Therapeutic Class Overview
Benign Prostatic Hyperplasia Agents

INTRODUCTION

- Benign prostatic hyperplasia (BPH) is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells of the prostate. A different but related term is benign prostatic enlargement, which is used when the prostate has an increased size (*McVary et al 2011*).
- BPH causes bladder outlet obstruction that leads to lower urinary tract symptoms (LUTS). The obstruction is caused by 2 main factors:
  - A static, structural component due to the bulk of the enlarged prostate impinging upon the urethra.
  - A dynamic, reversible component due to the tension of smooth muscle in the prostate (*McVary et al 2011*).
- LUTS include storage and voiding symptoms (*McVary 2019b, McVary et al 2011*).
  - Storage symptoms may include increased frequency of daytime urination, nocturia, urgency, and urinary incontinence.
  - Voiding symptoms may include a slow urinary stream, splitting or spraying of the urinary stream, intermittent urinary stream, hesitancy, straining to void, and terminal dribbling.
- The exact etiology of BPH is unknown (*McVary et al 2011*). Increased age is a major risk factor; the prevalence of BPH is 8% in men 31 to 40 years of age, 40% to 50% in men 51 to 60 years of age, and over 80% in men older than 80 years of age (*McVary 2019a*).
- The primary goals of treatment are to alleviate bothersome LUTS secondary to prostate enlargement, to alter the disease progression, and to prevent complications associated with BPH and LUTS (*McVary et al 2011*).
- Current treatment options include watchful waiting, surgical interventions, and pharmacological therapies (*Foster et al 2018, McVary et al 2011*).
  - Watchful waiting is the preferred management strategy for men with mild symptoms and for those with moderate to severe symptoms who are not bothered by their LUTS.
  - Surgical and minimally invasive therapies, such as transurethral resection of the prostate and transurethral microwave thermotherapy, are recognized as the most effective strategies for BPH management. Surgical therapy is an appropriate treatment alternative for patients with moderate-to-severe LUTS and for patients who have developed acute urinary retention or other complications.
  - Pharmacological therapies are appropriate for less frequent and severe symptom management. These therapies may include alpha $(\alpha)_1$-adrenergic blocking agents, 5-alpha (5-α)-reductase inhibitors, anticholinergic agents, and phosphodiesterase-5 (PDE5) inhibitors.
- This review focuses on the pharmacological agents that are Food and Drug Administration (FDA)-approved for the management of BPH and include the following drug classes:
  - α_1-adrenergic blocking agents: Cardura (doxazosin), Cardura XL (doxazosin extended-release), Flomax (tamsulosin), Hytrin (terazosin), Rapaflo (silodosin), and Uroxatral (alfuzosin)
    - Doxazosin and terazosin are non-uroselective α_1-adrenergic blocking agents. They cause relaxation in both the prostatic and vascular smooth muscles and are therefore associated with a higher incidence of orthostatic hypotension. Both agents are FDA-approved for the management of BPH and hypertension.
    - Cardura XL, an extended-release tablet, is only indicated for the management of BPH.
    - Tamsulosin, silodosin, and alfuzosin are uroselective α_1-adrenergic blocking agents and are therefore associated with a lower risk of orthostatic hypotension. They are FDA-approved for the management of BPH.
    - Minipress (prazosin) is also included in this review since it is an α_1-adrenergic blocking agent that could be used for the management of BPH, but it is only FDA-approved for the treatment of hypertension.
  - 5-α-reductase inhibitors: Avodart (dutasteride) and Proscar (finasteride)
    - Both agents are indicated for the treatment of BPH in men with enlarged prostate to improve symptoms, reduce the risk of acute urinary retention, and reduce the risk of BPH-related surgery. Finasteride is also indicated in combination with doxazosin to reduce the risk of symptomatic progression of BPH, and dutasteride is indicated in combination with tamsulosin for the treatment of symptomatic BPH in men with an enlarged prostate.
  - PDE5 inhibitor: Cialis (tadalafil)

  - In addition to the management of BPH symptoms in men with or without concomitant erectile dysfunction, Cialis is FDA-approved for the treatment of erectile dysfunction.
- Combination product: Jalyn (dutasteride/tamsulosin) is indicated for the treatment of symptomatic BPH in men with an enlarged prostate.

- Currently, doxazosin, prazosin, tamsulosin, terazosin, finasteride, dutasteride, alfuzosin, and the combination product dutasteride/tamsulosin are available generically. The brand product for Hytrin is no longer marketed; the product is only available generically.
- Medispan Therapeutic Class: Prostatic Hypertrophy Agents (tadalafil is classified with "Impotence Agents" but is also approved for BPH. Terazosin and doxazosin are classified with "antiadrenergic antihypertensives" but are also approved for BPH).

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single Entity Agents: α_1-Adrenergic Blocking Agents	
Cardura (doxazosin)	✔
Cardura XL (doxazosin extended-release)	-
Flomax (tamsulosin)	✔
Hytrin (terazosin)*	✔
Minipress (prazosin)	✔
Rapaflo (silodosin)	✔
Uroxatral (alfuzosin)	✔
Single Entity Agents: 5-α-Reductase Inhibitors	
Avodart (dutasteride)	✔
Proscar (finasteride)	✔
Single Entity Agents: PDE5 Inhibitors	
Cialis (tadalafil)	✔
Combination Product	
Jalyn (dutasteride/tamsulosin)	✔

*Brand product no longer marketed; product only available generically

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2a. FDA-Approved Indications: α_1-Adrenergic Blocking Agents

Indication	Cardura (doxazosin)	Cardura XL (doxazosin extended-release)	Flomax (tamsulosin)	Minipress (prazosin)	Hytrin (terazosin)	Rapaflo (silodosin)	Uroxatral (alfuzosin)
Treatment of signs and symptoms of BPH	✔	✔	✔		✔	✔	✔
Treatment of hypertension	✔			✔	✔		

(*Prescribing Information: Cardura 2019, Cardura XL 2017, Flomax 2019, Minipress 2016, Terazosin 2018, Rapaflo 2017, Uroxatral 2019*)

Table 2b. FDA-Approved Indications: 5-α-Reductase Inhibitors

Indication	Avodart (dutasteride)	Proscar* (finasteride)
Treatment of symptomatic BPH in men with an enlarged prostate to improve symptoms, reduce the risk of acute urinary retention, and to reduce the risk of need for BPH-related surgery	✔	✔
Treatment of symptomatic BPH in men with enlarged prostate in combination with tamsulosin	✔	

Indication	Avodart (dutasteride)	Proscar* (finasteride)
Reduction of the risk of symptomatic progression of BPH in combination with doxazosin		✔

*If finasteride is used with tadalafil to initiate BPH treatment, such use is recommended for up to 26 weeks because the incremental benefit of tadalafil decreases from 4 weeks until 26 weeks, and the incremental benefit of tadalafil beyond 26 weeks is unknown.

(*Prescribing information: Avodart 2020, Proscar 2013*)

Table 2c. FDA-Approved Indications: PDE5 Inhibitors

Indication	Cialis* (tadalafil)
Treatment of erectile dysfunction	✔
Treatment of signs and symptoms of BPH	✔
Treatment of signs and symptoms of BPH and erectile dysfunction	✔

*If tadalafil is used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks because the incremental benefit of tadalafil decreases from 4 weeks until 26 weeks, and the incremental benefit of tadalafil beyond 26 weeks is unknown.

(*Cialis prescribing information 2018*)

Table 2d. FDA-Approved Indications: Combination Product

Indication	Jalyn (dutasteride/tamsulosin)
Treatment of symptomatic BPH in men with enlarged prostate	✔

(*Jalyn prescribing information 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

α_1-Adrenergic Blocking Agents

- Overall, doxazosin, Cardura XL, tamsulosin, terazosin, silodosin, and alfuzosin have been shown in clinical trials to decrease International Prostate Symptom Score (IPSS) and improve LUTS in men with BPH (*Chang et al 2010, Choo et al 2014, Chung et al 2018, Demir et al 2009, Kawabe et al 2006, Kojima et al 2012, Leungwattanakij et al 2010, Marks et al 2013, Matsukawa et al 2009, Permpongkosol et al 2011, Ren et al 2010, Song et al 2011, Sun et al 2010, Sun et al 2011, Yamanishi et al 2010, Yokoyama et al 2011*).
- Although some studies showed small differences among agents on selected efficacy endpoints, most randomized controlled trials and reviews demonstrated very similar efficacy among products.
- A meta-analysis of α_1-adrenergic blocking agents (doxazosin, tamsulosin, terazosin, and alfuzosin) in men with LUTS secondary to benign prostatic obstruction did not identify any difference among agents in improving total urinary symptom scores or maximum urinary flow rate. However, tamsulosin and alfuzosin were better tolerated than doxazosin and terazosin (*Djavan et al 1999*).
- A systematic review of studies comparing alfuzosin to doxazosin and tamsulosin showed that doxazosin was associated with the greatest improvement in IPSS (*MacDonald et al 2005*).
- Cardura XL was associated with greater improvement in IPSS compared to tamsulosin in 2 randomized controlled trials (*Chung et al 2011, Kirby et al 2003a*); however, 2 other randomized controlled trials showed no difference between the 2 agents in the improvement in IPSS, nocturia, or quality of life (*Xue et al 2007, Zhang et al 2011*).
- Other head-to-head studies comparing the various α_1-adrenergic blocking agents have demonstrated no difference among these agents in the improvement of BPH symptoms (*Kaplan et al 1995, Kaplan et al 1997, Karadag et al 2011, Kirby et al 2001, Lapitan et al 2005, Rahardjo et al 2006, Samli and Dincel 2004, Tsai et al 2007*).
- Results from a meta-analysis and 2 crossover studies demonstrated that the efficacy of silodosin was similar to tamsulosin in improving IPSS and maximum urinary flow rate (*Cui et al 2012, Miyakita et al 2010, Shirakawa et al 2013, Watanabe et al 2011*). A 2017 Cochrane review reported the efficacy of silodosin is similar to other α_1-adrenergic blockers (tamsulosin and alfuzosin), but it is associated with a higher rate of sexual adverse effects (*Jung et al 2017*).
- Another meta-analysis examined combination therapy with an anticholinergic medication (eg, tolterodine, oxybutynin ER, solifenacin, fesoterodine) plus an α_1-adrenergic blocker (eg, doxazosin, tamsulosin) versus α_1-adrenergic blocker monotherapy in men with BPH. Study results demonstrated the addition of an anticholinergic to an α_1-adrenergic blocker

slightly reduced storage symptoms and urinary frequency; however, this combination may increase the risk of acute urinary retention (*Filson et al 2013*).

- A systematic review of 48 studies concluded that older α_1-adrenergic blocking agents had similar outcomes as newer α_1-adrenergic blocking agents, PDE5 inhibitors, antimuscarinics, and combination therapy with agents from more than one medication class. However, older α_1-adrenergic blocking agents had more adverse events than comparators (*Dahm et al 2017*).

5-α-Reductase Inhibitors

- Dutasteride has been shown to reduce prostate volume in men with BPH (*Na et al 2012, Page et al 2011*). Dutasteride has also been demonstrated to reduce the incidence of clinical progression of BPH compared to placebo in men with enlarged prostates (*Toren et al 2013*). A 2-year randomized controlled trial in Asian men also found significant reduction in prostate volume, as well as improvements in IPSS, when dutasteride was added to background tamsulosin therapy (*Haque et al 2018*).
- In a Cochrane review, finasteride improved total BPH symptom scores compared to placebo (*Tacklind et al 2010*). One clinical study also showed that finasteride reduced the risk of clinical progression of BPH compared to placebo in men with large prostate volume (*Kaplan et al 2011*).
- The Enlarged Prostate International Comparator Study (N = 1630) showed that there was no significant difference between dutasteride and finasteride in reducing prostate volume and improving LUTS and maximum urinary flow rate in men with BPH over a period of 12 months (*Nickel et al 2011*). A smaller head-to-head study and a meta-analysis of 4 studies showed similar results (*Jun et al 2017, Ravish et al 2007*). A network meta-analysis of 21 studies found that dutasteride may improve BPH symptoms but not urinary flow or prostate volume compared to finasteride (*Yin et al 2017*). When compared to α_1-adrenergic blocking agents, one study showed finasteride to be comparable to tamsulosin in improving LUTS; however, improvements were seen earlier with tamsulosin compared to finasteride (*Lee 2002*).

Combination Therapy with an α_1-Adrenergic Blocking Agent Plus a 5-α-Reductase Inhibitor

- In men with an enlarged prostate, combination therapy may lead to improved symptom control compared to monotherapy with either an α_1-adrenergic blocking agent or a 5-α-reductase inhibitor (*Kaplan et al 2006*). However, available data are inconsistent in this area, with another study demonstrating symptom control with combination therapy to be no better than with α_1-adrenergic blocking monotherapy (*Kirby et al 2003b*).
- In the 4-year, double-blind, randomized, parallel-group study known as the Combination of Avodart and Tamsulosin (CombAT) trial (N = 4844), Jalyn significantly reduced the risk of acute urinary retention or BPH-related surgery compared to tamsulosin monotherapy and demonstrated significantly greater symptom benefit (*Roehrborn et al 2010*). Jalyn was also associated with greater reduction in voiding and storage symptoms compared to dutasteride or tamsulosin monotherapy (*Becher et al 2009*).
- The 2-year, open-label CONDUCT trial compared Jalyn to watchful waiting with the addition of tamsulosin if symptoms did not improve in treatment-naïve men with moderately symptomatic BPH. Jalyn was shown to significantly improve the rate of clinical progression, health-related quality of life, and IPSS scores compared to the watchful waiting/tamsulosin group (*Roehrborn et al 2015*).
- A meta-analysis examining 5 studies found that the combination of tamsulosin and dutasteride had a significantly greater effect on symptom scores, prostate volume, urine flow rate, post-void residual urine volume, and clinical progression compared to tamsulosin alone (*Zhou et al 2019*).

PDE5 Inhibitors

- A meta-analysis showed that PDE5 inhibitors (tadalafil, vardenafil [Levitra], and sildenafil [Viagra]) were safe and effective in improving IPSS and LUTS secondary to BPH. However, no statistically significant difference was detected in maximum urine flow rate (Q_{max}) or post-void residual urine volume (*Gacci et al 2016*).
- Several clinical studies have also demonstrated the efficacy of tadalafil in improving LUTS secondary to BPH in men with or without concomitant erectile dysfunction (*Broderick et al 2010, Dmochowski et al 2013, Donatucci et al 2011, Egerdie et al 2012, Goldfischer et al 2012, Oelke et al 2012, Porst et al 2011, Roehrborn et al 2008, Takahashi et al 2018*). A meta-analysis of 13 clinical studies also confirmed the efficacy of tadalafil in improving LUTS associated with BPH and treating erectile dysfunction over 12 weeks (*Wang et al 2018*).

Combination Therapy with a PDE5 Inhibitor

- A randomized, double-blind trial showed combination therapy with a 5-α-reductase inhibitor, finasteride, combined with the PDE5 inhibitor, tadalafil, was associated with modest improvements in urinary symptoms and significantly improved patient, but not clinician, global impression of improvement when compared with finasteride monotherapy (*Casabe et al 2014*). A Cochrane review supported these findings and showed that combination therapy with a PDE5 inhibitor and 5-α-

reductase inhibitor may slightly improve IPSS in the short term compared to a 5-α-reductase inhibitor alone (*Pattanaik et al 2018*).

- Four meta-analyses demonstrated that combination therapy with a PDE5 inhibitor and an α_1-adrenergic blocking agent statistically significantly improved IPSS compared to an α_1-adrenergic blocking agent alone (*Gacci et al 2012, Kallidonis et al 2019, Pattanaik et al 2018, Zhang 2019*). A small benefit was also found with the combination compared to monotherapy with a PDE5 inhibitor. However, no adverse event data was available comparing the combination to PDE5 inhibitor alone, and adverse events increased with the combination when compared to an α_1-adrenergic blocking agent (*Pattanaik et al 2018*).
- A randomized controlled trial with a primary objective of evaluating the occurrence of dizziness when tadalafil was added to α_1-adrenergic blocking therapy demonstrated that changes in hemodynamic signs and symptoms were similar for tadalafil- and placebo-treated patients. There was a trend toward increased hemodynamic signs and symptoms in men treated with concomitant tadalafil and non-uroselective α_1-adrenergic blocking agents. Notably, this study did not demonstrate increased effectiveness with combination therapy compared to α_1-adrenergic blocking agent monotherapy, with an IPSS reduction of 2.2 in the tadalafil group and 1.33 in the placebo group ($p = 0.13$) (*Goldfischer et al 2012*).
- A randomized trial comparing tamsulosin alone with tamsulosin plus tadalafil failed to find a significant benefit with combination therapy compared to monotherapy in patients with acute urinary retention due to BPH (*Baghani et al 2018*).

CLINICAL GUIDELINES

- The American Urological Association guideline, which was published in 2011 and confirmed in 2014, has noted no differences in efficacy among doxazosin, tamsulosin, terazosin and alfuzosin in the management of BPH (*McVary et al 2011*). The European Association of Urology guideline notes that all α_1-adrenergic blocking agents have similar efficacy at appropriate doses (*Gravas et al 2019*).
- The American Urological Association guideline notes that there is no evidence to suggest that the clinical efficacy of 5-α-reductase inhibitors differs when used for the appropriate indication (*McVary et al 2011*). Similarly, the European Association of Urology guideline notes that available evidence indicates that dutasteride and finasteride are equally effective in the treatment of LUTS (*Gravas et al 2019*).
- The American Urological Association guideline currently does not have a recommendation for the place in therapy for PDE5 inhibitors (*McVary et al 2011*); however, the European Association of Urology guideline suggests that PDE5 inhibitors are effective for reducing moderate-to-severe LUTS symptoms (*Gravas et al 2019*).

SAFETY SUMMARY

- α_1-adrenergic blocking agents:
  - Use of α_1-adrenergic blocking agents may lead to intraoperative floppy iris syndrome during cataract and glaucoma surgery and warrant modification in surgical techniques as needed.
  - Orthostatic hypotension may occur with all agents, but is more common with doxazosin, prazosin, and terazosin, especially after the first dose.
  - Doxazosin, prazosin, and Cardura XL are contraindicated in patients with hypersensitivity to quinazolines (eg, prazosin, terazosin).
  - Use of α_1-adrenergic blocking agents has been associated with priapism. Patients must be advised about the seriousness of this condition.
  - Tamsulosin may cause serious allergic reactions in patients allergic to sulfa.
  - Silodosin and alfuzosin are contraindicated in patients with severe hepatic impairment and in those who are taking strong cytochrome P450 (CYP) 3A4 inhibitors. Tamsulosin also should not be used with strong CYP3A4 inhibitors.
  - Silodosin is contraindicated in patients with creatinine clearance of less than 30 mL/minute. Silodosin may also increase the risk of QT prolongation. Silodosin should not be used with concurrent strong inhibitors of P-glycoprotein.
- 5-alpha (5-α)-reductase inhibitors:
  - Dutasteride and finasteride are contraindicated in women who are pregnant or have child-bearing potential; these agents should also be avoided in pediatric patients.
  - These agents may increase the risk of high-grade prostate cancer. Since these agents can decrease plasma prostate specific antigen (PSA) levels, a new PSA baseline should be obtained after at least 3 months of therapy and used for monitoring of prostate cancer.
  - Blood donation should be avoided during and for at least 6 months after therapy discontinuation.

- PDE5 inhibitors:
  - Tadalafil is contraindicated with regular or intermittent use of any form of organic nitrates. Tadalafil should not be used in patients using a guanylate cyclase inhibitor, such as riociguat.
  - Tadalafil may cause vasodilation and should be used with caution with alcohol and avoided in patients with preexisting cardiac conditions.
  - The lowest PDE5 inhibitor dose should be used when starting therapy with concurrent α_1-adrenergic blocking agents due to the risk of additive hypotension, although the manufacturer of tadalafil recommends against its use with concurrent α_1-adrenergic blocking agents for the treatment of BPH.
  - Patients should be advised to stop tadalafil and seek immediate medical attention if they experience sudden hearing or vision loss, which could be a sign of nonarteritic anterior ischemic optic neuropathy (NAION). In patients with a history of NAION, tadalafil should be used only if benefits outweigh the risks.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single Entity Agents: a_1-Adrenergic Blocking Agents				
Cardura (doxazosin)	Tablets	Oral	Daily	• Not recommended in severe hepatic impairment. • Should be used with caution and blood pressure should be monitored for hypotensive symptoms in patients with mild or moderate hepatic impairment.
Cardura XL (doxazosin extended-release)	Tablets (extended-release)	Oral	Daily	
Minipress (prazosin)	Capsules	Oral	Twice daily	
Flomax (tamsulosin)	Capsules	Oral	Daily	• Should be taken 30 minutes following the same meal each day. • Not indicated for use in women.
Hytrin (terazosin)	Capsules	Oral	Daily at bedtime	
Rapaflo (silodosin)	Capsules	Oral	Daily	• Contraindicated in severe renal and/or hepatic impairment. • Dosage adjustment required in moderate renal impairment.
Uroxatral (alfuzosin)	Tablets (extended-release)	Oral	Daily	• Contraindicated in moderate to severe hepatic impairment. • Caution should be used in patients with severe renal impairment.
Single Entity Agents: 5-α-Reductase Inhibitors				
Avodart (dutasteride)	Capsules	Oral	Daily	• Contraindicated for use in pregnancy because it may cause harm to the male fetus. • Not indicated for use in women.
Proscar (finasteride)	Tablets	Oral	Daily	• Pregnancy Category X* • Not indicated for use in women. • Should be used with caution in patients with hepatic impairment.
Single Entity Agents: PDE5 Inhibitors				
Cialis (tadalafil)	Tablets	Oral	Daily	• Dosage adjustment may be required in mild or moderate renal and/or hepatic impairment. Use is not recommended in severe renal or hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Combination Product				
Jalyn (dutasteride/tamsulosin)	Capsules	Oral	Daily	• Pregnancy Category X* • Not indicated for use in women. • Should be taken 30 minutes following the same meal each day.

*Pregnancy Category X = contraindicated in pregnant women due to evidence of fetal abnormalities from adverse effects data from investigational or marketing experience. Risks of use of the drug in pregnant women clearly outweigh potential benefits.

See the current prescribing information for full details.

CONCLUSION

- BPH contributes to LUTS such as increased frequency of urination, nocturia, urinary hesitancy, and weak urinary streams (*McVary 2019b, McVary et al 2011*).
- Current treatment options include watchful waiting, surgical interventions, and pharmacological therapies (*McVary et al 2011*).
- α_1-adrenergic blocking agents are the most widely used agents for the management of BPH (*McVary et al 2011*).
  - Cardura (doxazosin), Minipress (prazosin), and Hytrin (terazosin) are non-uroselective and are associated with a higher risk of orthostatic hypotension; therefore, therapy should be started at the lowest possible dose and titrated to the maximally tolerated dose.
  - Flomax (tamsulosin), Rapaflo (silodosin), and Uroxatral (alfuzosin) are uroselective and are therefore associated with a lower risk of orthostatic hypotension.
  - The American Urological Association treatment guideline and a meta-analysis have indicated no differences in efficacy among doxazosin, tamsulosin, terazosin, and alfuzosin in the management of BPH (*Djavan et al 1999, McVary et al 2011*).
  - Silodosin was also shown to be similarly effective to tamsulosin in improving IPSS and LUTS secondary to BPH (*Choo et al 2014, Cui et al 2012, Jung et al 2017, Miyakita et al 2010, Shirakawa et al 2013, Watanabe et al 2011*).
- The 5-α-reductase inhibitors are FDA-approved for the management of BPH symptoms in men with an enlarged prostate and may be used to prevent clinical progression of BPH (*McVary et al 2011*).
  - Avodart (dutasteride) and Proscar (finasteride) are teratogenic and contraindicated in women. Therapy may increase the risk of high-grade prostatic cancer; therefore, evaluation for prostatic cancer should be performed prior to initiation of therapy and periodically during treatment.
  - Clinical trials have shown no significant differences between dutasteride and finasteride in reducing prostate volume and improving LUTS and maximum flow rate in men with BPH (*Nickel et al 2011*).
  - When compared to α_1-adrenergic blocking agents, 5-α-reductase inhibitors were associated with a slower onset of improvement in BPH symptoms (*Lee 2002*).
- Combination therapy with an α_1-adrenergic blocking agent and a 5-α-reductase inhibitor may be used in men with an enlarged prostate (*McVary et al 2011*).
  - In men with an enlarged prostate, combination therapy may lead to improved symptom control compared to monotherapy with either an α_1-adrenergic blocker or a 5-α-reductase inhibitor (*Kaplan et al 2006*). However, available data are inconsistent in this area, with another study demonstrating symptom control with combination therapy to be no better than with α_1-adrenergic blocker monotherapy (Kirby et al 2003b). A recent meta-analysis found benefit with the combination of dutasteride and tamsulosin, which was significant compared to tamsulosin alone (*Zhou et al 2019*).
  - Jalyn (dutasteride/tamsulosin) has been shown to reduce the risk of acute urinary retention or BPH-related surgery compared to tamsulosin monotherapy and watchful waiting (*Becher et al 2009, Roehrborn et al 2015*).
- Cialis (tadalafil), a PDE5 inhibitor, was approved by the FDA for the management of BPH. The American Urological Association treatment guideline currently does not have a recommendation for the place in therapy for PDE5 inhibitors (*McVary et al 2011*); however, the European Association of Urology treatment guideline suggests that PDE5 inhibitors are effective in patients with moderate-to-severe LUTS (*Gravas et al 2019*).
  - Tadalafil may cause hypotension and should not be administered within 48 hours of nitrate use.
  - Three meta-analyses and several other clinical studies have shown that tadalafil was safe and effective in improving IPSS and LUTS secondary to BPH in men with or without concomitant erectile dysfunction (*Broderick et al 2010,*

Dmochowski et al 2013, Donatucci et al 2011, Egerdie et al 2012, Gacci et al 2012, Gacci et al 2016, Goldfischer et al 2012, Oelke et al 2012, Porst et al 2011, Roehrborn et al 2008, Takahashi et al 2018, Wang et al 2018).
  - Combination therapy with the 5-α-reductase inhibitor finasteride and tadalafil was associated with modest improvements in urinary symptoms and significantly improved patient, but not clinician, global impression of improvement when compared with finasteride monotherapy (*Casabe et al 2014, Pattanaik et al 2018*). Guidance has been added to the tadalafil prescribing information regarding dosing for this combination.
  - Combination of a PDE5 inhibitor and an α_1-adrenergic blocking agent may have a small benefit on symptom score compared to monotherapy with an α_1-adrenergic blocking agent (*Gacci et al 2012, Kallidonis et al 2019, Pattanaik et al 2018, Zhang 2019*).
- Currently, Avodart, Cardura, Cialis, Minipress, Flomax, Hytrin, Jalyn, Proscar, Rapaflo, and Uroxatral are available generically. The brand product for Hytrin is no longer on the market; the product is only available generically.

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