective than finasteride (38% vs 20%) or placebo (38% vs 17%) in improving American Urological Association Symptom Score (AUA-SS). Peak urinary flow rates were similar among α blockers and higher with terazosin (22%) over finasteride (15%) and placebo (11%).[38]
    - A meta-analysis by Djavan et al of α-adrenergic blocking agents (alfuzosin, doxazosin, tamsulosin, and terazosin) in men with LUTS suggestive of benign prostatic obstruction did not identify any difference among agents in improving total urinary symptom scores or Q_{max}. However, alfuzosin and tamsulosin were better tolerated than doxazosin and terazosin.[39]
- Similar to the α-blocking agents, the 5-α reductase inhibitors have been compared to one another in a number of clinical trials, with mixed results. Dutasteride was shown to be non-inferior to finasteride for reducing prostate volume, post-void volume, and American Urological Association Symptom Score (AUA-SS).[47-50]
- Head-to-head trials between 5-α reductase inhibitors and α blockers have also been conducted.[51-62]
    - When compared to finasteride, tamsulosin showed comparable effect on urinary symptom scores at study end point (24 weeks and 1 year)[51,52], however a benefit was found with tamsulosin at earlier assessment (4 weeks) in both IPSS and Q_{max}.[51]
    - Tamsulosin in combination with dutasteride has been found to be associated with a greater benefit in IPSS and Q_{max} than each agent alone. As expected tamsulosin use resulted in a much lower decrease in prostate volume as compared to combination therapy (0.00%±0.84% and 26.90%±0.62%, respectively; P<0.001).[53,]
    - Four large, long-term trials comparing doxazosin, finasteride, each agent alone and in combination, and placebo.[58-61] Rates of nocturia were significantly reduced with monotherapy and combination treatment compared to placebo.[59]
    - Men with moderate to enlarged prostate glands benefited most from combination therapy (P<0.05), however doxazosin therapy alone was as effective as combination therapy for decreasing the risk of progression in men without an enlarged prostate.[60]
    - Doxazosin monotherapy and in combination with finasteride was associated with significantly greater improvements in Q_{max} and IPSS. Differences between finasteride alone and placebo did not reach statistical significane.[61]
    - Terazosin use alone and in combination with finasteride was associated with significantly greater reductions in symptom scores and greater increases in Q_{max} compared to finasteride monotherapy or placebo. Differences among combination therapy and terazosin monotherapy did not reach statistical significance, nor did difference between finasteride and placebo.[62]
- Studies have been conducted evaluating the safety and efficacy of combination therapy with two agents from different classes.[63-66]
    - A retrospective analysis showed that combination therapy with finasteride and an α-blocking agent significantly improved IPSS in patients with severe BPH symptoms, but was not statistically different from monotherapy in the same population.[63]
    - A meta-analysis conducted by Gacci et al found that a phosphodiesterase-5 inhibitor and α blocker combination therapy significantly improved IPSS, IIEF score and Q_{max} compared to a blockers alone (P<0.05, P<0.0001 and P<0.0001, respectively).[64]
    - Tadalafil 5 mg once daily coadministered with finasteride 5 mg for 12 weeks resulted in an IPSS total score improvement that was significantly better than finasteride/placebo (P=0.001).[66]
- A systematic review of alfuzosin studies showed a greater improvement in the primary outcome (IPSS) over placebo (weighted mean difference, -1.8 points; 95% confidence interval [CI], -2.49 to -1.11); however, when compared to other α-blockers (doxazosin, tamsulosin), doxazosin use was associated with the most favorable change from baseline IPSS. Alfuzosin alone and in combination with finasteride showed a greater improvement in LUTS compared to finasteride alone.

Key Points within the Medication Class

- According to Current Clinical Guidelines:[12,13]
  - Watchful waiting is recommended for mild symptoms of BPH (AUA symptom score <78) and patients with moderate or severe symptoms (AUA symptom score ≥8) who are not bothered by their symptoms.[12,13]
  - α blockers are considered first line; their rapid onset of action, good efficacy, and low rate and severity of adverse events, followed by a 5- α reductase inhibitor
    - The older, less costly, generic α-blockers remain reasonable choices.
  - Guidelines were published when little data was available on tadalafil.
  - Combination therapy is an appropriate and effective treatment for patients with LUTS associated with demonstrable prostatic enlargement based on volume measurement, prostate specific antigen level as a proxy for volume, and/or enlargement on digital rectal exam.[12]
- Other Key Facts:
  - Alfuzosin, doxazosin, terazosin and finasteride are available generically in standard formulations. The doxazosin sustained-release tablet (Cardura XL®) is not currently available generically.
  - Finasteride (Propecia®) is also available as a 1 mg tablet for the treatment of alopecia. Tadalafil (Adcirca®) is available as a 20 mg tablet for the treatment of pulmonary hypertension.[14]
  - 5-α reductase inhibitors are pregnancy category X; women who are pregnant or who could be pregnant should avoid handling dutasteride and dutasteride/tamsulosin capsules along with crushed finasteride tablets.[1-10]
  - Administration considerations:[1-10]
    - Alfuzosin, doxazosin extended-release, dutasteride, tamsulosin and dutasteride/ tamsulosin should all be swallowed whole and not crushed, chewed, or cut.
    - Doxazosin instant-release, finasteride, and tadalafil tablets may be crushed.
    - Silodosin capsules can be opened and the power sprinkled on applesauce.
    - Terazosin capsules can be dissolved in hot water (which may take five to 15 minutes) for administration through a feeding tube via an oral syringe if required.

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Overview/Summary

The agents approved for the treatment of signs and symptoms of benign prostatic hyperplasia will be the focus of this review. The α-adrenergic blockers including, alfuzosin, doxazosin, silodosin, tamsulosin, and terazosin, reduce smooth-muscle tone in the prostate and bladder neck decreasing lower urinary tract symptoms (LUTS) secondary to BPH. Alfuzosin, silodosin and tamsulosin are selective to the α-adrenergic receptors located in the prostate and therefore are only Food and Drug Administration (FDA) approved for BPH, whereas doxazosin and terazosin additionally inhibit α-adrenergic receptors found in the vascular smooth muscle and are additionally indicated for hypertension.[1-6] The 5-α reductase inhibitors, dutasteride and finasteride, are appropriate treatment options for LUTS associated with overall prostatic enlargement. They act by blocking the conversion of testosterone to dihydrotestosterone and in turn suppress the growth of the prostate.[7,8] Jalyn® (dutasteride/tamsulosin) is a combination of both an α-adrenergic blocker and a 5-α reductase inhibitors.[9] The final drug approved for use in BPH is a phosphodiesterase-5 inhibitor, tadalafil. The exact mechanism for reducing BPH symptoms is unknown.[10]

Clinical manifestations of BPH include LUTS (frequency of urination, nocturia, hesitancy, urgency, and weak urinary stream). The appearance and progression of symptoms is usually slow, over a couple of years, with a poor correlation between symptoms and the presence of an enlarged prostate on rectal exam.[11] Disease prevalence and the occurrence of symptoms are age dependent, with an initial onset of disease occurring patients greater than 50 years of age.[11] The American Urological Association (AUA) acknowledges that not all men with histological evidence of BPH will develop bothersome LUTS and not all patients with BPH and LUTS actually have prostate enlargement, one of the main features of symptomatic disease. Additionally, prostate enlargement may exist in the absence of LUTS.[12]

The AUA and European Association of Urology (EAU) standards of care include watchful waiting, surgical interventions (e.g., transurethral resection of the prostate and transurethral microwave thermotherapy), and drug therapies.[12,13] Medical therapies such as α-adrenergic blockers, 5-α reductase inhibitors, combination therapies, and phosphodiesterase-5 inhibitors are appropriate for less frequent and severe symptom management. Both the AUA and EAU recommend α-adrenergic blockers as first line drug therapy.[12,13] Due to similar efficacy and adverse event profiles, it is recommended to use older, generic agents before a more costly alternative.[12,13] The 5 α-reductase inhibitors are effective treatment options for patients with LUTS associated with prostatic enlargement and may also be used to prevent disease progression in patients with symptoms secondary to prostate enlargement but without bothersome signs/symptoms of the enlargement. However, these agents should not be used for LUTS in the absence of prostatic enlargement, due to a lesser effectiveness compared to α-blockers. Combination therapy with both an α-blocker and a 5-α reductase inhibitor is an effective treatment option for patients with LUTS associated with prostatic enlargement.[12] Guideline recommendations regarding the use of phosphodiesterase-5 inhibitors are lacking due to publication dates of the guidelines, but the EUA does state tadalafil may be used for moderate-to-severe (storage and voiding) LUTS in men with or without erectile dysfunction.[13]

Table 1 lists the BPH agents included in this review. Alfuzosin, doxazosin, terazosin and finasteride are available generically in standard formulations. The doxazosin sustained-release tablet (Cardura XL®) is not currently available generically; note that this formulation is not FDA indicated for the treatment of hypertension.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single-Entity Agents		
Alfuzosin hydrochloride (Uroxatral®)	α-adrenergic blocking agent	✔
Doxazosin mesylate (Cardura®*, Cardura XL®)	α-adrenergic blocking agent	✔
Dutasteride (Avodart®)	5-α reductase inhibitor	-
Finasteride (Proscar®)	5-α reductase inhibitor	✔
Silodosin (Rapaflo®)	α-adrenergic blocking agent	-
Tadalafil (Cialis®)	phosphodiesterase-5 inhibitor	-
Tamsulosin hydrochloride (Flomax®)	α-adrenergic blocking agent	-
Terazosin hydrochloride	α-adrenergic blocking agent	✔
Combination Products		
Dutasteride/tamsulosin hydrochloride (Jalyn®)	5-α reductase inhibitor/ α-adrenergic blocking agent	-

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration Approved Indications[1-10]

Generic Name	Treatment of signs and symptoms of benign prostatic hyperplasia	Treatment of hypertension	Treatment of erectile dysfunction
Single-Entity Agents			
Alfuzosin hydrochloride	✔		
Doxazosin mesylate	✔ #	✔ *	
Dutasteride	✔ † ‡		
Finasteride	✔ † §		
Silodosin	✔		
Tadalafil	✔		✔
Tamsulosin hydrochloride	✔		
Terazosin hydrochloride	✔	✔	
Combination Products			
Dutasteride/tamsulosin hydrochloride	✔ †		

*Instant release formulation only.
†In men with an enlarged prostate, to improve symptoms, reduce the risk of acute urinary retention and reduce the risk of the need for BPH-related surgery.
‡To treat symptomatic BPH in men with an enlarged prostate in combination with tamsulosin.
§To reduce the risk of symptomatic progression of BPH in combination with doxazosin.
#Doxazosin indicated for both the urinary outflow obstruction and obstructive and irritative symptoms associated with BPH.

Finasteride (Propecia®) is also available as a 1 mg tablet for the treatment of alopecia. Tadalafil (Adcirca®) is available as a 20 mg tablet for the treatment of pulmonary hypertension.[14]

Pharmacokinetics

Table 3. Pharmacokinetics[1-10,14]

Generic Name	Bio-availability (%)	Plasma Protein Binding (%)	Active Metabolites	Elimination (%)	Serum Half-Life (hours)
Alfuzosin hydrochloride	49	82 to 90	None	Feces (69); urine (24)	10
Doxazosin mesylate	65; 54 to 59 (ER)*	98	Yes	Feces (63); urine (9)	22; 15 to 19 (ER)
Dutasteride	60	99	6-β-hydroxy-dutasteride	Feces (45); urine (<1)	5 weeks
Finasteride	63	90	Yes†	Feces (57); urine (39)	6 to 8
Silodosin	32	97	Glucuronide conjugate	Feces (54.9); urine (33.5)	13.30 ± 8.07
Tadalafil	Unknown	94	None	Feces (61); Urine (36)	17.5
Tamsulosin hydrochloride	>90	94 to 99	Yes, activity not reported	Feces (21); urine (76)	9 to 15
Terazosin hydrochloride	90	90 to 94	Yes, activity not reported	Feces (20); urine (40)	9 to 12
Dutasteride/ tamsulosin hydrochloride	40 to 94; >90	99; 94 to 99	Yes; Yes	Feces (45; 21); Urine (<1; 76)	5 weeks; 9 to 15

ER=extended-release.
*Relative to the instant release formulation.
†<20% activity of finasteride.

Clinical Trials

Clinical studies including the benign prostatic hyperplasia (BPH) treatment agents are summarized in Table 4.[15-67] Trials evaluating doxazosin and terazosin in the treatment of hypertension are included in a separate review.

The Food and Drug Administration (FDA) approval of silodosin was based on two clinical trials where it was compared to placebo and demonstrated its efficacy in decreasing the International Prostate Symptom Score (IPSS) and improving general quality of life scores. In a pooled analysis of these two clinical trials, the mean change in total IPSS at baseline was -6.40 (±6.63) and -3.50 (±5.84) for the silodosin and placebo groups, respectively, with an adjusted mean difference reported as -2.8 (P<0.0001). The maximum urinary flow rate (Q_{max}) at endpoint was 2.6 mL/second (standard deviation [SD]±4.43) in the silodosin group and 1.5 mL/ second (SD±4.36) in the placebo group; corresponding to an adjusted mean group difference of 1.0 mL/ second (P=0.0007).[16]

A review of two trials comparing the standard doxazosin formulation to the doxazosin gastrointestinal therapeutic system (GITS), an extended-release product, revealed that both dosage forms were comparable in improving symptoms and urinary flow rate. Additionally, doxazosin-GITS and standard doxazosin showed modest but significant improvement in sexual function from baseline.[17]

The safety and efficacy of tadalafil for BPH has been evaluated in multiple studies. Tadalafil consistently showed significantly better improvement in IPSS compared to placebo.[18-25] One study evaluated men with BPH who had comorbid erectile dysfunction. Tadalafil was associated with statistically significant improvements in both internation index of erectile function (IIEF) scores and total IPSS (P<0.001 for both).[25]
Studies comparing the α-adrenergic blocking agents to each other have shown mixed and conflicting results. Although some trials have suggested superiority of one agent over another, most studies have shown non-inferiority within the α-blockers related to reducing IPSS.[26-46] A Cochrane review has evaluated tamsulosin in comparison to other α-adrenergic blocking agents. Tamsulosin was as effective as other α-adrenergic blockers in improving LUTS and urinary flow rates. Dizziness, rhinitis and abnormal ejaculation occurred significantly more frequently than placebo and withdrawal was reported more often with higher doses of tamsulosin. Additionally, terazosin use was associated with a higher rate of discontinuation than low dose tamsulosin.[37] A second Cochrane review evaluated terazosin to other α-blockers, finasteride alone or in combination with terazosin and placebo. Terazosin was comparable to tamsulosin in improving IPSS (40% vs 43%), and more effective than finasteride (38% vs 20%) or placebo (38% vs 17%) in improving American Urological Association Symptom Score (AUA-SS). Peak urinary flow rates were similar among α-blockers and higher with terazosin (22%) over finasteride (15%) and placebo (11%).[38] A meta-analysis by Djavan et al of α-adrenergic blocking agents (alfuzosin, doxazosin, tamsulosin, and terazosin) in men with LUTS suggestive of benign prostatic obstruction did not identify any difference among agents in improving total urinary symptom scores or Q_{max}. However, alfuzosin and tamsulosin were better tolerated than doxazosin and terazosin.[39]

Similar to the α-blocking agents, the 5-α reductase inhibitors have been compared to one another in a number of clinical trials, with mixed results. Dutasteride was shown to be non-inferior to finasteride for reducing prostate volume, post-void volume, and AUA-SS.[47-50]

Head-to-head trials between 5-α reductase inhibitors and α-blockers have also been conducted.[51-62] When compared to finasteride, tamsulosin showed comparable effect on urinary symptom scores at study end point (24 weeks and 1 year).[51,52], However, a benefit was found with tamsulosin at earlier assessment (four weeks) in both IPSS and Q_{max}.[51] Tamsulosin in combination with dutasteride has been found to be associated with a greater benefit in IPSS and Q_{max} than each agent alone. As expected tamsulosin use resulted in a much lower decrease in prostate volume as compared to combination therapy (0.00%±0.84% and 26.90%±0.62%, respectively; P<0.001).[53,] Four large, long-term trials comparing doxazosin, finasteride, each agent alone and in combination, and placebo.[58-61] Rates of nocturia were significantly reduced with monotherapy and combination treatment compared to placebo.[59] Men with moderate to enlarged prostate glands benefited most from combination therapy (P<0.05); however, doxazosin therapy alone was as effective as combination therapy for decreasing the risk of progression in men without an enlarged prostate.[60] Doxazosin monotherapy and in combination with finasteride was associated with significantly greater improvements in Q_{max} and IPSS. Differences between finasteride alone and placebo did not reach statistical significane.[61] Terazosin use alone and in combination with finasteride was associated with significantly greater reductions in symptom scores and greater increases in Q_{max} compared to finasteride monotherapy or placebo. Differences among combination therapy and terazosin monotherapy did not reach statistical significance, nor did difference between finasteride and placebo.[62]

Studies have been conducted evaluating the safety and efficacy of combination therapy with two agents from different classes.[63-66] A retrospective analysis showed combination therapy with finasteride and an α-blocking agent significantly improved IPSS in patients with severe BPH symptoms, but was not statistically different from monotherapy in the same population.[63] A meta-analysis conducted by Gacci et al found that a phosphodiesterase-5 inhibitor and α-blocker combination therapy significantly improved IPSS, IIEF score and Q_{max} compared to a blockers alone (P<0.05, P<0.0001 and P<0.0001, respectively).[64] Tadalafil 5 mg once daily coadministered with finasteride 5 mg for 12 weeks resulted in an IPSS total score improvement that was significantly better than finasteride/placebo (P=0.001).[66]

A systematic review of alfuzosin studies showed a greater improvement in the primary outcome (IPSS) over placebo (weighted mean difference, -1.8 points; 95% confidence interval [CI], -2.49 to -1.11); however, when compared to other α-blockers (doxazosin, tamsulosin), doxazosin use was associated with the most favorable change from baseline IPSS. Alfuzosin alone and in combination with finasteride showed a greater improvement in LUTS compared to finasteride alone. Additionally the change from baseline in peak urinary flow in patients on alfuzosin was comparable to the other α-blockers, finasteride and the combination of alfuzosin and finasteride and greater than placebo. The rates of withdrawal and adverse events were similar among α-blocker treatment. Otherwise, a greater incidence of dizziness, postural hypotension and syncope was reported with alfuzosin versus placebo. However, this did not result in a greater rate of withdrawal.[67]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment of Benign Prostatic Hyperplasia				
Tsai et al[15] Group A: Terazosin (generic) 1-4 mg once daily during period 1 (6 weeks) and terazosin (brand Hytrin®) 1-4 mg once daily in period 2 (6 weeks) vs Group B: Terazosin (brand Hytrin®) 1-4 mg once daily during period 1 (6 weeks) and terazosin (generic) 1-4 mg once daily in period 2 (6 weeks) The generic terazosin employed was manufactured by Purzer Pharmaceutical Co, Taipei, Taiwan.	OL, RCT Adult men in Taiwan newly diagnosed with symptomatic BPH who had not previously received treatment for BPH	N=53 13 weeks	Primary: IPSS, tolerability (using physical examination, including vital signs, laboratory analysis, and spontaneous reporting) Secondary: Not reported	Primary: At 2 and 6 weeks, no significant between-product differences were found in mean (SD) decreases from baseline in IPSS total score (generic, 2.46 [0.84] and 2.46 [1.00], respectively; branded, 1.56 [0.60] and 2.87 [0.71]) (P=0.29). At week 6, the between-product difference in mean (SD) increase from baseline in maximal uroflow rate was nonsignificant (generic, 2.36 [0.90] mL/second; branded, 2.03 [0.62] mL/second) (P=0.72). A total of 86 treatment-emergent adverse events were reported (45 with the generic drug; 41 with the branded drug), all of which were considered by the investigator as nonserious except for 1 case of acute epididymitis, which occurred with the generic drug. The most common adverse events reported with the generic and branded formulations were dizziness (7/48 [14.6%] and 10/50 [20.0%], respectively) and peripheral edema (1/48 [2.1%] and 3/50 [6.0%]). No significant differences in the prevalence of adverse events were found between the 2 treatments. Secondary: Not reported
Marks et al[16] Silodosin 8 mg once daily vs placebo	DB, MC, PC, PG, RCT (Pooled data of 2 trials) Men aged ≥50 years with an IPSS≥13, a peak	N=923 12 weeks	Primary: Mean change in total IPSS from baseline Secondary: Mean change in urodynamics	Primary: The mean change in total IPSS at baseline was -6.40±6.63 and -3.50±5.84 for the silodosin and placebo groups, respectively. The adjusted mean difference being -2.8 (95% CI, -3.6 to -2.0; P<0.0001). Secondary: The mean change in urinary flow rate (Q_{max}) after initial silodosin administration was 2.80±3.44 mL/second compared to 1.50±3.76

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	urinary flow rate of 4-15 mL/seconds and a post-void residual volume <250 mL		(Q_{max})	mL/second for placebo. At endpoint, the Q_{max} was 2.60±4.43 mL/second in the silodosin group and 1.50±4.36 mL/second in the placebo group; corresponding to an adjusted mean group difference of 1.0 mL/second (95% CI, 0.4 to 1.5; P=0.0007). A total of 257 silodosin-treated patients (55.2%) experienced a total of 462 adverse events compared with 168 placebo-treated patients (36.8%). The most commonly reported adverse event was retrograde ejaculation occurring in 28.1% of silodosin patients and 0.9% of placebo patients. This adverse event led to study discontinuation in 2.8% of patients treated with silodosin.
Kirby et al[17] Doxazosin vs doxazosin GITS vs placebo Comparison with placebo was evaluated in one of the two trials.	Two DB, MC, PG, RCT Men aged 50 to 80 years with BPH	N=1,475 (2 trials) 17 weeks	Primary: IPSS, Q_{max} Secondary: Sexual function, tolerability	Primary: A 45% decrease from baseline in IPSS was attained in both the doxazosin GITS and doxazosin groups, while a 34% reduction was noted with placebo at 13 weeks (P<0.001 vs placebo). Doxazosin GITS was as effective as doxazosin in improving IPSS with a least squares mean difference of 0.07 (SEM, 0.28; 95% CI, -0.47 to 0.61; P=0.799). Effect on Q_{max} was also comparable between active treatment groups. A least square mean difference of 0.19 (SEM, 0.23; 95% CI, -0.27 to 0.64; P=0.426) was reported. Improvement in Q_{max} was significantly greater with active treatment compared to placebo (P<0.001 for each vs placebo). Secondary: Only the non-placebo controlled trial evaluated sexual function. Both doxazosin GITS and doxazosin showed modest but significant improvement s in sexual function from baseline as measured by the International Index of Erectile Function (P≤0.001 for doxazosin GITS and P<0.05-0.001 for doxazosin). Forty-one percent of doxazosin GITS treated individuals, 54% of doxazosin treated individuals and 39% of placebo treated individuals experienced adverse events (P<0.001 for differences among treatments). Headache, dizziness, respiratory tract infections and asthenia were the

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Sample Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td>most frequently reported side effects of active treatment.</td></tr>
<tr><td>Porst et al[18]

Tadalafil 5 mg QD

vs

placebo</td><td>DB, PC, RCT

Men ≥45 years of age with BPH lower urinary tract symptoms for >6 months, IPSS ≥13 and Q_{max} between 4 and 15 ml/second</td><td>N= 325

12 weeks</td><td>Primary:
Total IPSS

Secondary:
IIEF-erectile function, BPH-II, IPSS storage, IPSS voiding, IPSS nocturia, IPSS QOL</td><td>Primary:
Treatment with tadalafil resulted in a decrease in IPSS of 5.6 compared to a decrease of 3.6 with placebo (P=0.004).

Secondary:
<table>
<tr><th>End point</th><th>Placebo (Mean change)</th><th>Tadalafil 5 mg (Mean change)</th><th>P value</th></tr>
<tr><td>IIEF-erectile function</td><td>2.0</td><td>6.7</td><td><0.001</td></tr>
<tr><td>Total IPSS at week four</td><td>-3.5</td><td>-5.3</td><td>0.003</td></tr>
<tr><td>BPH-II at week 12</td><td>-1.3</td><td>-1.8</td><td>0.057</td></tr>
<tr><td>Modified IPSS</td><td>-2.7</td><td>-3.4</td><td>0.146</td></tr>
<tr><td>BPH-II at week four</td><td>-1.2</td><td>-1.8</td><td>0.029</td></tr>
<tr><td>IPSS voiding</td><td>-2.3</td><td>-3.3</td><td>0.020</td></tr>
<tr><td>IPSS storage</td><td>-1.3</td><td>-2.3</td><td>0.002</td></tr>
<tr><td>IPSS nocturia</td><td>-0.4</td><td>-0.5</td><td>0.233</td></tr>
<tr><td>IPSS QOL</td><td>-0.7</td><td>-1.0</td><td>0.013</td></tr>
</table>
Treatment-emergent adverse events were experienced by 26 and 22% of the tadalafil and placebo groups, respectively. The most common adverse events that occurred in the tadalafil group were headache (N=6) and back ache (N=3). Three patients in the tadalafil group and one patient in the placebo group discontinued the study due to adverse events. The proportion of patients who experienced at least one treatment-emergent positive orthostatic test was similar between treatment groups.</td></tr>
<tr><td>Goldfischer et al[19]

Tadalafil 5 mg QD

vs

placebo</td><td>DB, MC, PG, PRO, RCT

Men ≥45 years of age with a diagnosis of lower urinary</td><td>N=317

2-week single-blind placebo lead-in followed by 12 week</td><td>Primary:
Proportion of men with lower urinary tract symptoms secondary to BPH reporting</td><td>Primary:
Treatment-emergent adverse effects occurred in 7.0% of the tadalafil treatment group compared to 5.7% in the placebo group (P=0.403). Dizziness occurred in 6.3% of the tadalafil treatment group compared to 5.0% in the placebo group and postural dizziness occurred in 0.6% of both groups (P value not reported).</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients were take concomitant therapy with uroselective α-blockers (alfuzosin, silodosin, tamsulosin) or non-uroselective α-blockers (doxazosin, terazosin).	tract symptoms secondary to BPH for >6 months that were receiving stable α-blocker therapy for ≥4 weeks	treatment period	treatment-emergent dizziness when tadalafil 5 mg QD was added to α-blocker therapy Secondary: IPSS change from baseline	A greater proportion of patients receiving tadalafil with a non-uroselective α-blocker experienced adverse effects compared to placebo with a non-uroselective α-blocker (15.4 vs 9.4%, respectively). A lower proportion of patients receiving tadalafil with an uroselective α-blocker experienced adverse effects compared to placebo with an uroselective α-blocker (3.8 vs 4.6%, respectively). In patients receiving tadalafil with a non-uroselective α-blocker, a greater proportion of patients experienced adverse effects with doxazosin compared to terazosin (22.6 vs 4.8%, respectively). In patients receiving placebo with a non-uroselective α-blocker, a greater proportion of patients experienced adverse effects with terazosin compared to doxazosin (16.0 vs 3.6%, respectively). In patients receiving tadalafil with an uroselective α-blocker, 20% of patients experienced adverse effects with alfuzosin compared to 0% with silodosin and tamsulosin. In patients receiving placebo with an uroselective α-blocker, 12.0% experienced adverse effects with alfuzosin compared to 2.4% with tamsulosin and 0% with silodosin. Secondary: Lower urinary tract symptoms were evaluated using change in IPSS. At visit three, 21.5 and 21.3% of the tadalafil and placebo groups, respectively, had an IPSS of 0 to 7; an IPSS of 8 to 19 was observed in 56.3 and 60.0% of the tadalafil and placebo groups, respectively. Severe lower urinary tract symptoms with IPSS of 20 to 35 were observed in 22.2 and 18.8% of the tadalafil and placebo groups, respectively. It was determined that of the tadalafil group, 43.7% had an IPSS <13 and 56.3% had an IPSS ≥13 at visit three. Of the placebo group, 41.3 had an IPSS <13 and 58.8% had an IPSS ≥ 13 at visit three. There was no significant difference in treatment-emergent adverse events between groups. Treatment-emergent adverse events occurred in 41.8% for the tadalafil group compared to 33.1% of the placebo group. The most commonly reported adverse events in the tadalafil group were dizziness,

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Sample Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td>dyspepsia, diarrhea, back pain and gastroesophageal reflux disease.</td></tr>
<tr><td>Donatucci, et al[20]

Tadalafil 5 mg QD

vs

placebo</td><td>ES, MC, OL

Men ≥45 years of age with >6 months of BPH lower urinary tract symptoms who completed the 12-week DB study</td><td>N=427

1 year</td><td>Primary:
IPSS, IPSS irritative, IPSS obstructive, IPSS nocturia, IPSS index and BPH-II

Secondary:
Not reported</td><td>Primary:
The following table includes the results of the primary efficacy endpoints, stratified according to the agent that was received during the 12-week DB study period.

<table>
<tr><th>End point</th><th>Previous Placebo</th><th>Previous Tadalafil 2.5 mg</th><th>Previous Tadalafil 5 mg</th><th>Previous Tadalafil 10 mg</th><th>Previous Tadalafil 20 mg</th></tr>
<tr><td colspan="6">Mean change in total IPSS</td></tr>
<tr><td>Week 0 to end</td><td>-4.1±6.8</td><td>-5.7±5.4</td><td>-5.0±7.2</td><td>-5.7±6.4</td><td>-4.6±7.7</td></tr>
<tr><td>Week 12 to end</td><td>-2.2±5.3</td><td>-2.5±5.1</td><td>0.2±5.4</td><td>-0.2±5.8</td><td>0.8±6.4</td></tr>
<tr><td colspan="6">Mean change in IPSS Irritative</td></tr>
<tr><td>Week 0 to end</td><td>-1.6±3.2</td><td>-2.1±2.6</td><td>-2.1±3.1</td><td>-1.9±2.7</td><td>-1.8±3.3</td></tr>
<tr><td>Week 12 to end</td><td>-0.9±2.4</td><td>-1.0±2.7</td><td>0.0±2.4</td><td>0.2±2.7</td><td>0.3±2.8</td></tr>
<tr><td colspan="6">Mean change in IPSS Obstructive</td></tr>
<tr><td>Week 0 to end</td><td>-2.5±4.2</td><td>-3.6±3.6</td><td>-3.0±4.8</td><td>-3.8±4.3</td><td>-2.8±4.9</td></tr>
<tr><td>Week 12 to end</td><td>-1.3±3.6</td><td>-1.6±3.1</td><td>0.2±3.4</td><td>-0.5±3.6</td><td>0.4±4.2</td></tr>
<tr><td colspan="6">Mean change in BPH-II</td></tr>
<tr><td>Week 0 to end</td><td>-1.2±2.5</td><td>-1.4±2.6</td><td>-1.3±2.8</td><td>-1.4±2.7</td><td>-1.2±2.8</td></tr>
<tr><td>Week 12 to end</td><td>-0.8±2.4</td><td>-0.8±2.3</td><td>0.1±2.5</td><td>0.1±2.7</td><td>0.3±2.0</td></tr>
</table>

Secondary:
Not reported</td></tr>
<tr><td>Roehrborn et al[21]</td><td>DB, MC, PC, RCT</td><td>N=1,058</td><td>Primary:
Change in IPSS</td><td>Primary:
The least squares mean improvement in IPSS from baseline was greater</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Tadalafil 2 mg QD vs tadalafil 5 mg QD vs tadalafil 10 mg QD vs tadalafil 20 mg QD vs placebo	Men ≥45 years of age with at least a six month history of LUTS secondary to BPH, IPSS ≥13, Q_{max} 4 to 15 mL/second from pre-void bladder volume and between 150 and 550 mL with a voided volume ≥125 mL	12 weeks	with tadalafil 5 mg daily compared to placebo at 12 weeks Secondary: Difference between tadalafil groups and placebo in IPSS, the irritative subscore, the obstructive subscore, IPSS QOL index, BPH-II, LUTS GAQ and uroflowmetry parameters	with tadalafil 5 mg daily compared to placebo (-5.17±0.49 vs -2.27±0.49; P<0.001). Secondary: Improvements in IPSS from baseline were significantly greater with tadalafil 2.5 mg (-3.88±0.50), 10 mg (-5.17±0.49) and 20 mg (-5.21±0.50) compared to placebo (P<0.001 for all). Improvements in the irritative subscore were significantly greater with tadalafil 5 mg (-1.89±0.23), 10 mg (-1.96±0.23) and 20 mg (-2.07±0.23) but not 2.5 mg (-1.59±0.23) compared to placebo (-0.99±0.23; P<0.05 for all except 2.5 mg). Improvements in the obstructive subscore were significantly greater with tadalafil 2.5 mg (-2.23±0.33), 5 mg (-2.94±0.33), 10 mg (-3.13±0.32) and 20 mg (-3.12±0.33) compared to placebo (-1.26±0.33; P<0.05 for all). Improvements in IPSS QOL were significantly greater with tadalafil 5 mg (-0.86±0.11), 10 mg (-0.92±0.10) and 20 mg (-0.88±0.11) but not 2.5 mg (-0.74±0.11) compared to placebo (-0.49±0.11; P<0.05 for all except 2.5 mg). Improvements in BPH-II were significantly greater with tadalafil 5 mg (-1.40±0.21) and 20 mg (-1.45±0.21) but not 2.5 mg (-0.96±0.21) and 10 mg (-1.38±0.20) compared to placebo (-0.83±0.21; P<0.05 for all except 2.5 and 10 mg). A higher percentage of patients answered “Yes” on LUTS GAQ in the tadalafil 5 mg (69.0%), 10 mg (73.0%) and 20 mg (74.2%) groups but not the 2.5 mg group (61.9%) compared to the placebo group (54.8%; P<0.05 for all except 2.5 mg). Improvements Q_{max} from baseline were significantly greater with tadalafil 2.5 mg (1.41±0.39), 5 mg (1.64±0.39), 10 mg (-1.58±0.38) and 20 mg (-1.96±0.39) compared to placebo (1.25±0.40; P<0.05 for all).

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Broderick, et al[22] Tadalafil 2.5 mg QD vs tadalafil 5 mg QD vs tadalafil 10 mg QD vs tadalafil 20 mg QD vs placebo	DB, MC, PC, RCT Men over the age of 45 years with a history of lower urinary tract symptoms secondary to BPH for >6 months, an IPSS ≥13 and Q_{max} between 4 and 15 ml/second, and PVR ≤300 ml	N=1,056 12 weeks	Primary: 12-week change in IPSS Secondary: 12-week change in IPSS QOL and BPH-II	Primary: Treatment with all doses of tadalafil resulted in a statistically significant improvement in IPSS compared to placebo (P not reported). The change in IPSS from baseline to week 12 for all doses of tadalafil or placebo was compared in men with and without erectile function, and no statistically significant differences were found. Secondary: There were no statistically significant differences across treatment groups for IPSS QOL and BPH-II; there were no differences in IPSS QOL or BPH-II found between subgroups of men with and without ED.
Oelke et al[23] Tadalafil 5 mg QD or tamsulosin 0.4 mg QD vs placebo	DB, MC,PC, PG, RCT Study Grade: Good Men >45 years of age with lower urinary tract symptoms and BPH for >6 months, an IPSS >13 and Q_{max} >4 mL to <15 mL	N=511 4 week placebo run-in period followed by 12 week treatment period	Primary: IPSS Secondary: BPH-II, IIEF-erectile function domain, IPSS storage and voiding subscores, nocturia question and IPSS QOL index	Primary: The change in IPSS from baseline to week 12 was statistically significant for both the tadalafil group (-2.1; P=0.001) and the tamsulosin group (-1.5; P=0.023). Secondary: The difference from placebo in BPH-IIx at week 12 was statistically significant for both the tadalafil group (-0.8; P=0.003) and the tamsulosin group (-0.6; P=0.26). There was also a statistically significant difference from placebo at week four for both the tadalafil (-0.8+0.2; P<0.001) and the tamsulosin (-0.9+0.2; P<0.002) groups. Significant improvements in the IPSS QOL index compared to placebo were reported with tadalafil (-0.3+0.1; P=0.022) but not with tamsulosin (-0.1+0.1; P=0.546).

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				Compared to placebo, the mean change from baseline to end point in the IIEF-erectile function domain in med with ED who were also sexually active was statistically significant with tadalafil (+4.0+1.0; P<0.001) while the mean change with tamsulosin was NS (=0.4+1.0; P=0.0699). The IPSS storage subscores for placebo, tadalafil and tamsulosin were 7.3+3.2, 6.8+2.7 and 7.1+3.0, respectively. The IPSS voiding subscores for placebo, tadalafil and tamsulosin were 10.1+4.1, 10.5+3.5 and 9.8+3.5. The IPSS nocturia question mean for placebo was 2.2+1.2 and 2.1+1.1 for both tadalafil and tamsulosin, respectively.
Liu et al[24] PDE5 inhibitors vs placebo The complete MA included 5 studies of which 4 studies compared tadalafil to placebo, 1 study compared sildenafil to placebo and 1 study compared vardenafil to placebo.	MA of 5 trials; DB,PG, RCT Men ≥45 years of age with BPH	5 trials N varied, range 99 to 212 Duration varied (8 to 12 weeks)	Primary: Change in IPSS and Q_{max} Secondary: IPSS irritative, IPSS obstructive, IPSS QOL, IIEF-erectile function, PVR volume, adverse events	Primary: The mean change in IPSS from baseline to endpoint compared to placebo was -5.00 vs -2.67 for tadalafil, -5.8 vs -3.6 for vardenafil and -6.3 vs -1.9 for sildenafil. The pooled mean change was -5.24 for the PDE-5 inhibitors compared to placebo, which was -2.64. Pooled data for tadalafil, vardenafil and sildenafil demonstrated an overall benefit for a change in IPSS from baseline with PDE-5 inhibitors compared to placebo (P<0.00001). In men with co-morbid BPH and ED, the mean change in IPSS for tadalafil and sildenafil was -2.3 (95% CI, -3.26 to -1.34) and -4.4 (95% CI, -6.87 to -1.93), respectively. The mean change in the Q_{max} for tadalafil, vardenafil and sildenafil was 0.20 (P=0.38), 0.60 (P=0.56) and 0.15 (P=0.91), respectively. Pooling of data for tadalafil, vardenafil and sildenafil demonstrated a similar effect on the change in Q_{max} when compared to placebo (P=0.32). Secondary: Pooled data demonstrated an overall benefit of tadalafil and vardenafil in reducing the IPSS irritative subscore compared to placebo (P<0.00001). Pooled data also demonstrated an overall benefit of tadalafil and vardenafil in reducing the IPSS obstructive subscore compared to placebo (P<0.00001).

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				Pooled data demonstrated a significant difference in IPSS-QOL in favor of tadalafil and sildenafil compared to placebo (P<0.00001). The mean change in IIEF-erectile function for tadalafil, vardenafil and sildenafil was 5.31 (95% CI, 4.06 to 6.55), 6.00 (95% CI, 4.20 to 7.80) and 7.30 (95% CI, 4.53 to 10.07), respectively. Pooling of data for two PDE-5 inhibitors demonstrated a significant difference in favor of PDE-5 inhibitors compared to placebo (P<0.00001). The change in PVR urine volume for tadalafil and vardenafil was 0.47 (95% CI, -5.17 to 6.10; P=0.87) and -0.90 (95% CI, -10.09 to 8.29; P=0.85), respectively. Pooling data for tadalafil and vardenafil demonstrated a similar effect on the change in PVR urine volume compared to placebo (P=0.97).
Egerdie et al[25] Tadalafil 2.5 mg QD vs tadalafil 5 mg QD vs placebo	DB, MC, PG, RCT Study rating: Good Sexually active men ≥45 years of age with at least a three months history of ED and at least a six month history of LUTS, IPSS ≥13, Q_{max} 4 to 15 mL/second from pre-void and at least four sexual encounters during a four-week lead-in	N=606 12 weeks	Primary: Change in IIEF-EF and total IPSS from baseline Secondary: Percentage of "yes" responses to SEP Question 3, changes in BPH-II, IIEF subscores, IPSS subscores, IPSS QOL, GAQ, PGI-I and CGI-I	Primary: Tadalafil 5 mg QD was associated with greater improvements in both IIEF and total IPSS compared to placebo (6.5±0.2 vs1.8±0.5 and -6.1±0.1 vs -3.8±0.5, respectively; P<0.001 for both). Tadalafil 2.5 mg QD was associated with a greater improvement in IIEF (5.2±0.5; P>0.001) but not total IPSS (-4.6±0.4; P=0.18) compared to placebo. Secondary: More patients answered "yes" to SEP Question 3 ("Did your erection last long enough for you to have successful intercourse?") in the tadalafil 2.5 and 5 mg groups compared to the placebo group (difference from baseline, 24.6 and 31.7 vs 12.0%; P<0.001 for both). Improvements from baseline in BPH-II were greater with tadalafil 5 mg (-2.1±0.2; P<0.001) but not 2.5 mg (-1.6±0.2; P=0.16) compared to placebo (-1.2±0.2). Compared to placebo, both tadalafil 2.5 and 5 mg were associated with greater improvement in IIEF intercourse satisfaction, overall satisfaction domains, Questions 3 (penetration) and 4 (maintenance of erection) as well as a higher percentage of "yes" response to SEP Questions 2

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	period			(insertion), 4 (hardness) and 5 (overall satisfaction; P<0.001 for all). Tadalafil 5 mg was associated with greater improvements in IPSS voiding and storage subscores compared to placebo (P<0.001 for both) but not in IPSS nocturia question (P=0.075) or QOL index (P=0.082). There were no significant differences between tadalafil 2.5 mg and placebo in any of the IPSS subscores (P>0.05).
Lapitan et al[26] Alfuzosin 10 mg once daily vs tamsulosin 0.2 mg once daily Authors note the traditional tamsulosin dose is 0.2mg once daily in the Philippines and other Asian countries.	DB, RCT Men >40 years of age with symptomatic BPH	N=76 8 weeks	Primary: IPSS Secondary: Mean change in IPSS, Q_{max}, mean change in Q_{max}, DAN-PSS, adverse events	Primary: A mean IPSS of 16.53±6.16 was reported in the alfuzosin group vs 15.73±5.67 in the tamsulosin group. This difference did not reach statistical significance (P value not reported). Secondary: No significant difference in the mean change in IPSS was detected between the groups. After 8 weeks of treatment, both groups showed a comparable improvement from baseline in Q_{max} (P=0.048) and the Q_{max} (P value not reported). The only reported difference in the DAN-PSS between groups was in the erection bother score, which was higher with alfuzosin therapy (1.19±1.12), compared to tamsulosin (0.70±0.99). There was no significant difference in the rates of dizziness, weakness, fever or constipation noted between groups.
Kirby et al[27] Doxazosin GITS 4-8 mg once daily vs tamsulosin 0.4-0.8 mg once daily	DB, RCT, XO Men aged 50 to 80 years with symptoms of BPH and prostate enlargement	N=52 20 weeks	Primary: IPSS, Q_{max} Secondary: Tolerability	Primary: Doxazosin GITS demonstrated a significantly greater benefit in the change from baseline in total IPSS (-8.0 vs -6.4 with tamsulosin; P=0.019), but not Q_{max} (2.6 mL/second vs 1.7 mL/second; P=0.089). Secondary: Both agents were fairly well tolerated with dizziness, headache and asthenia reported in greater than 5.0% of patients in both groups. Hypotension occurred in 4.0% of doxazosin treated patients and 2.0% of tamsulosin patients.
Rahardjo et al[28]	MC, OL	N=101	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Doxazosin 2 mg once daily vs tamsulosin 0.2 mg once daily	Patients with LUTS due to BPH	6 weeks	IPSS, Q_{max}, average urinary flow rate and residual urine; safety Secondary: Not reported	The total IPSS decreased significantly in both the tamsulosin and doxazosin groups compared to baseline (P<0.001). There was a significant difference in the decrease in total IPSS between two groups (P=0.036) in favor of tamsulosin. Q_{max}, average urinary flow rate and residual urine significantly improved only in the tamsulosin group (P<0.001, P<0.001, and P<0.05, respectively). There were no significant differences in systolic blood pressure, diastolic blood pressure or heart rate in the tamsulosin group; however, doxazosin resulted in a significant difference from baseline in systolic blood pressure (P<0.01) but not in diastolic blood pressure (P=NS) at the end of the study. Tamsulosin was well tolerated; only three patients (6%) in the tamsulosin group reported an adverse event (dizziness) while 11 patients (22%) in the doxazosin group reported an adverse event (dizziness), one of whom withdrew from the study. Secondary: Not reported
Xue et al[29] Doxazosin (controlled-release) 4 mg once daily vs tamsulosin 0.2 mg once daily	RCT Chinese men with confirmed BPH	N=117 8 weeks	Primary: Efficacy, safety Secondary: Not reported	Primary: Both drugs significantly improved the IPSS (total, irritative subscore, and obstructive subscore; P=0.001 for all) and Q_{max} (P=0.001). Secondary: Not reported
Pompeo et al[30] Doxazosin GITS 4 mg plus tamsulosin placebo four	DB, DD, RCT Brazilian patients with BPH	N=165 12 weeks	Primary: Absolute and percentage change from	Primary: Doxazosin GITS and tamsulosin improved IPSS with no significant differences between groups at week 12. During weeks 4-8, tamsulosin-treated patients demonstrated a slower improvement (P<0.001) in IPSS

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times a day vs tamsulosin 0.4 mg plus doxazosin placebo four times a day			baseline in symptoms measured by IPSS Secondary: QOL question from the IPSS, and SFAQ	than doxazosin GITS-treated patients. Secondary: The proportion of satisfied patients did not change over the course of the study with doxazosin GITS, while it did change significantly between weeks 4 and 8 with tamsulosin (P=0.006); this suggests that a change for the better was observed earlier with doxazosin. At week 12, the proportion of patients with little or no difficulty at ejaculation (question 6 of SFAQ) was higher in the doxazosin GITS group (P=0.019). Both treatments were well tolerated.
Kaplan, Te, et al[31] Doxazosin 4-8 mg once daily vs terazosin 5-10 mg once daily	OL, PRO Men with BPH and >80 years of age	N=36 6 months	Primary: Peak urinary flow rate, AUA SS Secondary: Not reported	Primary: There was significant improvement in Q_{max} (P<0.008) and AUA SS (P<0.01) in both treatment groups. Secondary: Not reported
Samli et al[32] Doxazosin 8 mg once daily vs terazosin 10 mg once daily	XO Men with LUTS associated with BPH	N=50 3 months	Primary: IPSS, Q_{max} Secondary: Not reported	Primary: Forty four percent of the subjects in the doxazosin arm and 40% in the terazosin arm showed improvement in both IPSS and Q_{max}. After 3 months of treatment, both treatment groups resulted in an increased Q_{max} (P<0.001) and a decreased IPSS (P<0.01). Nineteen subjects did not show improvement and switched to the other treatment drug. Of these subjects, 2/19 showed improvement in both IPSS and Q_{max}, 2/19 showed improvement in IPSS only but not in Q_{max}, 15/19 did not show any improvement. Secondary: Not reported
Kaplan, Soldo, et al[33] Doxazosin 4 mg every	RCT Normotensive	N=43 4-17 months	Primary: Boyarsky symptom score,	Primary: There were significant improvements from baseline in Boyarsky symptom score and Q_{max} in all four treatment groups (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
morning (DOX-AM) vs doxazosin 4 mg every evening (DOX-PM) vs terazosin 5 mg every morning (TER-AM) vs terazosin 5 mg every evening (TER-PM)	men with symptomatic prostatism		Q_{max}, blood pressure, and occurrence of adverse events Secondary: Not reported	There was no significant difference in Boyarsky symptom score and Q_{max} improvement between the four groups. Adverse events were significantly decreased in groups with evening administration dosing schedule (P<0.05). Secondary: Not reported
Kawabe et al[34] Silodosin 4 mg twice a day vs tamsulosin 0.2 mg once daily vs placebo Authors note the traditional tamsulosin dose is 0.2 mg once daily in Japan.	DB, MC, PC, RCT Japanese men aged ≥50 years with an IPSS ≥8, a QOL score ≥3, a Q_{max}<15 mL/second, a voided volume ≥100 mL, residual urine volume of <100 mL, and a prostate volume of ≥20 mL	N=457 12 weeks	Primary: Mean change in total IPSS from baseline Secondary: Mean change in Q_{max}, urodynamics and QOL symptom scores	Primary: The mean change in total IPSS from baseline was -8.3±6.4, -6.8±5.7, -5.3±6.7 for silodosin, tamsulosin and placebo groups, respectfully. The mean intergroup differences between silodosin and placebo and tamsulosin in the total IPSS were -3.0 (95% CI, -4.6 to -1.3) and -1.4 (95% CI, -2.7 to -0.2), respectively; P<0.001 for both groups indicating superiority over placebo and non-inferior status to tamsulosin. Secondary: The mean change in QOL score from baseline was -1.7±1.4, -1.4±1.3, and -1.1±1.2 in the silodosin, tamsulosin, and placebo groups, respectively (P value for silodosin-placebo comparison=0.002). The mean change at endpoint in Q_{max} from baseline was 2.24±3.96, 2.95±4.64, and 2.42±5.50 mL/second for the silodosin, tamsulosin, and placebo groups, respectively (intergroup differences not significant). The drug-related adverse event incidence rates were 69.7%, 47.4%, and 36.4% in the silodosin, tamsulosin, and placebo groups, respectively. The

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				most common adverse event in the silodosin group was abnormal ejaculation. Abnormal ejaculation was reported in 22.3% of silodosin-treated patients, 1.6% of tamsulosin patients, and 0% of placebo patients. A total of 2.9% of silodosin patients discontinued treatment as a result of this adverse event.
Tsujii[35] Tamsulosin 0.1-0.2 mg once daily vs terazosin 0.5-1 mg twice a day vs prazosin 0.5-1 mg twice a day	RCT, XO Patients with symptomatic BPH	N=121 4 weeks	Primary: Symptom score, changes in Q_{max} and average urinary flow rate , post void residual urine volume, and blood pressure Secondary: Not reported	Primary: The terazosin-treated group showed significant improvement in 4 out of 9 symptoms compared with tamsulosin (P<0.05). There were significant increases in Q_{max} with the prazosin group, and in average urinary flow rate with the tamsulosin groups (P<0.05). There were no significant changes in residual urine volume with any of the treatment groups. Significant blood pressure reductions were observed in the hypertensive subjects in the prazosin, terazosin, and tamsulosin groups (P<0.05 for all). In the normotensive subjects, no significant changes in blood pressure were observed with any of the drugs. Secondary: Not reported
Bozlu et al[36] Alfuzosin 2.5 mg three times a day vs doxazosin 4 mg once daily vs tamsulosin 0.4 mg once daily	RETRO Patients with LUTS suggestive of BPH with and without diabetes	N=281 6 months	Primary: Symptoms and bother score according to the Turkish validation of the IPSS, Q_{max}, post-void residual urine volume Secondary: Not reported	Primary: α1-Blockers significantly improved the IPSS, bother score, Q_{max}, and post-void residual urine volume compared with baseline (P<0.001). IPSS and bother score were significantly improved more in the diabetic patients compared with the nondiabetic patients (P<0.01). There was no significant difference among the groups in the improvement rates of any of the parameters (P>0.05). Secondary: Not reported

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vs terazosin 5 mg once daily				
Wilt et al[37] Tamsulosin 0.2-0.8 mg once daily vs other α-antagonists, Permixon®* , or placebo	SR Men with BPH and LUTS	N=4,122 (14 trials) 4-26 weeks	Primary: Change in urological symptom scale scores from baseline Secondary: Changes in urinary flow measures (peak urine flow rate), adverse effects	Primary: The WMD in the Boyarsky symptom score for tamsulosin compared to placebo was -1.1 points (95% CI, -1.49 to -0.72) or a 12% improvement with 0.4 mg and -1.6 points (95% CI, -2.3 to -1.0) or a 16% improvement with 0.8 mg. Secondary: The WMD in peak urine flow was 1.1 mL/second with both 0.4 mg and 0.8 mg strengths (95% CI, 0.59 to 1.51 with 0.4 mg; 95 % CI, 0.65 to 1.48 with 0.8 mg). Tamsulosin was reported to be as effective as other α-antagonists, or Permixon® in the improvement of LUTS and urinary flow rates. Dizziness, rhinitis and abnormal ejaculation occurred significantly more often with tamsulosin than placebo. The rates of adverse events and withdrawal increased with higher doses of tamsulosin. Terazosin was associated with a higher rate of discontinuation than low dose tamsulosin.
Wilt et al[38] Terazosin vs other α-antagonists, finasteride alone or in combination with terazosin, or placebo	SR Men with symptomatic benign prostatic obstruction	N=5,151 (17 trials) 4-52 weeks	Primary: Change in urological symptom scale scores from baseline Secondary: Urodynamic measures, adverse effects	Primary: Boyarsky symptom score improved by 37% with terazosin and 15% with placebo. AUA scores improved by 38% in the terazosin treatment group vs 20% with finasteride and 17% with placebo. Terazosin was comparable to tamsulosin (40% and 43%, respectively) in improving IPSS. Secondary: The improvement in peak urinary flow rates reported with terazosin (22%) was similar to other α-antagonists, but higher than finasteride (15%) and placebo (11%). Side effects, including dizziness, asthenia, headache and postural hypotension, occurred more often with terazosin vs placebo. Rates of discontinuation with terazosin were higher than other α-blockers,

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				but similar to finasteride and placebo.
Djavan et al[39] Alfuzosin vs doxazosin vs tamsulosin vs terazosin vs placebo	MA Men with LUTS suggestive of benign prostatic obstruction	N=6,333 (placebo-controlled trials) N=507 (comparative trials)	Primary: Total symptom score and Q_{max}, tolerability Secondary: Not reported	Primary: There was no difference in efficacy among the four drugs. Alfuzosin immediate release 2.5 mg three times daily, alfuzosin sustained-release 5 mg twice daily, terazosin 5-10 mg daily, doxazosin 4-8 mg daily, and tamsulosin 0.4 mg daily all produced comparable improvements in LUTS and Q_{max} (no P values reported). Alfuzosin and tamsulosin were better tolerated than terazosin and doxazosin. Alfuzosin and tamsulosin had similar study withdrawal rates as placebo. With terazosin and doxazosin, an additional 4% to 10% of patients withdrew from the study due to intolerability (no P value reported). Tamsulosin had less effect on blood pressure than alfuzosin (no P value reported). Tamsulosin also caused less symptomatic orthostatic hypotension than terazosin (no P value reported). Secondary: Not reported
Karadag et al[40] Alfuzosin 10 mg QD followed by tamsulosin 0.4 mg QD (Alf-Tam group) vs tamsulosin 0.4 mg QD followed by alfuzosin 10 mg QD (Tam-Alf group) Each treatment was administered for 8 weeks for a total treatment	PRO, RCT, XO Men with BPH admitted to urology department with LUTS	N=100 16 weeks	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported Patients in the Tam-Alf group experienced overall improvements in IPSS and Q_{max} at week eight. Additionally, 21 patients (42%) experienced significant improvements in Q_{max} and IPSS, 20 patients (40%) experienced significant improvements in just one of these parameters, and nine patients (18%) had no significant changes in either parameter at week eight. Analysis of IPSS and Q_{max} in this group at week eight and week 16 indicated that 29 patients (58%) appeared to benefit from the change in treatment.

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duration of 16 weeks.				Patients in the Alf-Tam group experienced overall improvements in IPSS and Q_{max} at week eight. Additionally, 26 patients (52%) experienced significant improvements in Q_{max} and IPSS, 22 patients (44%) experienced significant improvements in just one of these parameters, and 2 patients (4%) had no changes in either parameter at week eight. Analysis of IPSS and Q_{max} in this group at week eight and week 16 indicated that 32 patients (64%) appeared to benefit from the change in treatment. For the Alf-Tam group and the Tam-Alf group, Q_{max} at week eight was significantly higher than at baseline and remained significantly higher at week 16 (P<0.001 for both groups vs baseline at both time points). Similar significant differences were seen with IPSS total score, IPSS irritative symptom score, IPSS obstructive symptom score and QOL when compared to baseline (P<0.001 for all comparisons vs baseline at both time points). For both groups, QOL at the time of cross-over was significantly lower than before treatment and remained significantly lower at week 16. In the Tam-Alf group, there were no differences in voided urine volume at initiation, week eight, and at week 16. In the Alf-Tam group, there was a significant increase in voided urine volume at week eight which was sustained at week 16 (P=0.01 and P=0.002 vs baseline, respectively).
Zhang et al[41] Doxazosin-GITS 4 mg QD vs tamsulosin 0.2 mg QD	MC, OL, PG, RCT Chinese males ≥50 years of age with moderate to severe LUTS (total IPSS score ≥8), prostate enlargement on DRE, Q_{max} 5 to 15 mL/s on ≥150	N=200 10 weeks 2-week screening phase followed by an 8-week active treatment phase	Primary: Change from baseline in self-reported nocturia according to the IPSS-question 7 and three-day FVC, quality of sleep evaluated by patients and QOL evaluated by the QOL index	Primary Endpoint: Although the treatment groups did not differ in frequency of nocturia at baseline, week four or week eight, mean nocturia on the FVC was reduced more by doxazosin-GITS than by tamsulosin (1.7 vs 1.3 at week 4; 2.1vs 1.7 at week eight, both P=0.001). More than 25% reduction in nocturia was selected as the cut-off for improved subjective nocturnal frequency. More patients receiving doxazosin-GITS than tamsulosin showed improved subjective nocturnal frequency by FVC at week four (81.9 vs 52.6%; P<0.001) and week eight (95.7 vs 85.3%; P=0.014). On multivariate analysis, among baseline variables, doxazosin-GITS treatment predicted more improved subjective nocturnal frequency both at week four (P<0.001, OR, 11.497; 95% CI, 4.75 to 27.824) and week

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	mL void, nocturia once or more per night according to both the FVC and question 7 of the IPSS		of the IPSS Secondary: IPSS score, Q_{max}, and PVR	eight (P=0.007, OR, 6.806; 95% CI, 1.673 to 27.688). The reduction from baseline for the IPSS-question 7 was greater for patients receiving doxazosin-GITS than tamsulosin (1.5 vs 1.1 at four weeks; P=0.001; 2.0 vs 1.6 at eight weeks; P<0.001). The proportion of patients with >25% improved IPSS-question 7 significantly differed at week 4 (74.5 and 50.5%; P<0.001) and week eight (95.7 and 82.1%; P=0.002). More patients receiving doxazosin-GITS than tamsulosin reported significant improvement in quality of sleep (43.6 vs 27.4% at four weeks; P=0.020; 81.9 vs 67.4% at eight weeks; P=0.022). QOL was better for patients receiving doxazosin-GITS than tamsulosin (score 2.5 vs 2.8 at four weeks; P=0.001; 2.1 vs 2.5 at eight weeks; P<0.001). Secondary: Doxazosin FITS treatment resulted in better scores than tamsulosin for total IPSS, storage sub scores at weeks four and eight and voiding sub score at week eight (P<0.05 for all). Q_{max} and PVR did not differ between treatment groups at week eight (P>0.05 for all).
Chung et al[42] Doxazosin-GITS 4 mg QD vs tamsulosin 0.2 mg QD	MC, PRO, RCT Male ambulatory patients over 50 years of age with LUTS (total IPSS >12) and a PV ≥20 cm^3	N=207 12 weeks	Primary: Compare the early onsets of efficacy between doxazosin-GITS and tamsulosin for the relief of LUTS associated with BPH assessed via changes from baseline in total IPSS (questions 1 to 7) at three days, one week and four weeks.	Primary: After 12 weeks of treatment, both groups showed significant improvements from baseline in total IPSS score (P<0.0001). However, doxazosin-GITS showed significantly greater improvements in total IPSS at weeks one, four, and 12 when compared to the tamsulosin group (-7.62 vs -5.02; P=0.021; -8.56 vs -6.34; P=0.030, -9.27 vs -5.48; P=0.0005, respectively). Secondary: For both obstructive and irritative sub scores, there were significant improvements from baseline to the final visit, for both drugs (P<0.0001). Treatment with doxazosin-GITS resulted in significantly greater improvement in obstructive sub score at week one and week four when compared to the tamsulosin group (P=0.018, 0.017, respectively). The percentages of improvement from baseline in the total and obstructive IPSS scores were also higher in the doxazosin-GITS group than the tamsulosin group at weeks one and four. Improvements in irritative sub

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Compare the improvement in IPSS obstructive/ irritative sub scores at each visit between the two groups and to compare improvements in QOL due to urinary symptoms (question 8 of IPSS) with two drugs	scores with doxazosin-GITS were NS different from those with tamsulosin within four weeks. IPSS QOL score after treatment with both drugs was also improved significantly at 12 weeks (P<0.0001).
Watanabe et al[43] Tamsulosin 0.2 mg QD vs silodosin 4 mg BID	AC, OL, RCT, XO Patient with BPH-related LUTS, an IPSS ≥8 and an IPSS-QOL ≥2	N=102 8 weeks (XO after 4 weeks)	Primary: Patient preference and reason (good efficacy, no/few adverse events, prefer QD, unknown) Secondary: IPSS, IPSS-QOL, Q_{max}, Q_{ave}, PVR	Primary: More patients preferred tamsulosin compared to silodosin (P<0.001). Tamsulosin was the preferred treatment in 70.2% of patients (27.4% for good efficacy, 20.2% for no/few adverse events, 16.7% for preferred once-daily treatment and 6.0% for unknown reason). Silodosin was the preferred treatment in 21.4% of patients (13.1% for good efficacy, 2.4% for no/few adverse events, 0 for preferred once-daily treatment and 6.0% for unknown reason). Neither drug was preferred by 8.3% of patients. Subgroup analysis of patients aged 70 or older and in patients with severe BPH (IPSS ≥20) also demonstrated that tamsulosin was the preferred drug compared to silodosin (P<0.001). Secondary: Total IPSS and IPSS-QOL improved in both groups at weeks four and eight compared to baseline (P<0.001). Total IPSS improved significantly between four and eight weeks in patients crossing over to tamsulosin (P<0.01), but not in patients XO to silodosin. Q_{max}, Q_{ave} and PVR improved in both groups at weeks four and 8 compared to baseline (P<0.001, P<0.01 and P<0.05, respectively). However, there were no significant changes regarding these endpoints in either group between

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				weeks four and eight.
Cui et al[44] Silodosin vs tamsulosin or placebo The complete MA included 4 studies of which 3 studies compared silodosin with placebo and 3 studies compared silodosin with tamsulosin.	MA of 6 RCT Men with BPH	4 trials N=2,543 Duration varies	Primary: Total IPSS, IPSS voiding, IPSS storage, change in Q_{max}, QOL Secondary: Not reported	Primary: Pooled data for silodosin compared to placebo showed a standardized mean difference in total IPSS, IPSS voiding and IPSS storage of 2.92 (95% CI, 2.19 to 3.65; P<0.00001), 1.92 (95% CI, 1.44 to 2.39; P<0.00001) and 0.92 (95% CI, 0.60 to 1.24; P<0.00001), respectively. Pooled data for silodosin compared to placebo also showed a standardized mean difference in Q_{max} of 1.56 (95% CI, 1.38 to 1.75; P<0.00001). The change in total IPSS, IPSS voiding, IPSS storage, Q_{max} and QOL for silodosin compared to tamsulosin was 1.14 (95% CI, 0.18 to 2.11; P=0.37), 0.78 (95% CI, 0.07 to 1.48; P=0.42), 0.23 (95% CI, -0.20 to 0.66; P=0.37), -0.71 (95% CI, -1.35 to 0.06; P=0.99) and 0.26 (95% CI, 0.05 to 0.47; P=0.05), respectively. Secondary: Not reported
Miyakita et al[45] Silodosin 4 mg BID for 4 weeks, followed by tamsulosin 0.2 mg QD for 4 weeks vs tamsulosin 0.2 mg QD for 4 weeks, followed by silodosin 4 mg BID for 4 weeks	MC, PRO, RCT, XO Patients with BPH or lower urinary tract symptoms were included if they had an IPSS ≥8 points, QOL score ≥3 points, PV measured by ultras-onographic method ≥20 mL, void volume ≥100 mL and Q_{max} <15	N=97 8 weeks	Primary: Change in total IPSS from baseline Secondary: Changes in objective parameters (Q_{max}, residual urinary volume, blood pressure, heart rate) and evaluation of subjective symptoms (IPSS	Primary: The cross-over analysis of the change in total IPSS showed no significant difference in carry-over effect but there was a significant difference in period effect. The IPSS total score improved significantly from baseline to after administration during the first treatment period in both the silodosin and tamsulosin treatment groups. During the crossover treatment period, only treatment with silodosin resulted in further significant improvement compared to prior drug treatment. The change in IPSS total score after administration of the first drug was -7.7±5.5 for silodosin and -4.6±5.4 for tamsulosin; change after XO was -2.6±3.8 for silodosin and +0.3±4.3 for tamsulosin, with a significant difference between groups in both administration periods (P<0.05 for first treatment and P<0.01 for crossover treatment). Secondary:

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Sample Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td></td><td>mL</td><td></td><td>voiding and storage subscores and QOL score)</td><td>
<table>
<tr><th>End point</th><th>Group</th><th>Base-line</th><th>Four Weeks</th><th>Eight Weeks</th><th>Base-line vs Four Weeks</th><th>Base-line vs Eight Weeks</th></tr>
<tr><td rowspan="2">Voiding</td><td>S-T</td><td>8.0±4.1</td><td>4.1±2.7</td><td>4.4±3.2</td><td>P<0.001</td><td>NS</td></tr>
<tr><td>T-S</td><td>8.5±3.3</td><td>6.2±3.2</td><td>5.2±3.3</td><td>P<0.001</td><td>P<0.05</td></tr>
<tr><td rowspan="2">Storage</td><td>S-T</td><td>6.2±3.1</td><td>3.7±2.1</td><td>3.8±2.0</td><td>P<0.001</td><td>NS</td></tr>
<tr><td>T-S</td><td>7.5±3.6</td><td>5.8±3.2</td><td>4.5±2.9</td><td>P<0.001</td><td>P<0.01</td></tr>
<tr><td rowspan="2">QOL score</td><td>S-T</td><td>4.9±0.9</td><td>3.2±1.4</td><td>3.3±1.4</td><td>P<0.001</td><td>NS</td></tr>
<tr><td>T-S</td><td>4.9±0.9</td><td>4.0±1.0</td><td>3.3±1.4</td><td>P<0.001</td><td>P<0.001</td></tr>
<tr><td rowspan="2">Q_{max}</td><td>S-T</td><td>9.4 ± 3.5</td><td>11.3 ± 4.9</td><td>10.0±4.3</td><td>P<0.001</td><td>NS</td></tr>
<tr><td>T-S</td><td>9.7 ± 4.4</td><td>11.6 ± 6.0</td><td>12.2±5.3</td><td>P<0.05</td><td>NS</td></tr>
<tr><td rowspan="2">Residual urine volume</td><td>S-T</td><td>95.8 ± 102.4</td><td>48.7 ± 62.9</td><td>50.8±54.7</td><td>P<0.01</td><td>NS</td></tr>
<tr><td>T-S</td><td>97.3± 113.3</td><td>83.8± 111.3</td><td>101.6± 123.6</td><td>P<0.05</td><td>NS</td></tr>
</table>
Systolic blood pressure decreased significantly from baseline following administration of first silodosin treatment and heart rate increased significantly with crossover tamsulosin treatment, however, neither change was clinically significant. No other significant changes in blood pressure or heart rate were observed.</td></tr>
<tr><td>Yokoyama et al [46]

Silodosin 4 mg BID

vs

tamsulosin 0.2 mg QD

vs</td><td>PRO, RCT

Patients between 50 and 80 years of age with IPSS ≥8</td><td>N=136

12 weeks</td><td>Primary: Clinical determination of IPSS, QOL indexes, IIEF, Q_{max} and PVR detected by ultrasonography before, and one</td><td>Primary:
<table>
<tr><th>End point</th><th>Silodosin</th><th>Tamsulosin</th><th>Naftopidil</th></tr>
<tr><td>IPSS</td><td></td><td></td><td></td></tr>
<tr><td>Baseline</td><td>18.7±0.7</td><td>18.0±1.1</td><td>17.4±0.8</td></tr>
<tr><td>4 weeks</td><td>14.7±0.9</td><td>12.2±1.1</td><td>12.2±0.8</td></tr>
<tr><td>Intragroup significance</td><td>P <0.001</td><td>P <0.001</td><td>P <0.001</td></tr>
<tr><td>12 weeks</td><td>13.8±1.2</td><td>10.7±1.4</td><td>11.3±1.1</td></tr>
<tr><td>Intragroup</td><td>P <0.001</td><td>P <0.001</td><td>P <0.001</td></tr>
</table></td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
naftopidil‡ 50 mg QD			and three months after treatment end Secondary: Not reported	

significance			
QOL index			
Baseline	4.5±0.1	4.5±0.1	4.5±0.1
4 weeks	3.4±0.2	3.2±0.2	3.2±0.2
Intragroup significance	P <0.001	P <0.001	P <0.001
12 weeks	3.4±0.2	2.7±0.3	3.1±0.2
Intragroup significance	P <0.001	P <0.001	P <0.001
IIEF			
Baseline	6.2±0.8	6.6±0.9	7.0±1.0
4 weeks	5.4±0.7	6.1±1.1	7.4±1.1
Intragroup significance	P=0.111	P=0.841	P=0.010
12 weeks	5.0±0.7	5.2±1.2	7.6±1.3
Intragroup significance	P=0.682	P=0.342	P=0.013
Q_{max}			
Baseline	9.0±0.6	8.5±3.4	8.6±0.6
4 weeks	10.7±0.8	11.7±0.9	11.0±0.8
Intragroup significance	P=0.010	P<0.001	P=0.0035
12 weeks	9.2±0.9	12.0±1.5	11.3±1.1
Intragroup significance	P=0.471	P=0.0943	P=0.114
PVR			
Baseline	57.6±6.9	29.7±5.5	39.1±7.7
4 weeks	42.7±8.7	27.1±6.7	28.0±5.5
Intragroup significance	P=0.0088	P=0.584	P=0.0021
12 weeks	34.8±8.4	24.6±6.5	28.3±5.0
Intragroup significance	P=0.003	P=0.067	P=0.0220

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Gilling et al[47] Dutasteride 0.5 mg once daily vs finasteride 5 mg once daily	RCT Men >50 years of age with BPH and an enlarged prostate	N=1,630 48 weeks	Primary: Prostate volume, AUA SS, Q_{max}, post-void residual volume, adverse events Secondary: Not reported	Primary: There were no significant differences noted between the treatment groups in reduction in prostate volume (27.4% for both) and post-void residual volume (21.8% vs 16.1%) or in improvements in AUA SS (6.2 vs 5.8) and Q_{max} (2.1 mL/second vs 1.8 mL/second; P values not reported). No significant differences in the prevalence of adverse events were found between the 2 treatments. Secondary: Not reported
Hagerty et al[48] Dutasteride vs finasteride	OS, PRO Men with benign prostatic enlargement and symptomatic BPH	N=240 3 months	Primary: AUA SS Secondary: Not reported	Primary: Dutasteride use was associated with a significantly greater improvement in AUA SS score compared to finasteride (estimated difference, 20%; 95% CI, 7.5% to 32.5%; P<0.0016). Secondary: Not reported
Ravish et al[49] Dutasteride 0.5 mg once daily vs finasteride 5 mg once daily	DB, RCT Patients with LUTS and an enlarged prostate	N=Not reported 12 weeks	Primary: IPSS Secondary: Q_{max}, total prostate volume, QOL (BPH Impact Index), adverse effects	Primary: A mean difference in IPSS of 4.33 was reported with dutasteride, while an IPSS of 2.67 was reported with finasteride use (P value not reported). Secondary: Over 12 weeks, dutasteride was associated with a mean increase in Q_{max} of 2.31 mL/second vs 1.79 mL/second with finasteride. A reduction in total prostate volume of 5.43% and 5.31% was reported for dutasteride and finasteride, respectively. The mean reduction from baseline in the BPH Impact Index score was 0.61 with dutasteride and 0.41 with finasteride (P values not reported). There was no difference noted between groups in the rate of sexually related adverse events.
Nickel et al[50] EPICS	DB, DD, MC, PG, RCT	N=1,630	Primary: Change in PV	Primary: Both dutasteride and finasteride were effective in reducing PV, with no

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Dutasteride 0.5 mg QD vs finasteride 5 mg QD The 12-month study period was followed by a 24-month OL phase during which patients received dutasteride 10 mg QD.	Men ≥50 years of age with a clinical diagnosis of BPH according to medical history and physical examination (including DRE) with AUA Symptom Index score ≥12 points at the screening visit, PV ≥30 cm^3, two voids with Q_{max} <15 mL/s and a minimum voided volume ≥125 mL	12 months	Secondary: Improvement in AUA-SI scores, improvement in Q_{max} and long-term safety in the 24-month OL phase	significant differences between the two treatments. At month three, there was an adjusted mean percentage reduction in PV of 18.5% for men in the finasteride group vs 18.3% in the dutasteride group (P=0.76). At month 12, the reduction was 26.7 vs 26.3% in the finasteride and dutasteride groups, respectively (P=0.65). Treatment difference at month 12 was 0.4% (CI, 1.4 to -2.3). Patients in both groups with a baseline PV ≥40 cm^3 exhibited slightly greater reductions in PV at month 12 compared to those patients with baseline PV <40 cm^3. The reduction seen from baseline in patients with PV ≥40 cm^3 was 27.7% in the finasteride group and 27.6% in the dutasteride group (P=0.90). For patients with baseline PV <40 cm^3, these reductions were 24.2 and 22.6%, respectively (P=0.37). Secondary: At month 12, the mean AUA-SI scores were reduced by 5.5 and 5.8 in the finasteride and dutasteride groups, respectively (P=0.38). Q_{max} at month 12 improved by 1.7 and 2.0 mL/s in the finasteride and dutasteride groups, respectively (P=0.14). In both treatment groups, PSA levels consistently decreased from baseline to months three and 12. In the finasteride group, PSA levels decreased from baseline by a mean of 38.9 and 47.7% at months three and 12 respectively. In the dutasteride group, PSA levels decreased from baseline by a mean of 40.3 and 49.5% at months three and 12, respectively.
Lee[51] Tamsulosin 0.2 mg once daily vs finasteride 5 mg once daily	RCT, SB Korean patients 51 to 80 years of age with LUTS associated with BPH	N=205 24 weeks	Primary: IPSS, Q_{max}, QOL Secondary: Prostate volume, number of patients with a clinically significant response (>20% decrease in total	Primary: At 4 weeks, a benefit was seen with tamsulosin in both IPSS (17.6% vs 10.0% for finasteride) and Q_{max} (10.9% vs 3.1% for finasteride) from baseline over finasteride. At 24 weeks, finasteride and tamsulosin were associated with a similar effect on IPSS (30.5% and 34.7%, respectively; P>0.05) and Q_{max} (22.2% and 23.9%, respectively; P>0.05). Changes from baseline in QOL scores were significantly greater with tamsulosin vs finasteride at both 4 weeks (14.6% vs 7.7%; P<0.05) and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			IPSS or >20% improvement over baseline in Q_{max}), safety	24 weeks (34.1% vs 23.1%; P<0.05). Secondary: A similar number of patients receiving finasteride met criteria for clinical response compared to tamsulosin. Side effects were reported more often with finasteride use (22.5% of patients) than with tamsulosin (3.9% of patients; P<0.001). Decreased libido, decreased potency, decreased ejaculatory volume, impotence and loose stools were seen in individuals on finasteride therapy. No significant change in blood pressure or pulse rate was reported in either arm.
Rigatti et al[52] Tamsulosin 0.4 mg once daily vs finasteride 5 mg once daily	DB, MC, PG, RCT Men 50 to 80 years of age with LUTS associated with BPH	N=403 1 year	Primary: SPI (7 questions regarding urinary symptoms on a scale of 0-no problems to 4-big problem) from baseline to week 26 Secondary: Change from baseline in total SPI, voiding and storage SPI subscores, total IPSS, IPSS QOL score, Q_{max}, voided volume and safety	Primary: A 31.5% decrease in the total SPI score was detected in the finasteride group while a 37.4% decrease was noted with tamsulosin, however this difference did not reach statistical significance (P=0.055). Secondary: A significant difference in total SPI and voiding and storage SPI was noted at weeks 1, 6 and 18, indicating a faster improvement rate with tamsulosin compared to finasteride (P<0.05). The only difference between groups in secondary outcomes that did reach statistical significance at 26 weeks was the change in voided volume, which was higher with tamsulosin (29.9%) than with finasteride (16.4%; P=0.043). The remaining endpoints were reported as follows (at 26 weeks): the change in SPI-storage points was -22.0% with finasteride vs -34.3% with tamsulosin (P=0.90), change in SPI-voiding points was -27.3% and -35.0%, respectively (P=0.069), change in total IPSS points was -32.0% and -37.3%, respectively (P=0.080), and change in IPSS QOL points was -25.8% and -31.2%, (P=0.271). Safety was assessed over 1 year of therapy and it was determined that both treatment options resulted in a similar rate of adverse events (29.4% with finasteride vs 32.1% with tamsulosin. The most commonly reported adverse events included influenza-like symptoms (3.4% in the finasteride

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				group vs 6.1% with tamsulosin), impotence (3.4% vs 3.1% for finasteride and tamsulosin, respectively), abdominal pain (2.5% vs 3.1% for finasteride and tamsulosin, respectively) and ejaculation disorder (1.0% vs 3.1% for finasteride and tamsulosin, respectively).
Roehrborn et al[53] CombAT Tamsulosin 0.4 mg once daily vs dutasteride 0.5 mg once daily vs dutasteride 0.5 mg once daily and tamsulosin 0.4 mg once daily	DB, MC, PG, RCT Men ≥50 years of age with BPH and moderate to severe LUTS and prostatic enlargement	N=4,844 2 years (interim analysis of 4 year trial)	Primary: IPSS Secondary: IPSS responders, Q_{max}, prostate volume	Primary: The IPSS was reduced from baseline by 4.90±0.15 points with dutasteride, by 4.30±0.15 points with tamsulosin and by 6.20±0.15 points with combination therapy (P<0.001 for each monotherapy regimen vs combination therapy). Secondary: A decrease in IPSS of at least 25% was observed more often with combination therapy (67%), than dutasteride (59%) or tamsulosin (55%; P<0.001 for each monotherapy regimen vs combination therapy). A significantly greater reduction in Q_{max} was reported with combination therapy (2.40±0.12 mL/second) vs dutasteride (1.90±0.12 mL/second) and finasteride (0.90±0.12 mL/second; P≤0.003 for each monotherapy regimen vs combination therapy). Total prostate volume was decreased by 26.9%±0.62% in the combination group, by 28.0%±0.61% in the dutasteride group and by 0.0%±0.84% with tamsulosin therapy. However, only the difference between combination therapy and tamsulosin monotherapy reached statistical significance (P<0.001).
Roehrborn et al[54] CombAT Dutasteride 0.5 mg QD plus tamsulosin 0.4 mg QD vs dutasteride 0.5 mg QD	Subanalysis of CombAT[53] DB, MC, PG, RCT Men ≥50 years of age with a BPH clinical diagnosis by medical	N=4,844 4 years	Primary: Time to first event of acute urinary retention or BPH-related prostatic surgery at four years (number of days from the date of first dose of	Primary: The time to first acute urinary retention or BPH-related surgery was significantly lower with combination therapy compared to tamsulosin (P<0.001). There was no difference between combination therapy and dutasteride (P=0.18). Combination therapy reduced the RR of acute urinary retention or BPH-related surgery by 65.8 (95% CI, 54.7 to 74.1) and 19.6% (95% CI, -10.9 to 41.7) compared to tamsulosin and dutasteride. When acute urinary retention and BPH-related surgery were considered

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs tamsulosin 0.4 mg QD	history and physical examination, an IPSS ≥12 points, PV ≥30 cm^3 by TRUS, total serum PSA ≥1.5 ng/mL and Q_{max} >5 and ≤15 mL/s with a minimum voided volume ≥125 mL		medication to the date of the initial event), proportion of patients experiencing acute urinary retention or BPH-related surgery Secondary (combination therapy vs tamsulosin): Time to BPH clinical progression, change in IPSS and BPH-related health status, IPSS responders (≥25% and ≥3 point improvement), Q_{max}, total and transition zone PV, safety and tolerability	separately, time to first event was significantly lower with combination therapy compared to tamsulosin (RRR, 67.6%; P<0.001 and 70.6%; P<0.001). Compared to dutasteride, the RRR with combination therapy was NS different (18.3%; P=0.37 and 31.1%; P=0.074). Secondary: Time to first BPH clinical progression was significantly different in favor of combination therapy vs tamsulosin and dutasteride (P<0.001 for both comparisons). Combination therapy reduced the RR of BPH clinical progression by 44.1 and 31.2%. Symptom deterioration was the most common progression event in each treatment group. The adjusted mean change in IPSS from baseline to year four was -6.3 points for combination therapy compared to -3.8 (P<0.001) and -5.3 (P<0.001) points for tamsulosin and dutasteride. "Superiority" of combination therapy vs tamsulosin was seen from month nine and vs dutasteride from month three, and it was maintained for the trial duration (P<0.001 for all comparisons). The adjusted mean change from baseline in BPH-related health status at month 48 were -1.5, -1.1 and -1.3 points with combination therapy, tamsulosin and dutasteride, respectively (P<0.001 for both comparisons). The proportion of patients with an IPSS response ≥25% at month 48 were 67, 52 and 61% with combination therapy, tamsulosin and dutasteride, respectively (P<0.01 for both comparisons). The corresponding numbers for the proportion of patients with at least a three point IPSS improvement were 71, 59 and 66% (P<0.01 for both comparisons). At month 48, the adjusted mean increase in Q_{max} from baseline was 2.4 mL/s for combination therapy compared to 0.7 (P<0.001) and 2.0 (P=0.05) mL/s with tamsulosin and dutasteride. Changes resulted in mean values of 13.3, 11.5 and 12.8 mL/s in the groups, respectively. At month 48, the adjusted mean percentage change from baseline in total PV was -27.3% for combination therapy compared to 4.6 (P<0.001) and -

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				28.8% (P=0.42) with tamsulosin and dutasteride. The corresponding numbers for adjusted mean change from baseline in transition zone volume (n=656) were -17.9, 18.2 (P<0.001) and -26.5% (P=0.053). The occurrence of drug-related adverse events was significantly greater in the combination group; however, withdrawal rates due to drug-related adverse events were similar across the treatment groups (six, four and four percent). There were no reports of "floppy iris syndrome" or malignant breast tumors in any treatment group.
Becher et al[55] CombAT Dutasteride 0.5 mg QD plus tamsulosin 0.4 mg QD vs dutasteride 0.5 mg QD vs tamsulosin 0.4 mg QD	Subanalysis of CombAT[53] Analysis of the CombAT trial results on storage and voiding symptoms at 2 years Men ≥50 years of age with a BPH clinical diagnosis by medical history and physical examination, an IPSS ≥12 points, PV ≥30 cm^3 by TRUS, total serum PSA ≥1.5 ng/mL and Q_{max} >5 and ≤15 mL/s with a minimum voided volume	N=4,844 2 years	Primary: IPSS storage and voiding subscores Secondary: Not reported	Primary: At month 24, the mean reduction in storage subscore from baseline was significantly greater with combination therapy (-2.20±0.07) compared to dutasteride (-1.70±0.07; P<0.001) and tamsulosin (-1.60±0.07; P<0.001). Additionally, for each individual storage question (three total), the reduction in score was significantly greater with combination therapy (P<0.001 for all comparisons). The mean reduction was significantly greater with combination therapy compared to dutasteride from month three, and then from month 12 compared to tamsulosin. At month 24, the mean reduction in IPSS voiding subscore from baseline was significantly greater with combination therapy (-4.0±0.1) compared to dutasteride (-3.2±0.1; P<0.001) and tamsulosin (-2.7±0.1; P<0.001). Additionally, for each individual voiding question (four total), the reduction in score was significantly greater with combination therapy (P≤0.001 for all comparisons). The mean reduction was significantly greater with combination therapy compared to dutasteride from month three, and from month six with tamsulosin. When evaluating the change in IPSS symptoms from baseline, a significant treatment by baseline postvoid interaction was observed at month 24 for both storage (P=0.01) and voiding (P<0.001) subscores. Men with baseline postvoid in the lower two tertiles (30 to <42 and 42 to <58 cm^3) had reductions in storage subscores that were significantly greater with combination therapy. Men with baseline postvoid in the highest tertile (≥58 cm^3) had reduction in storage subscores that were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	≥125 mL			significantly greater with both combination therapy and dutasteride. Men with baseline postvoid in the lowest tertile had a reduction in voiding subscores that were significantly greater with combination therapy. In both the middle and upper tertiles, the reductions in voiding subscores were significantly greater with both combination and dutasteride therapy. Secondary: Not reported
Montorsi et al[56] CombAT Dutasteride 0.5 mg QD plus tamsulosin 0.4 mg QD vs dutasteride 0.5 mg QD vs tamsulosin 0.4 mg QD	Subanalysis of CombAT[53] Post hoc analysis of the CombAT trial focusing on patient-reported QOL and treatment satisfaction at 4 years Men ≥50 years of age with a BPH clinical diagnosis by medical history and physical examination, an IPSS ≥12 points, PV ≥30 cm^3 by TRUS, total serum PSA ≥1.5 ng/mL and Q_{max} >5 and ≤15 mL/s with a minimum voided volume	N=4,844 4 years	Primary: IPSS (question 8), BPH-II, PPSM Secondary: Not reported	Primary: The mean change in IPSS question eight from baseline was -1.5 with combination therapy compared to -1.3 and -1.1 with dutasteride and tamsulosin (P<0.001 for both comparisons). “Superiority” of combination therapy vs dutasteride and tamsulosin was seen from month three and 12, and it was maintained for the trial duration. The mean change from baseline in BPH-II was -2.2 with combination therapy compared to -1.8 and -1.2 with dutasteride and tamsulosin (P<0.001 for both comparisons). “Superiority” of combination therapy vs dutasteride and tamsulosin was seen from month three and nine, and it was maintained for the trial duration. At two years, the proportion of patients reporting an improvement, satisfaction or desire to request study treatment in response to each of the 12 PPSM questions was significantly higher with combination therapy compared to either monotherapy, except for question five on pain before urination. The “superiority” of combination therapy observed at two years was sustained out to four years. At four years, the mean change from baseline in PPSM total score was -7.0 with combination therapy compared to -5.5 and -4.1 with dutasteride and tamsulosin (P<0.001 for both comparisons). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	≥125 mL			
Roehrborn et al[57] CombAT Dutasteride 0.5 mg QD plus tamsulosin 0.4 mg QD vs dutasteride 0.5 mg QD vs tamsulosin 0.4 mg QD	DB, MC, PG, RCT Men ≥50 years of age with BPH and moderate to severe LUTS and prostatic enlargement	N=4,844 4 year trial	Primary: IPSS changes after four years Secondary: IPSS responders, Q_{max}, prostate volume	Primary: Of the 4,844 patients randomized to treatment, 3,195 (66%) completed the month 48 visit. As previously reported, the rate of discontinuation in CombAT was 39% in the tamsulosin group, compared with 31% in the combination group and 33% in the dutasteride group. Combination therapy resulted in a significantly greater improvement from baseline IPSS at 48 months than was seen with tamsulosin therapy across all baseline subgroups (P≤0.01). Compared with dutasteride monotherapy, combination therapy was associated with greater improvements from baseline IPSS (P≤0.01) in specific baseline subgroups, including: PV, 30 to <40 mL (N=1,353) and 40 to <60 mL (N=2,003); PSA level, 1.5 to <2.5 ng/mL (N=1,323) and 2.5 to <4.0 ng/mL (N=1,557); IPSS, <20 (N=3,447) and ≥16 (N=2,497); Q_{max}, <10.4 (N=2,419) and ≥10.4 (N=2,425); BMI ≥26.8 (N=2,427); BII ≥5 (N=2,729); IPSS QOL ≥4 (N=2,545); and age <66 years (N=2,264). Secondary: Combination therapy resulted in a significantly greater improvement in IPSS than was seen with tamsulosin monotherapy from month 18 in the lowest baseline PSA subgroup (1.5 to <2.5 ng/mL; P≤0.01), from month 12 in the middle PSA subgroup (2.5 to <4 ng/mL; P≤0.01), and from month nine in the highest PSA subgroup (≥4 ng/mL; P≤0.01). There was also significantly greater improvement in IPSS with combination therapy than with dutasteride monotherapy at all time points for the lowest (1.5 to <2.5 ng/mL; P≤0.01) and middle (2.5 to <4 ng/mL; P≤0.01) baseline PSA subgroups. However, in the highest baseline PSA subgroup (≥4 ng/mL), combination therapy was only significantly improved compared to dutasteride monotherapy up to and including the month 12 assessment (P≤0.01), after which dutasteride was not significantly different from combination therapy. In comparison with tamsulosin monotherapy, combination therapy

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				resulted in significantly greater improvements in IPSS at month 24 and from month 36 in the lowest PV subgroup (30 to <40 mL), from month 9 in the second (40 to <60 mL) and highest (≥80 mL) PV subgroups, and from month 12 in the third PV subgroup (60 to <80 mL) (P≤0.01). Combination therapy with dutasteride and tamsulosin resulted in a significantly greater improvement in Q_{max} than with tamsulosin monotherapy for all baseline subgroups (P≤0.01). There was no significant difference in Q_{max} improvement between dutasteride monotherapy and combination therapy, apart from the BII ≥5 subgroup, where combination therapy provided significant improvement compared to dutasteride monotherapy (P<0.01). There appeared to be a trend for increased Q_{max} improvement with combination therapy with increasing PV and this was greatest in the subgroup with the highest PV (≥80 mL); by contrast, Q_{max} improvement with tamsulosin was lowest in this subgroup. The proportion of subjects with an IPSS QOL ≤2 (at least mostly satisfied) at 48 months was significantly higher with combination therapy than with dutasteride for subgroups with PV 40–60 mL (N=2,003) and PSA level <4 ng/mL (1.5 to <2.5 ng/mL [N=1,323]; 2.5 to <4 ng/mL [N=1,557]), and compared with tamsulosin for all PSA subgroups (1.5 to <2.5 ng/mL [N=1,323]; 2.5 to <4 ng/mL [N=1,557]; ≥4 ng/mL [N=1,925]) and PV subgroups (40 to <60 mL [N=2,003]; 60 to <80 mL [N=879]; ≥80 mL [N=563]), with the exception of the PV subgroup 30 to <40 mL [N=1,353]). Compared with monotherapy, combination therapy provided significantly greater improvement at 48 months in IPSS QOL (P≤0.01) than was the case with tamsulosin for all subgroups and with dutasteride in several subgroups, including baseline PV 30 to <60 mL, PSA level <4 ng/mL, baseline IPSS subgroups (IPSS <16, IPSS ≥16, IPSS <20 and ≥20), IPSS QOL ≥4, age <66 years, Q_{max} <10.4 and ≥10.4 mL/s, BMI ≥26.8 kg/m2, BII ≥5, and previous BPH treatment with or without α-blockers. Combination therapy resulted in a significantly greater median percentage change from baseline in IPSS at 48 months for all baseline variables when compared with tamsulosin (P≤0.01 for all variables), and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				for selected baseline variables when compared with dutasteride. The proportion of subjects who showed IPSS improvement at 48 months and who would no longer qualify for inclusion in CombAT (i.e., IPSS <12) was significantly higher with combination therapy than with tamsulosin monotherapy for all PV and PSA baseline groups (P≤0.01), with the exception of the group with the smallest prostates at baseline (PV of 30 to <40 mL). By contrast, the proportion of subjects who would no longer qualify for inclusion in CombAT (i.e., IPSS <12) was only significantly higher with combination therapy than with dutasteride in subjects with a PSA level of 1.5 to <2.5 ng/mL and a PV of 40–60 mL.
Crawford et al[58] Doxazosin 4-8 mg once daily vs finasteride 5 mg once daily vs doxazosin 4-8 mg once daily and finasteride 5 mg once daily vs placebo	PC, RCT Men with LUTS suggestive of BPH	N=737 4 years	Primary: Time to overall clinical progression of BPH (defined as either a confirmed 4-point or greater increase in AUA SS, acute urinary retention, incontinence, renal insufficiency, or recurrent urinary tract infection) Secondary: Not reported	Primary: The rate of overall clinical progression of BPH events in the placebo group was 4.5 per 100 person-years, for a cumulative incidence (among men who had at least 4 years of follow-up data) of 17%. The risk of BPH progression was significantly greater in patients on placebo with a baseline total postvoid residual urine volume of ≥31 mL vs those with a baseline total postvoid residual urine volume <31 mL (P<0.0001). The risk of BPH progression was significantly greater in patients on placebo with a baseline prostate-specific antigen of ≥1.6 ng/dL vs those with a baseline prostate-specific antigen<1.6 ng/dL (P=0.0009). The risk of BPH progression was significantly greater in patients on placebo with a baseline maximal urinary flow rate of less than 10.6 mL/second vs those with a baseline maximal urinary flow rate ≥10.6 mL/second (P=0.011) The risk of BPH progression was significantly greater in patients on placebo with a baseline postvoid residual urine volume of ≥39 mL vs those with a baseline postvoid residual urine volume <39 mL (P=0.0008). The risk of BPH progression was significantly greater in patients on

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				placebo with baseline age ≥62 years or older vs those aged <62 years (P=0.0002). Secondary: Not reported
Johnson et al[59] Doxazosin (2, 4, 8 mg) once daily vs finasteride 5 mg once daily vs doxazosin (2, 4, 8 mg) once daily and finasteride 5 mg once daily vs placebo	PC, RCT Men with LUTS suggestive of BPH	N=3,047 4 years	Primary: Efficacy (mean reduction in self-reported nightly nocturia at 1 and 4 years) Secondary: Not reported	Primary: The number of men reporting 1 or more episodes of nocturia who finished 12 or more months of the trial came to a total of 2,583. Mean nocturia was similar in all groups at baseline. Mean nocturia was reduced at 1 year by 0.35, 0.40, 0.54 and 0.58 in the placebo, finasteride, doxazosin and combination groups, respectively. Reductions with doxazosin and combination therapy were statistically greater than with placebo (P<0.05). At 4 years, nocturia was also significantly reduced in patients treated with doxazosin and combination therapy (P<0.05 vs placebo). In men older than 70 years (n=495) all drugs significantly reduced nocturia at 1 year (finasteride, 0.29; doxazosin, 0.46; and combination, 0.42) compared to placebo (0.11; P<0.05). Secondary: Not reported
Kaplan, McConnell, et al[60] Doxazosin 4-8 mg once daily vs finasteride 5 mg once daily vs doxazosin 4-8 mg once	PC, RCT Men with LUTS suggestive of BPH	N=3,047 4 years	Primary: Overall clinical progression of BPH (defined as a confirmed 4 point or greater increase in AUA SS, acute urinary retention, incontinence, renal insufficiency or	Primary: In patients with a small prostate (baseline total prostate volume>25 mL) combination therapy was no better than doxazosin alone for decreasing the risk of clinical progression of BPH and need for invasive therapy as well as improving AUA SS and Q_{max}. However, in patients with moderate size (25 to >40 mL) or enlarged (≥40 mL) glands, combination therapy led to a clinical benefit in these outcomes that was superior to that of doxazosin or finasteride (P<0.05). Secondary: In men with baseline total prostate volume<25 mL, there was no significant difference in the risk of invasive therapy for combination

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
daily and finasteride 5 mg once daily vs placebo			recurrent urinary tract infection) Secondary: Need for invasive therapy for BPH, AUA SS, and Q_{max}	therapy relative to doxazosin or finasteride alone. However, in the baseline total prostate volume subgroups of 25 to <40 mL and ≥40 mL there was a significant and marked percent risk decrease in invasive therapy, of around 60% to 80% for combination therapy vs doxazosin alone (P<0.05). In men with baseline total prostate volume<25 mL the improvement at year 4 in AUA SS for combination therapy relative to doxazosin alone was not significantly different, whereas the improvement for combination therapy vs finasteride alone was significantly different in favor of combination therapy (P<0.05). In the baseline total prostate volume subgroups of 25 to <40 mL and ≥40 mL, the improvement in AUA SS with combination therapy was significantly better than that for doxazosin alone and finasteride alone (P<0.05).
Kirby et al[61] (PREDICT trial) Doxazosin 1-8 mg once daily vs finasteride 5 mg once daily vs doxazosin 1-8 mg once daily and finasteride 5 mg once daily vs placebo	DB, MC, PC, PRO, RCT Men 50 to 80 years of age with BPH and an enlarged prostate	N=1,095 52 weeks	Primary: Q_{max}, IPSS Secondary: Tolerability	Primary: Doxazosin alone (3.6±0.3 mL/second), and in combination with finasteride (3.8±0.3 mL/second), was associated with a significantly greater improvement in Q_{max} at 1 year compared to finasteride alone (1.8±0.3 mL/second; P≤0.0001) or placebo (1.4±0.3 mL/second; P≤0.0001). Any difference detected between doxazosin and combination therapy or finasteride and placebo did not reach statistical significance. Similar results were found with total IPSS. Again, doxazosin monotherapy (3.6±0.3 mL/second) and combination therapy (3.8±0.3 mL/second) caused a significantly greater improvement in score over finasteride alone (1.8±0.3 mL/second; P<0.01) or placebo (1.4±0.3 mL/second; P≤0.0001). There was no statistically significant difference detected among the other groups. Secondary: Doxazosin use increased the risk of asthenia, dizziness and hypotension, while impotence was reported most frequently in the combination group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lepor et al[62] Terazosin 1-10 mg once daily vs finasteride 5 mg once daily vs finasteride 5 mg once daily and terazosin 1-10 mg once daily vs placebo	DB, MC, RCT Men 45 to 80 years of age with symptomatic BPH	N=1,229 1 year	Primary: AUA SS, Q_{max} Secondary: Not reported	Primary: A significantly greater reduction in symptom scores was found in patients receiving terazosin alone and in combination compared to those taking finasteride and placebo (6.1 points, 6.2 points, 3.2 points, 2.6 points respectively; P<0.001 for terazosin vs finasteride, combination vs finasteride, terazosin vs placebo and combination vs placebo). There was no significant difference in scores noted between terazosin and combination treatment (P=1.00) or finasteride and placebo (P=0.63). Terazosin and combination therapy was also associated with a greater increase in Q_{max} than finasteride or placebo (2.7 mL/second, 3.2 mL/second, 1.6 mL/second, and 1.4 mL/second). Differences between finasteride and terazosin, finasteride and combination therapy, combination therapy and placebo and terazosin and placebo all reached statistical significance (P<0.001 for all comparisons), whereas the difference between terazosin and combination therapy (P=0.15) and finasteride and placebo (P=0.07) did not. Secondary: Not reported
Lee et al[63] Finasteride plus an a adrenergic blocking agent vs finasteride Patients were divided into two groups based on treatment pattern (a blocker monotherapy vs a blocker combined with	MC, RETRO Patients 50 years of age and older with lower urinary tract symptoms consistent with moderate to severe BPH	N=1315 4 years	Primary: PV, PSA, IPSS, Q_{max} Secondary: Not reported	Primary: All groups showed significant improvements in IPSS total scores, IPSS voiding subscores and QOL at one year (P values not reported). Total IPSS from baseline to year four decreased by -11.5 in group IV compared to -0.18 in group I (P<0.001), -6.1 in group II (P=0.97) and -2.6 in group III (P=0.031). However, IPSS storage subscores only improved in patients with high (≥6) storage subscores at baseline (P value not reported). After one year, PV and PSA were reduced by 21.3 and 47.0%, respectively, in the combination groups compared to an increase of 9 and 18%, respectively, in the monotherapy groups (P<0.001 for both). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
finasteride) and further divided into four subgroups based on severity of storage symptoms (IPSS storage domain score ≥6 vs <6). Group I was classified as monotherapy and storage scores <6, group II as monotherapy and storage scores ≥6, group III as combination therapy and storage scores <6 and group IV as combination therapy and storage scores ≥6.				
Gacci et al[64] PDE5 inhibitors (sildenafil, tadalafil, vardenafil) vs placebo and PDE5 inhibitors plus a blockers (alfuzosin, tamsulosin) vs a blockers	MA (12 RCT), SR Patients with BPH-related LUTS	N=3,430 Duration varies	Primary: IPSS, IIEF, Q_{max} Secondary: Not reported	Primary: PDE5 inhibitors significantly improved IPSS and IIEF score compared to placebo (P<0.0001 for both), but not Q_{max}. PDE5 inhibitor plus a blocker combination therapy significantly improved IPSS, IIEF score and Q_{max} compared to a blockers alone (P<0.05, P<0.0001 and P<0.0001, respectively). Higher baseline IPSS values were associated with a greater effect of PDE5 inhibitors on IPSS improvement. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Regadas et al[65] Tamsulosin 0.4 mg and tadalafil 5 mg QD vs tamsulosin 0.4 mg and placebo QD	DB, PC, RCT Men ≥45 years of age with BPH or LUTS	N=40 4 weeks	Primary: Changes in urodynamic variables of the voiding phase, $PdetQ_{max}$, and Q_{max}, from baseline to week four Secondary: Change in IPSS	Primary: Detrusor overactivity in the filling phase was observed in 12 (60%) patients in the tamsulosin/tadalafil group and eight (40%) patients in the tamsulosin/placebo group. After treatment, the detrusor overactivity disappeared in seven (58.3%) of patients in the combination group and three (37.5 %) in tamsulosin/placebo group (P=0.64). The mean change of $PdetQ_{max}$ from baseline to end point was −13 ± 17.0 in the tamsulosin/tadalafil group and was −1.22 ± 14.3 in the tamsulosin/placebo group. Comparing the groups, $PdetQ_{max}$ decreases significantly in the tamsulosin/tadalafil group (P=0.03). The mean change of Qmax from baseline to end point was 1.05 ± 0.5) in the tamsulosin/tadalafil group and was 1.22 ± 0.5 in the tamsulosin/placebo group. No significant difference was observed in Qmax between the treatment groups (P=0.65). Secondary: Significant decrease was observed in the tamsulosin/tadalafil group in total IPSS (P=0.01), IPSS storage (P=0.05), and voiding sub-score (P=0.01) compared with the tamsulosin/placebo group.
Casabé et al[66] Tadalafil 5 mg and finasteride 5 mg QD vs finasteride 5 mg and placebo QD	DB, MC, PC, RCT Men ≥45 years of age with BPH or LUTS with an IPSS score ≥45, prostate volume ≥30 mL and 5α-reductase inhibitor naïve	N= 6 months	Primary: Improvement of IPSS total score after 12 weeks Secondary: Other IPSS measures after 4, 12 and 26 weeks, IIEF-EF erectile dysfunction domain at 4, 12, and 26 weeks,	Primary: There were 659 patients that completed 12 weeks of double-blind therapy and 592 (tadalafil/finasteride, 306 [88.4%]; placebo/finasteride, 286 [81.7%]) completed the entire 26-week period. Tadalafil 5 mg once daily coadministered with finasteride 5 mg for 12 weeks resulted in an IPSS total score improvement that was significantly better than finasteride/placebo. The least square mean change from baseline with tadalafil/finasteride at 12 weeks was −5.2 versus −3.8 for finasteride/placebo (resulting in a least square treatment difference of −1.4; 95% CI, −2.3 to −0.6; P=0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			and the PGI-I and CGI-I after 26 weeks	Significant LUTS improvements were observed with tadalafil/finasteride at four and 26 weeks after baseline. After four weeks the least square mean change in IPSS total score with tadalafil/finasteride was −4.0 compared to −2.3 with placebo/finasteride (least square treatment difference of −1.7; 95% CI, −2.4 to −0.9; P<0.001) while the least square mean change for tadalafil/finasteride at 26 weeks was −5.5 compared to −4.5 for placebo/finasteride (least square treatment difference of −1.0; 95% CI, −1.9 to −0.2; P=0.022). Among sexually active patients who had ED at baseline (201 placebo/finasteride, 203 tadalafil/finasteride), tadalafil/finasteride led to significant improvements in IIEF-EF scores at all three points after baseline. Least square mean changes in IIEF-EF scores were 3.7, 4.7 and 4.7 after 4, 12 and 26 weeks of tadalafil/finasteride, respectively. Meanwhile, least square mean changes in IIEF-EF scores with placebo/finasteride were −1.1, 0.6 and −0.0 at 4, 12 and 26 weeks, respectively, resulting in least square treatment differences of 4.9, 4.1 and 4.7 favoring tadalafil/finasteride over placebo/finasteride (P<0.001 for all three points). Compared to placebo/finasteride, tadalafil/finasteride significantly improved IPSS storage and voiding subscores at week four and week 12 only as well as IPSS voiding subscores at week 26 only (P<0.05). The IPSS-QOL index was numerically improved with tadalafil/finasteride (compared to placebo/finasteride) at all three post-baseline assessments but only reached statistical significance at week four (P<0.001). No differences were observed between tadalafil/finasteride and placebo/finasteride treatment for IPSS-nocturia at any post-baseline assessments. In addition, after 26 weeks of therapy no significant differences were observed between the treatment groups in the distribution of responses to the CGI-I (P=0.328). However, the corresponding response distribution for the PGI-I significantly favored tadalafil/finasteride (P=0.034).
MacDonald et al[67]	SR	N=3,901	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Alfuzosin vs doxazosin or tamsulosin or finasteride vs alfuzosin and finasteride or placebo	(11 trials) Men with symptomatic BPH	4-26 weeks	IPSS Secondary: Changes in peak urinary flow, urinary symptom scores, adverse effects, incidence of treatment discontinuation	In the two trials comparing alfuzosin to other α blockers, doxazosin demonstrated the greatest improvement in IPSS (WMD, 1.70; 95% CI, 0.76 to 1.64; P=0.05). One study involved alfuzosin monotherapy versus finasteride or in combination with finasteride. Alfuzosin, both alone and in combination, significantly improved LUTS compared to finasteride alone. When compared to placebo, alfuzosin demonstrated a greater improvement in the IPSS with a WMD of -1.8 points (95% CI, -2.49 to -1.11). Secondary: No difference was found among α blockers in peak urinary flow, while alfuzosin and tamsulosin 0.4 mg showed similar improvement in Boyarsky symptom scores. Alfuzosin, finasteride and combination treatment all had similar changes in peak urinary flow; however, a subgroup analysis showed greater improvement in patients with obstruction in the alfuzosin and combination therapy treatment groups over finasteride alone. Peak urinary flow was 2.6 mL/second (10% to 54%) with alfuzosin treatment vs 1.1 mL/second with placebo (2% to 29%). Alfuzosin showed benefit over placebo in the mean urinary symptom score with a WMD of -0.90 point (95% CI, -0.94 to -0.87). The incidences of adverse events as well as withdrawal rates were comparable among α blockers. Vasodilatory effects were similar with alfuzosin, finasteride and combination therapy, whereas impotence occurred significantly more often with finasteride alone and in combination. Discontinuation of treatment was higher with alfuzosin than finasteride and lower with alfuzosin monotherapy compared to combination therapy. Dizziness was the most frequently reported side effect with alfuzosin compared to placebo. Postural hypotension, syncope, and somnolence were reported in less than 2% of alfuzosin patients, but more often than with placebo. Withdrawal rates were similar between groups.

*Not available in the United States.
Study abbreviations: DB=double-blind, DD=double dummy, MA=meta-analysis, MC=multi-center, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective study, RCT=randomized controlled trial, RETRO=retrospective study, SB=single blinded, SR=systematic review, XO=cross over

AUA-SS=American Urological Association Symptom Score, BII-BPH impact index, BMI=body mass index, BPH=benign prostatic hyperplasia, BOOI=bladder outlet obstruction index , CI=confidence interval, CGI-I=Clinician Global Impression of Improvement, DAN-PSS=Danish prostatic symptom sexual function score, ED=erectile dysfunction, GITS=gastrointestinal therapeutic system, IIEF-EF=International Index of Erectile Function-Erectile Function, IPSS=International Prostate Symptom Score, LUTS=lower urinary tract symptoms, NS=not significant, PdetQmax=detrusor pressure at maximum flow, PCG-I=Patient Global Impression of Improvement, PSA=prostate-specific antigen, PV=prostate volume, QOL=quality of Life, Q_{max}=maximum urinary flow rate, SD=standard deviation, SEM=standard error of the mean, SFAQ=Sexual Function Abbreviated Questionnaire, SPI=Symptom Problem Index, WMD=weighted mean difference

Special Populations

Table 5. Special Populations[1,10]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Alfuzosin hydrochloride	No dosage adjustment required in the elderly. Not indicated for use in children.	Caution should be used in patients with severe renal impairment.	Not studied in mild hepatic impairment. Contraindicated in patients with moderate to severe hepatic impairment.	B*	Not reported.
Doxazosin mesylate	No dosage adjustment required in the elderly for the treatment of BPH; start at lower the lower end of the dosing range for the treatment of hypertension in the elderly. Safety and effectiveness in pediatric patients have not been established.	No significant alterations compared to with normal renal function.	Caution should be used in patients with hepatic impairment.	C	Unknown
Dutasteride	No dosage adjustment required in the elderly. Contraindicated for use in pediatric patients.	No dosage adjustment required in patients with renal impairment.	Not studied in hepatic impairment.	X*	Unknown
Finasteride	No dosage adjustment required in the elderly. Safety and effectiveness in pediatric patients have not been established.	No dosage adjustment required in patients with renal impairment.	Caution should be used in patients with hepatic impairment.	X*	Unknown
Silodosin	No dosage adjustment required in the elderly.† Safety and effectiveness in pediatric patients have not been established; not indicated for use in pediatric patients.	Reduce dose to 4 mg in patients with moderate renal impairment; contra-indicated in patients with severe renal impairment.	No dosage adjustment in patients with mild-moderate hepatic impairment; contra-indicated in patients with severe hepatic impairment.	B*	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Tadalafil	No dosage adjustment required in the elderly. Safety and effectiveness in pediatric patients have not been established.	Reduce dose to 2.5 mg in moderate impairment (may increase to 5 mg based on response); not recommended in severe impairment or hemodialysis patients.	No dosage adjustment required in patients with mild to moderate hepatic impairment; not studied in patients with severe hepatic impairment.	B*	Not reported
Tamsulosin hydrochloride	No dosage adjustment required in the elderly. Safety and effectiveness in pediatric patients have not been established.	No dosage adjustment required in patients with renal impairment; not studied in endstage renal disease.	No dosage adjustment required in patients with mild to moderate hepatic impairment; not studied in patients with severe hepatic impairment.	B*	Not reported.
Terazosin hydrochloride	No dosage adjustment recommended in the elderly. Safety and effectiveness in pediatric patients have not been established.	No dosage adjustment required in patients with renal impairment.	Dosage adjustment may be required in patients with hepatic impairment.	C	Unknown
Dutasteride/ tamsulosin hydrochloride	No dosage adjustment recommended in the elderly. Contraindicated for use in pediatric patients.	No dosage adjustment required in patients with mild to moderate renal impairment; not studied in severe impairment.	Use cation when used in patients with mild to moderate hepatic impairment; not studied in severe hepatic impairment.	X*	Unknown

*Not indicated for use in women.
†Orthostasis was reported at a greater rate among older patients in clinical trials.

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-10]

Adverse Event	Single-Entity Agents								Combination
	Alfuzosin	Doxazosin	Dutasteride	Finasteride	Silodosin	Tadalafil‡	Tamsulosin	Terazosin	Dutasteride/ Tamsulosin*
Cardiovascular									
Chest pain	-	2	-	-	-	✔	4.0 to 4.1	-	✔*
Myocardial infarction	-	-	-	-	-	✔	-	-	-
Palpitations	-	2	-	-	-	-	-	0.9 to 4.3	-
Postural hypotension	-	1.2-2.2	-	9.1	2.6	2.6	-	1.3 to 3.9	-
Sudden cardiac death	-	-	-	-	-	✔	-	-	-
Tachycardia	-	-	-	-	-	✔	-	-	-
Central Nervous System									
Amnesia, transient global	-	-	-	-	-	✔	-	-	-
Asthenia	-	3.9 to 6.9	-	5.3	-	-	7.8to 8.5	7.4 to 11.3	✔*
Dizziness	5.7	5.3 to 19.0	-	7.4	3.2	-	14.9 to 17.1	9.1 to 19.3	1.1
Fatigue	2.7	8to 12	-	-	-	-	-	-	-
Headache	3	5.1 to 14.0	-	2	2.4	-	19.3 to 21.1	4.9 to 16.2	✔*
Insomnia	-	-	-	-	-	-	1.4 to 2.4	-	✔*
Migraine	-	-	-	-	-	✔	-	-	
Nervousness	-	2	-	-	-	-	-	2.3	-
Paresthesia	-	-	-	-	-	-	-	2.9	-
Seizure					-	✔	-	-	
Somnolence	-	5	-	-	-	-	3.0 to 4.3	3.6 to 5.4	✔*
Vertigo	-	1.5 to 4.1	-	-	-	-	-	-	-
Gastrointestinal									
Abdominal pain	-	1.8 to 2.4	-	-	-	-	-	-	-
Diarrhea	-	2.0 to 2.3	-	-	2.6	-	4.3 to 6.2	-	✔*
Dry mouth	-	2	-	-	-	-	-	-	-
Nausea	-	1.2 to 3.0	-	-	-	-	2.6 to 3.9	1.7 to 4.4	✔*
Genitourinary									
Abnormal ejaculation	-	-	-	7.2	-	-	8.4 to 18.1	-	✔*
Decreased ejaculate volume	-	-	-	1.5 to 3.7	-	-	-	-	-
Ejaculation disorders	-	-	-	-	-	-	-	-	7.8

Adverse Event	Single-Entity Agents								Combination
	Alfuzosin	Doxazosin	Dutasteride	Finasteride	Silodosin	Tadalafil‡	Tamsulosin	Terazosin	Dutasteride/ Tamsulosin*
Impotence	-	-	0.8 to 18.5	5.1 to 8.1	-	-	-	-	✔*
Polyuria	-	2	-	-	-	-	-	-	-
Retrograde ejaculate	-	-	-	-	28.1	-	-	-	-
Sexual dysfunction	-	2	2.5	-	-	-	-	-	✔*
Musculoskeletal									
Back pain	-	1.7 to 2.9	-	-	-	-	7.0 to 8.3	2.4	✔*
Respiratory									
Cough increased	-	-	-	-	-	-	3.4 to 4.5	-	✔*
Dyspnea	-	1 to 2.6.0	-	-	-	-	-	1.7 to 3.1	-
Nasal congestion	-	-	-	-	2.1	-	-	1.9 to 5.9	-
Nasopharyngitis	-	-	-	-	2.4	-	-	-	-
Pharyngitis	-	-	-	-	-	-	5.1 to 5.8	-	✔*
Respiratory tract infection	-	4.5 to 4.8	-	-	-	-	-	-	-
Rhinitis	-	3	-	-	-	-	13.1 to 17.9	-	✔*
Sinusitis	-	-	-	-	-	-	2.2 to 3.7	2.6	✔*
Upper respiratory tract infection	3	-	-	-	-	-	-	-	-
Other									
Blurred vision	-	-	-	-	-	-	0.2to 2.0	-	✔*
Breast disorders	-	-	-	-	-	✔	-	-	1.1
Decreased libido	-	-	0.2 to 3.3	2.6 to 10.0	-	-	1.0 to 2.0	-	4.5
Edema	-	2.7 to 4.0	-	-	-	-	-	-	-
Gynecomastia	-	-	-	2.2	-	-	-	-	-
Hearing loss	-	-	-	-	-	✔	-	-	-
Infection	-	-	-	-	-	-	9.0 to 10.8	-	✔*
Influenza syndrome	-	-	-	-	-	-	-	2.4	-
Pain	-	2	-	-	-	-	-	-	-
Pain in extremities	-	-	-	-	-	-	-	3.5	-
Peripheral edema	-	-	-	-	-	-	-	0.9 to 5.5	-
Tooth disorder	-	-	-	-	-	-	1.2 to 2.0	-	✔*
Vision abnormal	-	2	-	-	-	✔	-	-	-

- Event not reported or < 2%.
*Extrapolated from single-entity agent.

‡No data provided on frequency; events included either due to their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors.

Contraindications

Table 7: Contraindications[1-10]

Contraindications	Single-Entity Agents								Combination
	Alfuzosin	Doxazosin	Dutasteride	Finasteride	Silodosin	Tadalafil	Tamsulosin	Terazosin	Dutasteride/ Tamsulosin*
CYP3A4 inhibitor (strong) coadministration	✔				✔				
Hepatic impairment, moderate to severe	✔								
Hepatic impairment, severe					✔				
Hypersensitivity to the active agent or any component	✔	✔	✔	✔	✔	✔	✔	✔	✔
Nitrate coadministration, regularly and/or intermittently						✔			
Pediatric Patients			✔						✔
Pregnancy			✔	✔					✔
Renal impairment, severe					✔				
Women of childbearing potential			✔						✔

Warnings and Precautions

Table 8: Warnings and Precautions[1-10]

Warnings and Precautions	Single-Entity Agents								Combination
	Alfuzosin	Doxazosin	Dutasteride	Finasteride	Silodosin	Tadalafil	Tamsulosin	Terazosin	Dutasteride/ Tamsulosin*
Alcohol consumption may increase hypotension; limit consumption						✔			
Angina pectoris; if symptoms appear or worsen discontinue medication	✔	✔ (ER)							

Warnings and Precautions	Single-Entity Agents								Combination
	Alfuzosin	Doxazosin	Dutasteride	Finasteride	Silodosin	Tadalafil	Tamsulosin	Terazosin	Dutasteride/ Tamsulosin*
Bleeding may be increased; use caution						✔			
Blood donation; do not donate for six months			✔						✔
Coadministration with (other) α adrenergic antagonists	✔				✔	✔	✔		✔
Coadministration with CYP3A4 (strong) inhibitors	✔	✔ (ER)			✔	✔	✔		✔
Coadministration with CYP3A4 (moderate) inhibitors							✔		✔
Coadministration with CYP2D6 (strong or moderate) inhibitors or poor metabolizers of CYP2D6							✔		✔
Coadministration with cimetidine							✔		✔
Coadministration with hypertension agents					✔	✔			
Coadministration with phosphodiesterase-5 inhibitors	✔	✔ (ER)			✔	✔	✔		✔
Coadministration with warfarin							✔		✔
Gastrointestinal disorders; markedly increased gastrointestinal retention		✔ (ER)							
Hearing loss, sudden						✔			
Hepatic impairment, mild and moderate						✔			
Hepatic impairment, moderate to severe	✔								

Warnings and Precautions	Single-Entity Agents								Combination
	Alfuzosin	Doxazosin	Dutasteride	Finasteride	Silodosin	Tadalafil	Tamsulosin	Terazosin	Dutasteride/ Tamsulosin*
Hepatic impairment, severe		✔ (ER)			✔				
Hypotension, postural; potential for syncope; "first dose effect"	✔	✔			✔	✔	✔	✔	✔
Intraoperative Floppy Iris Syndrome during cataract surgery	✔	✔ (ER)			✔		✔		✔
Nitrate use; wait appropriate amount of time between nitrite and medication						✔			
Pediatric patients and women; not indicated				✔					
Priapism	✔	✔				✔	✔	✔	
Prostatic carcinoma	✔	✔ (ER)	✔	✔	✔		✔		✔
Prostate specific antigen reduced, use caution in prostate cancer detection			✔	✔					✔
QT prolongation, acquired or congenital	✔								
Renal impairment, moderate or severe					✔	✔			
Renal impairment, severe	✔								
Semen characteristics; total sperm count, volume, motility reduced			✔						✔
Semen characteristics; volume and total sperm count				✔					
Sexual activity is inadvisable						✔			
Sexually transmitted diseases, counseling; does not protect from sexually transmitted diseases						✔			

Warnings and Precautions	Single-Entity Agents								Combination
	Alfuzosin	Doxazosin	Dutasteride	Finasteride	Silodosin	Tadalafil	Tamsulosin	Terazosin	Dutasteride/ Tamsulosin*
Sulfa allergy							✔		✔
Urological disease; rule out conditions that cause similar symptoms			✔	✔		✔			✔
Ventricular outflow obstruction						✔			
Vision loss, sudden (non-arteritic anterior ischemic optic neuropathy); stop medication and seek medical help						✔			
Women, exposure; do not handle if pregnant or if could become pregnant			✔	✔					✔

ER=extended release formulation.

Drug Interactions

Table 9. Drug Interactions[1-10]

Generic Name	Interacting Medication or Disease	Potential Result
α-adrenergic blockers (alfuzosin, doxazosin, silodosin, tamsulosin), dutasteride, dutasteride/tamsulosin tadalafil	CYP3A4 inhibitors	Blood levels of BPH medications increased.
α-adrenergic blockers (alfuzosin, silodosin, tamsulosin, terazosin) dutasteride, dutasteride/tamsulosin tadalafil	α-adrenergic blockers	Additive vasodilatory effects; blood pressure decreases.
α-adrenergic blockers (alfuzosin, silodosin,	Nitrates and/or other anti-hypertensives	Increased risk of hypotension/postural hypotension and syncope.
α-adrenergic blockers (alfuzosin, doxazosin, silodosin, tamsulosin)	Phosphodiesterase-5 inhibitors	Additive vasodilatory effects; blood pressure decreases.
Dutasteride	Calcium channel antagonists	Decreased clearance of BPH medication; no dose adjustment required
Dutasteride/tamsulosin, tamsulosin	Atenolol, nifedipine, enalapril	Dose adjustment for tamsulosin is required.
Dutasteride/tamsulosin, tamsulosin	CYP2D6 inhibitors	Blood levels of BPH medications increased.
Dutasteride/tamsulosin, tamsulosin	Cimetidine	Decreased clearance of BPH medication.
Dutasteride/tamsulosin, tamsulosin	Warfarin	Use caution as an interaction study was not conducted.
Tadalafil	Alcohol	Additive hypotensive effects, blood pressure decreased; potential for orthostatic hypotension
Tadalafil	Anti-hypertensives	Additive hypotensive effects, blood pressure decreased
Tadalafil	Nitrates	Contraindicated; potentiation of hypotensive effects
Silodosin	Strong P-glycoprotein inhibitors	Blood levels of BPH medications increased.

Dosage and Administration

The usual dosing regimens for the benign prostatic hyperplasia (BPH) treatments are summarized in Table 10. Treatment with doxazosin and terazosin should be initiated at bedtime and at the lowest dose to minimize the likelihood of the "first-dose" effect which can cause marked hypotension (especially postural hypotension) and syncope with sudden loss of consciousness with the first few doses. Dosages should be titrated up slowly to achieve the desired response. If therapy is interrupted for more than a few days, the initial dosing regimen and titration schedule should be reinstituted. Other antihypertensive agents should be added cautiously to reduce the risk of developing significant hypotension. Alfuzosin, doxazosin extended-release, dutasteride, tamsulosin and, dutasteride/tamsulosin should all be swallowed whole and not crushed, chewed, or cut. Doxazosin instant-release, finasteride, and tadalafil tablets may be crushed if needed. Silodosin capsules can be opened and the power sprinkled on applesauce.

Terazosin capsules can be dissolved in hot water (which may take five to 15 minutes) for administration through a feeding tube via an oral syringe if required. Women who are pregnant or who could be pregnant should avoid handling dutasteride and dutasteride/tamsulosin capsules along with crushed finasteride tablets.[1-10]

Table 10. Dosing and Administration[1-10]

Generic Name	Adult Dose	Pediatric Dose	Availability
Alfuzosin hydrochloride	Treatment of signs and symptoms of benign prostatic hyperplasia: Extended release tablet: 10 mg once daily; administer with food and with the same meal each day.	Safety and effectiveness in pediatric patients have not been established.	Tablet, extended release: 10 mg
Doxazosin mesylate	Treatment of signs and symptoms of benign prostatic hyperplasia[#]: Tablet: Initial, 1 mg once daily; maintenance, 1 to 8 mg once daily; maximum, 8 mg/day Extended-release tablet: Initial, 4 mg once daily, administered with breakfast; maintenance, 4 to 8 mg daily; maximum, 8 mg/day Treatment of Hypertension: Tablet[*]: Initial, 1 mg once daily; maintenance, 1 to 16 mg once daily; maximum, 16 mg/day	Safety and effectiveness in pediatric patients have not been established.	Tablet, extended release: 4 mg 8 mg Tablet: 1 mg 2 mg 4 mg 8 mg
Dutasteride	Treatment of signs and symptoms of benign prostatic hyperplasia[† ‡]: Capsule: Initial, 0.5 mg once daily; do not chew or open capsule	Contraindicated for use in pediatric patients.	Capsule: 0.5 mg
Finasteride	Treatment of signs and symptoms of benign prostatic hyperplasia[† §]: Tablet: Initial, 5 mg once daily	Safety and effectiveness in pediatric patients have not been established.	Tablet: 5 mg
Silodosin	Treatment of signs and symptoms of benign prostatic hyperplasia: Capsule: Initial, 8 mg once daily with a meal	Safety and effectiveness in pediatric patients have not been established.	Capsule: 4 mg 8 mg
Tadalafil	Treatment of signs and symptoms of benign prostatic hyperplasia: Tablet: Initial: 5 mg daily, taken at approximately the same time each day; limit therapy to 26 weeks when initiated with finasteride Treatment of erectile dysfunction: Tablet: Initial (daily), 2.5 mg daily, taken at approximately the same time each day without regard to sexual activity; Initial (as needed), 10 mg taken prior to anticipated	Safety and effectiveness in pediatric patients have not been established.	Tablet: 2.5 5 10[¶] 20[¶]

Generic Name	Adult Dose	Pediatric Dose	Availability
	sexual activity; Maintenance (daily), 5 mg daily; Maintenance (as needed), 5 to 20 mg; Maximum (daily), 5 mg/day; Maximum (as needed), 20 mg/72 hours (tadalafil is effective for 72 hours after administration)		
Tamsulosin hydrochloride	Treatment of signs and symptoms of benign prostatic hyperplasia: Capsule: Initial, 0.4 mg once daily, administered one-half hour following the same meal each day; maintenance, 0.4 to 0.8 mg once daily	Safety and effectiveness in pediatric patients have not been established.	Capsule: 0.4 mg
Terazosin hydrochloride	Treatment of signs and symptoms of benign prostatic hyperplasia: Capsule: Initial, 1 mg at bedtime; maintenance, 1 to 10 mg/day; maximum, 20 mg/day Treatment of Hypertension: Capsule: Initial, 1 mg at bedtime; maintenance, 1 to 20 mg once daily; maximum, 20 mg/day	Safety and effectiveness in pediatric patients have not been established.	Capsule: 1 mg 2 mg 5 mg 10 mg
Dutasteride/ tamsulosin hydrochloride	Treatment of signs and symptoms of benign prostatic hyperplasia†: Capsule: Initial, 0.5 mg/0.4 mg once daily approximately 30 minutes after the same meal each day	Contraindicated for use in pediatric patients.	Capsule: 0.5 mg/0.4 mg

*Instant release formulation only.
†In men with an enlarged prostate, to improve symptoms, reduce the risk of acute urinary retention and reduce the risk of the need for BPH-related surgery.
‡To treat symptomatic BPH in men with an enlarged prostate in combination with tamsulosin.
§To reduce the risk of symptomatic progression of BPH in combination with doxazosin.
#Doxazosin indicated for both the urinary outflow obstruction and obstructive and irritative symptoms associated with BPH.
¶Strengths not approved for use in BPH (erectile disfunction only).

Clinical Guidelines

Current treatment guidelines addressing the treatment of benign prostatic hyperplasia (BPH) are summarized in Table 11. The review will focus on the drug therapy of BPH. Clinical guidelines evaluating the role of doxazosin and terazosin in the treatment of hypertension and tadalafil in erectile dysfunction and pulmonary hypertension are included in a separate review.

Table 11. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American Urological Association (AUA): **AUA Guideline: Management of Benign Prostatic Hyperplasia (BPH) (2010)**[12]	Watchful Waiting: • A period of physician monitoring and no active intervention is recommended for patients with mild symptoms of BPH (AUA symptom score <8) and patients with moderate or severe symptoms (AUA symptom score ≥8) who are not bothered by their symptoms or who have not yet developed complications of BPH (e.g., renal insufficiency, urinary retention, or recurrent infection).

Clinical Guideline	Recommendation(s)
	Moderate-to-severe symptoms of BPH: • Drug and procedural therapeutic options exist for patients with bothersome moderate to severe symptoms. • Drug treatments options include α-blockers and α-reductase inhibitors or a combination of both. • α -adrenergic Blockers (α Blockers) o Alfuzosin, doxazosin, tamsulosin, and terazosin are appropriate and effective treatment alternatives for patients with bothersome, moderate to severe lower urinary tract symptoms (LUTS) secondary to BPH (AUA-SI score ≥8). o All four appear to have equal clinical effectiveness; although; studies directly comparing these agents is currently lacking. o There are slight differences in adverse effects, but all four agents remain similar. o The older, less costly, generic α blockers remain reasonable choices. These require dose titration and blood pressure monitoring. o Prazosin and non-selective α blockers were not reviewed citing insufficient data for treatment in BPH. • α -adrenergic blockers and 5- α reductase inhibitor combination o Combination therapy is an appropriate and effective treatment for patients with LUTS associated with demonstrable prostatic enlargement based on volume measurement, PSA level as a proxy for volume, and/or enlargement on digital rectal exam. • Intraoperative floppy iris syndrome o Avoid the initiation of α blockers (or combinations containing alpha-blockers) in patients who plan to have cataract surgery. o α blockers (or combinations) may be initiated after cataract surgery is completed. • 5-α reductase inhibitors (5-ARIs) o 5-ARIs may be used to prevent progression of LUTS secondary to BPH and to reduce the risk of urinary retention and future prostate-related surgery. o 5-ARIs should not be used in men with LUTS secondary to BPH without prostatic enlargement. o The 5-ARIs are appropriate and effective treatment alternatives for men with LUTS secondary to BPH who have demonstrable prostate enlargement. • Anticholinergic agents o Anticholinergic agents are appropriate and effective treatment alternatives for the management of LUTS secondary to BPH in men without an elevated post-void residual and when LUTS are predominantly irritative. o Prior to initiation of anticholinergic therapy, baseline postvoid residual urine should be assessed. Anticholinergics should be used with caution in patients with a post-void residual greater than 250 to 300 mL
European Association of Urology (EAU): **Guidelines on the management of**	• The watchful watching policy should be recommended to patients with mild LUTS that have minimal or no impact on their quality of life. • Men with LUTS should always be offered lifestyle advice prior to or concurrent with treatment

Clinical Guideline	Recommendation(s)
Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO) (2014)[13]	Drug Treatment: • α blockers can be offered to men with moderate to severe LUTS o α blockers are often considered the first-line drug treatment of male LUTS because of their rapid onset of action, good efficacy, and low rate and severity of adverse events. o Indirect comparisons between agents show similar efficacy. o The clinical impact of the different formulations is modest. o The most frequent adverse events of α blockers are asthenia, dizziness and (orthostatic) hypotension. Vasodilating effects are most pronounced with doxazosin and terazosin, and are much less common for alfuzosin and tamsulosin. o A systematic review concluded that α blockers do not adversely affect libido, have a small beneficial effect on erectile function, but sometimes cause abnormal ejaculation. o It is not prudent to initiate α blocker treatment prior to scheduled cataract surgery. o Ophthalmologists should be informed about α blocker use prior to cataract surgery. • 5-α reductase inhibitors o Treatment with 5-α reductase inhibitors should be considered only in men with moderate-to-severe LUTS and an enlarged prostate (>40 mL) or elevated PSA concentration (>1.4 to 1.6 ng/mL). o Due to the slow onset of action, 5-α reductase inhibitors are suitable only for long-term treatment (many years). o Clinical effects relative to placebo are seen after minimum treatment duration of at least 6 to 12 months. o Comparative trials suggest similar efficacy between agents. o Comparative studies with α blockers and a recent meta-analysis have demonstrated that 5-α reductase inhibitors reduce LUTS more slowly and that finasteride is less effective than either doxazosin or terazosin, but equally effective compared with tamsulosin. o 5-α Reductase inhibitors, but not α blockers, reduce the long-term (>1 year) risk of acute urinary retention (AUR) or need for surgery. o 5-α reductase inhibitors (finasteride) might reduce blood loss during transurethral prostate surgery, probably due to their effects on prostatic vascularization. o The most relevant adverse effects of 5-α reductase inhibitors are related to sexual function, and include reduced libido, erectile dysfunction and, less frequently, ejaculation disorders such as retrograde ejaculation, ejaculation failure, or decreased semen volume. o Men taking a 5-α reductase inhibitor should be followed up regularly using serial PSA testing. • Muscarinic receptor antagonists (anticholinergics) o Muscarinic receptor antagonists may be used in men with moderate-to-severe LUTS who predominantly have bladder storage symptoms. o Use cation in patients with bladder outlet obstruction.

Clinical Guideline	Recommendation(s)
	o These drugs should be prescribed with caution, due to long-term studies on the efficacy of muscarinic receptor antagonists in men with LUTS not yet available. o Regular re-evaluations of the International Prostate Symptom Score and Prostate Symptom Score are advised. o Although not all antimuscarinic agents have been tested in elderly men with LUTS and overactive bladder symptoms, they are all likely to present similar efficacy and adverse events. • Phosphodiesterase-5 (PDE-5) inhibitors o PDE-5 inhibitors reduce moderate-to-severe (storage and voiding) LUTS in men with or without erectile dysfunction o Meta-analysis suggests that younger men with low body mass index and more severe LUTS profit the most from treatment with PDE-5 inhibitors. o There is limited information at present about the reduction of prostate size and no information on the slowing of disease progression. o Insufficient information is available about combinations between phosphodiesterase-5 inhibitors and other LUTS medications.

Conclusions

In men with bothersome moderate to severe lower urinary tract symptoms associated with benign prostatic hyperplasia, medical treatment, particularly with an α-adrenergic blocking agent, is warranted. Treatment with these agents has resulted in a rapid improvement in symptoms and improvement in urinary flow rate. These changes have been shown to be significant in randomized controlled studies. There is a lack of head to head trials comparing silodosin, the newest agent in this class, with other α-adrenergic blockers. 5-α reductase inhibitor therapy, either alone or in combination with an α-adrenergic blocker, is indicated in the setting of prostate enlargement. Dutasteride and finasteride use is associated with a reduction in prostate volume and the improvement of symptom scores and flow rates.

Differences in the rates of adverse events do differ slightly among the α-adrenergic blockers. Alfuzosin, silodosin and tamsulosin are less likely than terazosin and doxazosin to have hypotensive side effects secondary to their affinity for the α_{1a} receptor, thus the latter two agents require dose titration. There is no evidence to support any one of the α-adrenergic blocking agents or 5-α reductase inhibitors included in this review to be more efficacious than another in their class for the treatment of benign prostatic hyperplasia. Alfuzosin, doxazosin, terazosin and finasteride are available generically in standard formulations. The doxazosin sustained-release tablet (Cardura XL®) is not currently available generically.

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