Therapeutic Class Overview
Benign Prostatic Hyperplasia (BPH) Treatments

Therapeutic Class

- **Overview/Summary:** The agents approved for the treatment of signs and symptoms of benign prostatic hyperplasia (BPH) 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 also 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, act by blocking the conversion of testosterone to dihydrotestosterone and in turn suppress the growth of the prostate. making them appropriate treatment options for LUTS associated with overall prostatic enlargement.[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] Another drug approved for use in BPH is the phosphodiesterase-5 inhibitor, tadalafil. The exact mechanism for reducing BPH symptoms is unknown.[10] Although 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] Current treatment guidelines acknowledge 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.[12-13]

Table 1. Current Medications Available in the Therapeutic Class[1-10,14]

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	✔

*Immediate-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.
**** When used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks.
†† In men with an enlarged prostate.

Evidence-based Medicine[15-67]

- 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 <8) 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 treatment choices.
  - PDE-5 inhibitors reduce moderate-to-severe (storage and voiding) LUTS in men with or without erectile dysfunction.[13].
  - 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 immediate-release, tamsulosin, terazosin, dutasteride, and finasteride are available generically in standard formulations. The doxazosin sustained-release tablet (Cardura XL®), silodosin (Rapaflo®), and tadalafil (Cialis®) are 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:[1-5,7-10]
    - Alfuzosin, doxazosin extended-release, dutasteride, tamsulosin and dutasteride/ tamsulosin should all be swallowed whole and not crushed, chewed, or cut.
    - Doxazosin immediate-release, finasteride, and tadalafil tablets may be crushed.
    - Silodosin capsules can be opened and the powder sprinkled on applesauce.

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