Benign Prostatic Hyperplasia (BPH) Treatments Therapeutic Class Review (TCR)

December 1, 2022

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCREditor@magellanhealth.com.

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Hypertension	BPH
Alpha-Blockers			
alfuzosin ER (Uroxatral®)[1]	generic, Concordia		X
doxazosin (Cardura®)[2]	generic, Pfizer/Viatris	X	X
doxazosin ER (Cardura XL®)[3]	Pfizer/Viatris		X
silodosin (Rapaflo®)[4]	generic, Allergan		X
tamsulosin (Flomax®)[5]	generic, Sanofi-Aventis		X
terazosin[6]	generic	X	X
5-Alpha Reductase (5AR) Inhibitors			
dutasteride (Avodart®)[7]	generic, GlaxoSmithKline/ Woodward		▪ Treatment of symptomatic BPH in men with enlarged prostate to improve symptoms, reduce the risk of acute urinary retention, and reduce the risk of the need for BPH-related surgery ▪ Treatment of symptomatic BPH in combination with the alpha-blocker, tamsulosin, in men with an enlarged prostate ▪ Limitations of use: Not approved for the prevention of prostate cancer
finasteride (Proscar®)[8]	generic, Merck Sharp & Dohme/ Organon		▪ Treatment of symptomatic BPH in men with enlarged prostate to improve symptoms, reduce the risk of acute urinary retention, and reduce the risk of the need for BPH-related surgery including transurethral resection of the prostate (TURP) or prostatectomy ▪ Treatment of symptomatic BPH in combination with the alpha-blocker, doxazosin, to reduce the risk of symptomatic progression of BPH ▪ Limitations of use: Not approved for the prevention of prostate cancer
5-Alpha Reductase (5AR) Inhibitor / Alpha-Blocker Combinations			
dutasteride/tamsulosin (Jalyn®)*[9]	generic, GlaxoSmithKline/ Woodward		▪ Treatment of symptomatic BPH in men with enlarged prostate ▪ Limitations of use: Not approved for the prevention of prostate cancer
Phosphodiesterase 5 (PDE5) Inhibitors			
tadalafil (Cialis®)[10]	generic, Eli Lilly		▪ Treatment of signs and symptoms of BPH ▪ Note: tadalafil is also indicated for the treatment of erectile dysfunction, with or without BPH; this indication will not be included in this review ▪ Limitations of use: If tadalafil is used with finasteride to begin BPH treatment, its use is recommended for up to 26 weeks ▪ The incremental benefit of tadalafil decreases from 4 weeks until 26 weeks, and the incremental benefit of tadalafil beyond 26 weeks is unknown

BPH = Benign Prostatic Hyperplasia; ER = extended release

FDA-Approved Indications (continued)

Drug	Manufacturer	Hypertension	BPH
5-Alpha Reductase (5AR) Inhibitor / Phosphodiesterase 5 (PDE5) Inhibitor Combinations			
finasteride/tadalafil (Entadfi™)*[11]	Veru		▪ Treatment of symptomatic BPH in men with enlarged prostate for up to 26 weeks ▪ The incremental benefit of tadalafil decreases from 4 weeks until 26 weeks, and the incremental benefit of tadalafil beyond 26 weeks is unknown

BPH = Benign Prostatic Hyperplasia

* Approved under the FDA's 505(b)(2) pathway that allows at least some of the information submitted for approval to be from studies not conducted by or for the applicant.

OVERVIEW

Benign prostatic hyperplasia (BPH) is one of the most common conditions in aging men. As many as 14 million men in the United States have symptoms related to BPH.[12] An estimated 50% of men experience histopathologic BPH by age 60 years; by age 85, 90% of men have BPH. The symptoms of BPH are induced by hyperplastic changes in prostate tissue, leading to prostatic enlargement. The resulting obstruction increases urinary outflow resistance and results in an impaired detrusor muscle response. Although prostatic enlargement is mediated by epithelial and smooth muscle cells, the etiology of initial hyperplastic changes is currently unknown. Hormonal changes associated with aging are likely involved.

Patients with BPH may present with bothersome lower urinary tract symptoms (LUTS) resulting from irritation (categorized as storage symptoms of urinary frequency, nocturia, urgency, urge incontinence) and/or obstruction (categorized as voiding symptoms such as difficulty initiating urination or passing urine, weak stream, involuntary postvoid dripping of urine, and sensation of incomplete bladder emptying).[13] Most men with BPH experience only mild or moderate symptoms of obstruction. Severe BPH, more likely to occur beyond the 6th decade of life, can lead to bladder outlet obstruction which may result in complications such as renal insufficiency, recurrent urinary tract infections, hematuria, and bladder stones.[14,15] More serious complications, such as uremia and irreversible bladder dysfunction, are uncommon.

Drugs used in the treatment of BPH relieve LUTS and prevent complications and, in some cases, are an alternative to surgical intervention. The 2021 American Urological Association (AUA) guidelines state that alfuzosin (Uroxatral), doxazosin (Cardura), silodosin (Rapaflo), tamsulosin (Flomax), and terazosin should be offered for patients with bothersome, moderate to severe LUTS/BPH.[16] When an alpha-blocker is chosen, the specific choice should be based on patient age, comorbidities, and the adverse event profile of the specific medication. Although there are slight differences in the adverse event profiles of these agents, the AUA states that all agents have equal clinical effectiveness. Additionally, equal efficacy for all alpha-blockers has been demonstrated with regard to various subsets of patients; therefore, it is not recommended to switch between different alpha-blockers if a patient fails to have adequate improvement with the first agent at an appropriate dose. However, switching alpha-blockers can be done to improve an adverse effect, if needed. The AUA recommends that when alpha-blocker therapy is started, patients with planned cataract surgery are informed of the potential risks regarding intraoperative floppy iris syndrome and should discuss these risks with their ophthalmologist. The guidelines also state that the 5-alpha reductase inhibitors, finasteride (Proscar) and dutasteride (Avodart), should be used as a treatment option for patients with LUTS/BPH associated with demonstrable prostatic enlargement. The 5-alpha reductase inhibitors alone or in combination with

alpha-blockers may be used to prevent progression of LUTS/BPH and to reduce the risk of urinary retention and future prostate-related surgery.[17] They may also be considered to reduce intraoperative bleeding and peri- or postoperative need for blood transfusion after transurethral resection of the prostate (TURP) or other surgical intervention for BPH. Patients should be counseled on the risks of side effects with 5-alpha reductase inhibitors, including sexual dysfunction, and the low risk of prostate cancer. The guidelines recommend the PDE5 inhibitor tadalafil at a dose of 5 mg daily as a potential treatment option, regardless of comorbid erectile dysfunction (ED). For patients with LUTS associated with demonstrable prostatic enlargement, the combination of a 5-alpha reductase inhibitor and an alpha-blocker may be considered, however, the combination of low-dose 5 mg daily tadalafil with an alpha-blocker for LUTS/BPH should not be used, as it does not offer an advantage for symptom improvement over either agent alone.

PHARMACOLOGY[18,19,20,21,22,23,24,25,26,27,28]

The dynamic component of BPH is associated with prostatic smooth muscle tone. A normal prostate gland is comprised of smooth muscle or stromal tissue and glandular tissue. Unlike a normal prostate, the prostate in patients with BPH contains a higher ratio (5:1) of stromal to glandular tissue.[29] Prostatic smooth muscle is innervated by α_1- and α_2-adrenergic receptors. The outer prostatic capsule, bladder neck, and proximal urethra also have a high concentration of α_1-adrenergic receptors. Excessive stimulation of postsynaptic α_1-adrenergic receptors causes the smooth muscle of the prostate, prostatic capsule, bladder neck, and proximal urethra to contract, and causes a decrease in the urethral lumen. Resultant obstructive voiding symptoms include difficulty in urination, a decreased force of urinary stream, urinary hesitancy, straining to void, incomplete bladder emptying, urinary dribbling, and intermittent urinary stream.[30]

Administration of α_1-blockers relaxes both the bladder neck and prostatic smooth muscle, thus decreasing pressure in the bladder and urethra and improving urinary flow.[31] These agents are more effective at improving obstructive symptoms than irritative symptoms.[32] Tamsulosin (Flomax), alfuzosin (Uroxatral), and silodosin (Rapaflo) are α-blockers related to doxazosin and terazosin. Unlike the other agents, tamsulosin, alfuzosin, and silodosin have higher affinity and selectivity for α_{1a}-adrenergic receptors, which are located in nonvascular smooth muscle, as is found in the prostate, than for α_{1b}-adrenergic receptors located in vascular smooth muscle. This selectivity may result in a decreased incidence of adverse cardiovascular effects with tamsulosin, alfuzosin, and silodosin.[33]

The static element of BPH is associated with increased prostatic tissue mass; this mass mechanically blocks the urethra and produces resistance to urinary flow from the bladder. Testosterone is a key element in the pathophysiology of BPH in that it is converted in the prostate to 5α-dihydrotestosterone (DHT), which stimulates growth of glandular and stromal cells.[34,35] Over time, progressive proliferation may lead to increased prostate size and bladder outlet obstruction.[36] The intracellular enzyme 5-alpha-reductase (5AR) is responsible for the conversion of testosterone to DHT, and 5α-reductase (5AR) inhibitors block this action.[37] Proliferation of prostatic epithelial cells declines, resulting in decreased size of the prostate gland.

Dutasteride (Avodart) and finasteride (Proscar) are selective inhibitors of 5AR (5-alpha reductase). When given on a chronic basis, these agents decrease the serum concentration of DHT. Dutasteride inhibits both type I and type II isoforms of 5AR, while finasteride specifically inhibits the type II isoform. The type II isoenzyme is primarily active in the reproductive tissues. The type I isoenzyme is also responsible for testosterone conversion in the skin and liver. These agents have no affinity for the androgen receptor.

Tadalafil (Cialis) is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). The effect of PDE5 inhibition on cGMP concentration in the corpus cavernosum and pulmonary arteries is also observed in the smooth muscle of the prostate, the bladder, and their vascular supply. The mechanism for reducing BPH symptoms has not been established.

PHARMACOKINETICS[38,39,40,41,42,43,44,45,46,47,48]

Drug	Bioavailability (%)	Protein Binding (%)	Peak Concentration (hrs)	Half-Life (hrs)	Liver Metabolism	Excretion in Urine (%)
Alpha-Blockers[49]						
alfuzosin ER (Uroxatral)	49-64*	82-90	8	10	0-demethylation N-dealkylation oxidation	24
doxazosin (Cardura)	65	98	2-3	22	0-demethylation hydroxylation	9
doxazosin ER (Cardura XL)	54-59†	98	8-9	15-19	cytochrome P450	9
silodosin (Rapaflo)	32	97	2.6	13.3	glucuronidation, alcohol and aldehyde dehydrogenase and cytochrome P450	33.5
tamsulosin (Flomax)	90	94-99	4-6‡	14-15	cytochrome P450	76
terazosin	90	90-94	1-2	12-14	0-demethylation N-dealkylation hydrolysis	40
5-Alpha Reductase (5AR) Inhibitors						
dutasteride (Avodart)	60	> 96	-3	5 weeks	cytochrome P450 (CYP3A4 and CYP 3A5)	< 1
finasteride (Proscar)	63		-2	6-8	cytochrome P450 (CYP3A4)	39
5-Alpha Reductase (5AR) Inhibitors / Alpha-Blocker Combinations						
dutasteride/ tamsulosin (Jalyn)	Refer to data on component ingredients above					
Phosphodiesterase 5 (PDE5) Inhibitors						
tadalafil (Cialis)	not determined	94	2	17.5	cytochrome P450	36
5-Alpha Reductase (5AR) Inhibitor / Phosphodiesterase 5 (PDE5) Inhibitor Combinations						
finasteride/ tadalafil (Entadfi)	finasteride: 63% tadalafil: not determined	finasteride: 90% tadalafil: 94%	finasteride: 1.8-2 tadalafil: 3	finasteride: 6.63 tadalafil: 22.33	finasteride: CYP3A4 tadalafil: CYP3A4	finasteride: 39 tadalafil: 36

* The extent, but not the rate, of absorption is reduced by 50% in fasting conditions.

† Relative bioavailability compared to doxazosin IR.

‡ Food delays time to achieve peak tamsulosin (Flomax) serum concentrations by 2 to 3 hours and decreases total amount of drug absorbed by 30%. The manufacturer recommends that tamsulosin (Flomax) be taken about 30 minutes after the same meal each day.

Finasteride (Proscar) has a shorter terminal half-life (6 hours) than dutasteride (Avodart) (5 weeks). Compared to the α-blockers, the onset of action of 5AR inhibitors is slower (1 to 3 months for dutasteride and 3 to 6 months for finasteride). This difference is related to the mechanism of action of the drugs more than to the pharmacokinetics.

CONTRAINDICATIONS/WARNINGS[50,51,52,53,54,55,56,57,58,59,60]

Alpha-Blockers

In patients with moderate or severe hepatic insufficiency, a reduction in clearance results in 3-fold to 4-fold higher plasma concentrations of alfuzosin (Uroxatral) compared to those in healthy subjects. As a result, alfuzosin (Uroxatral) is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh categories B and C). Alfuzosin should not be co-administered with potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and ritonavir, since alfuzosin blood levels are increased by these agents. Alfuzosin is contraindicated in patients with known hypersensitivity. Alfuzosin should be discontinued if symptoms of angina pectoris should newly appear or worsen. Additionally, patients with a congenital or acquired QT prolongation who are receiving alfuzosin should be observed for QT prolongation. There has been no signal of torsades de pointes in the extensive post-marking experience with alfuzosin.

Doxazosin (Cardura, Cardura XL) and terazosin are contraindicated in patients with a known sensitivity to quinazolines. The FDA has issued a boxed warning for doxazosin and terazosin regarding syncope and a potential "first-dose" hypotension and/or syncope with these agents, especially when given in conjunction with other antihypertensive drugs. Marked lowering of blood pressure can occur with alpha-blockers. Postural hypotension or syncope can occur with the first dose or first few days of therapy. Treatment with alpha-blockers should be initiated at bedtime using the lowest dose, and then increased slowly. Additional hypotensive agents should be co-administered with caution. If syncope does occur, patients should be placed in a recumbent position and treated supportively, as necessary. Doxazosin extended-release (Cardura XL) should be used with caution in patients with evidence of mild or moderate hepatic dysfunction and is not recommended for use in patients with severe hepatic impairment.

Tamsulosin (Flomax) is contraindicated in patients with known hypersensitivity to tamsulosin; reactions include skin rash, urticaria, pruritus, angioedema, and respiratory symptoms. For patients that report a serious or life threatening sulfa allergy, caution is warranted with administering of tamsulosin. Doses of tamsulosin higher than 0.4 mg (e.g., 0.8 mg) should not be used in combination with strong inhibitors of CYP3A4, such as ketoconazole.

Silodosin (Rapaflo) is contraindicated in patients who are hypersensitive to silodosin or any other component of the formulation, patients taking other alpha-blockers, and patients on CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, itraconazole, ritonavir). Silodosin has not been studied in patients with severe hepatic impairment and is, therefore, contraindicated in these patients. The use of silodosin is also contraindicated in patients with severe renal impairment (creatinine clearance [CrCl] ≤ 30 mL/minute). Clinical studies have shown that the effect of moderate renal impairment (CrCl 30 to 50 mL/min) on the pharmacokinetics have resulted in approximately a 3-fold higher plasma concentration

of silodosin compared to subjects with normal renal function. Dosages of silodosin should be reduced in patients with moderate renal impairment.

Patients should be evaluated to rule out carcinoma of the prostate prior to initiating therapy for BPH since this cancer and BPH cause many of the same symptoms.

Marked lowering of blood pressure can occur with alpha-blockers. Postural hypotension or syncope can occur with the first dose or first few days of therapy. Treatment with alpha-blockers should be initiated at bedtime using the lowest dose, and then increased slowly. Additional hypotensive agents should be co-administered with caution.

Intraoperative floppy iris syndrome (IFIS) has been observed during cataract or glaucoma surgery in some patients treated with α_1-blockers. Most reports involved patients taking an α_1-blocker when IFIS occurred, but, in some cases, the α_1-blocker had been stopped prior to surgery. It is recommended that male patients being considered for cataract surgery be specifically questioned during their pre-operative medication history to ascertain whether they have previously taken any of the α_1-blockers and that therapy not be initiated prior to the scheduled surgery.[61]

Priapism is a rare occurrence with alpha-blockers, but it can lead to permanent impotence if not properly treated.

5AR Inhibitors

Dutasteride (Avodart) and finasteride (Proscar) are not to be administered to women or children. Additionally, women who are pregnant or who may become pregnant should not handle dutasteride capsules or finasteride tablets, as the drug may be absorbed through the skin and broken or leaking capsules pose a fetal anomaly risk to a male fetus. In addition, to prevent exposure of dutasteride to a pregnant female transfusion recipient, men being treated with dutasteride should not donate blood for at least 6 months following their last dose.

Dutasteride capsules should be swallowed whole due to the risk of irritation of the oropharyngeal mucosa if crushed or chewed.

5AR inhibitors may reduce total serum prostate-specific antigen (PSA) concentrations by approximately 50% within 3 to 6 months of treatment. Interpretation of serial PSAs should follow the establishment of a baseline PSA after 3 to 6 months of therapy. Increases in PSA values above this baseline may indicate the presence of prostate cancer. Interpretation of values after 6 months or more of therapy should be made by doubling the PSA value for comparison with normal values in untreated patients.

Two studies, 1 with dutasteride (Avodart) and 1 with finasteride (Proscar), show that 5AR inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5AR inhibitors to reduce prostate volume, or study-related factors, impacted the results of the studies has not been established.

Patients with large residual urinary volume and/or severely diminished urinary flow should be carefully monitored for obstructive uropathy and may not be candidates for therapy with the 5AR inhibitors, dutasteride and finasteride. Prior to initiating treatment with dutasteride or finasteride for BPH, consideration should be given to other urological conditions that may cause similar symptoms.

Alpha-Blocker and 5AR Inhibitor Combinations

As a combination alpha blocker and 5AR inhibitor product, adverse reactions, warnings, and contraindications consist of the reactions listed above for the component drugs.

Phosphodiesterase 5 (PDE5) Inhibitors

Tadalafil (Cialis) is contraindicated in patients who are using any form of organic nitrate, either regularly or intermittently. Tadalafil is also contraindicated in patients with a history of known serious hypersensitivity reaction to tadalafil. PDE5 inhibitors, such as tadalafil, may potentiate hypotensive effects of guanylate cyclase (GC) stimulators (e.g., riociguat); concomitant use is contraindicated.

Tadalafil can cause mild systemic vasodilatory effects that may result in transient decreases in blood pressure. Patients with severely impaired autonomic control of blood pressure may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors. Tadalafil is not recommended in combination with alpha blockers for the treatment of BPH because efficacy of the combination has not been adequately studied and because of the risk of blood pressure lowering.

Patients should not use tadalafil if sexual activity is inadvisable due to cardiovascular status.

Patients should seek emergency treatment if they experience an erection lasting > 4 hours. Use tadalafil with caution in patients predisposed to priapism.

Patients should stop tadalafil and seek medical care if a sudden loss of vision occurs in 1 or both eyes, which could be a sign of non-arteritic ischemic optic neuropathy (NAION). Discuss increased risk of NAION in patients with history of NAION.

Patients should stop tadalafil and seek prompt medical attention in the event of sudden decrease or loss of hearing.

A risk assessment should be conducted prior to initiating tadalafil in patients with bleeding disorders or active peptic ulcers due to the potential for PDE5 inhibition to affect platelet activity.

Prior to initiating treatment with tadalafil for BPH, consideration should be given to other urological conditions that may cause similar symptoms.

PDE5 Inhibitor and 5AR Inhibitor Combinations

Warning and contraindications for the PDE5 inhibitor and 5AR inhibitor combination product for the treatment of BPH, Entadfi (finasteride and tadalafil), consist of the reactions listed above for the component drugs.

DRUG INTERACTIONS[62,63,64,65,66,67,68,69,70,71,72]

Alpha-Blockers

Concomitant use of alpha-blockers with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, itraconazole, ritonavir) may cause an increased alpha-blocker exposure. The manufacturers of alfuzosin (Uroxatral) and silodosin (Rapaflo) state that use of these agents with strong CYP3A4 inhibitors are contraindicated. The manufacturer recommends against the concomitant administration of tamsulosin (Flomax, Jalyn) and strong CYP3A4 inhibitors, due to significant increase in tamsulosin exposure. Co-administration of tamsulosin-containing products should be used with caution with moderate CYP3A4 inhibitors (diltiazem, erythromycin, verapamil), strong (e.g., paroxetine) or moderate (e.g., terbinafine)

CYP2D6 inhibitors, or a combination of both CYP3A4 and CYP2D6 inhibitors. Also, caution should be used when prescribing tamsulosin to patients who are poor metabolizers of CYP2D6.

Concurrent administration of doxazosin (Cardura) and terazosin with diuretics or other antihypertensive agents results in additive reduction in blood pressure. Initiation of terazosin in patients receiving beta-blockers can result in an accentuated first-dose effect. Based on differences in dose and formulation, the applicability of interactions to doxazosin ER (Cardura XL) is unknown.

Alfuzosin should not be co-administered with potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and ritonavir, since alfuzosin blood levels are increased by these agents. Doxazosin ER, dutasteride, and tamsulosin should be co-administered with CYP3A4 inhibitors with caution.

In addition, tamsulosin should be co-administered with caution in combination with moderate or strong inhibitors of CYP2D6 or CYP3A4. Tamsulosin, when given concurrently, should not exceed 0.4 mg daily due to the CYP 450 inhibition by cimetidine, paroxetine, and other strong CYP3A4 inhibitors. While definitive evidence of interaction with warfarin is inconclusive, the manufacturer recommends caution in concomitant administration with tamsulosin.

Although the pharmacokinetic and pharmacodynamic interactions with use of multiple alpha-blockers have not been determined, interactions may be expected, and these products should not be used in combination. Therefore, concomitant use of more than one alpha-blocker, including tamsulosin, alfuzosin, silodosin, prazosin, terazosin, and doxazosin, is not recommended. Concurrent use of alpha-blockers with reserpine or mecamylamine is not recommended. Alpha-blocker use with centrally acting alpha agonists, including clonidine, methyldopa, guanfacine, and guanabenz, is not recommended.

The administration of alpha-blockers and antihypertensive medications has the potential to cause hypotension in some patients. Caution is advised when alpha-adrenergic blocking agents are co-administered with phosphodiesterase type 5 inhibitors. Both agents are vasodilators that may lower blood pressure and concomitant use can result in symptomatic hypotension.

The administration of food may lead to decreased plasma concentrations of alpha-blockers. The manufacturers of these products recommend that alfuzosin, tamsulosin, and silodosin should be taken immediately following a meal, which may decrease the risk of adverse effects.

The release of doxazosin ER may be delayed if given with drugs that decrease gastrointestinal motility.

5AR Inhibitors

Dutasteride (Avodart, Jalyn) is extensively metabolized by CYP3A4 isoenzymes. Although the effect of potent CYP3A4 inhibitors on dutasteride has not been studied, the potential for drug-drug interactions exists between these agents and caution is advised when prescribing dutasteride in patients chronically taking potent CYP3A4 enzyme inhibitors (e.g., ritonavir). No clinically significant drug-drug interactions have been identified with finasteride (Proscar) and drugs that are linked to CYP P450 enzymes.

The clearance of dutasteride is reduced by approximately 40% in patients given diltiazem or verapamil. The bioavailability of dutasteride is increased by 31% when given concomitantly with terazosin. Due to the large therapeutic index of dutasteride, the interactions are, in most cases, of little clinical significance.

Alpha-Blocker and 5AR Inhibitor Combinations

The drug interactions for the combination product dutasteride and tamsulosin are in keeping with the interactions of the individual components. The combination does not produce any new or increased interactions with other medications.

Phosphodiesterase 5 (PDE5) Inhibitors

Tadalafil (Cialis) can potentiate the hypotensive effects of nitrates, alpha blockers, antihypertensives, guanylate cyclase (GC) stimulators, or alcohol.

CYP3A4 inhibitors (e.g., ketoconazole, ritonavir) may increase tadalafil exposure. For concomitant use with potent CYP3A4 inhibitors, dose adjustment of tadalafil may be needed.

CYP3A4 inducers (e.g., rifampin) may decrease tadalafil exposure.

PDE5 Inhibitor and 5AR Inhibitor Combinations

Drug interactions for the combination product finasteride and tadalafil (Entadfi) align with the interactions of the individual components. The combination does not produce any new or increased interactions with other medications.

ADVERSE EFFECTS[73,74,75,76,77,78,79,80,81,82,83]

Drug	Asthenia	Headache	Dizziness	Hypotension	Altered libido	Abnormal ejaculation	Impotence
Alpha-Blockers							
alfuzosin ER (Uroxatral)	2.7	3	5.7	0.4	nr	nr	1-2
doxazosin (Cardura)	8	9.9	15.6	1.7	0.8	≤ 1	1.1
doxazosin ER (Cardura XL)	3.9	6	5.3	1.7	nr	nr	< 1
silodosin (Rapaflo)	1-2	2.4	3.2	2.6	nr	28.1	nr
tamsulosin (Flomax)	7.8-8.5	19.3-21.1	14.9-17.1	0.2-0.4	1-2	8.4-18.1	reported
terazosin	7.4	4.9	9.1	≤ 5.5	nr	nr	1.6-2
5-Alpha Reductase (5AR) Inhibitors							
dutasteride (Avodart)	nr	nr	< 0.4	nr	< 3	1.4	0.8-4.7
finasteride (Proscar)	1.6-5.3	2	2.3-7.4	1.2	2-10	1.8-7.2	2-18.5
5-Alpha Reductase (5AR) Inhibitors / Alpha-Blocker Combinations							
dutasteride/ tamsulosin (Jalyn)	nr	nr	0.2-1.1	nr	0.1-4.5	0.1-7.6	0.3-5.5
Phosphodiesterase 5 (PDE5) Inhibitors							
tadalafil (Cialis)	< 2	4.1	1	< 2	nr	nr	nr

nr = not reported

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive.

The safety profile of finasteride/tadalafil (Entadfi) was based on placebo-controlled trials of tadalafil monotherapy and finasteride monotherapy.

As with any other non-deformable material, caution should be used when administering doxazosin ER (Cardura XL) to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic). Rare reports of obstructive symptoms in patients with known strictures administered another drug in this non-deformable extended-release formulation exist. Markedly increased GI retention times, as may occur in patients with chronic constipation, can increase systemic exposure to doxazosin and thereby potentially increase adverse effects.

In post-marketing experience with finasteride, the following additional adverse events have been reported: testicular pain, male infertility and/or poor seminal quality, hematospermia, depression, male breast cancer, and erectile dysfunction (ED) and decreased libido that continued after discontinuation of treatment.

A meta-analysis evaluated the impact of alpha blockers and 5AR inhibitors on ejaculatory dysfunction (23 trials).[84] Both alpha blockers (odds ratio [OR], 5.88; p<0.0001) and 5AR inhibitors (OR, 2.73; p<0.0001) were associated with a higher risk of ejaculatory dysfunction compared to placebo. The risk was higher for tamsulosin (OR, 8.58; p=0.006) and silodosin (OR, 32.5; p<0.0001) than doxazosin and terazosin, which both had a similar risk to placebo. Both finasteride (OR, 2.7; p<0.001) and dutasteride (OR, 2.81; p=0.0002) had a higher risk of ejaculatory dysfunction than placebo.

SPECIAL POPULATIONS[85,86,87,88,89,90,91,92,93,94,95]

Pediatrics

None of the drugs are indicated for use in the pediatric population nor are there significant studies in children available.

Pregnancy

Women who are pregnant or may become pregnant should not come into contact with dutasteride (Avodart, Jalyn) or finasteride (Proscar, Entadfi) because of the possibility of fetal anomaly to a male fetus. Dutasteride and finasteride were previously Pregnancy Category X, but labeling has been updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR); use of these agents is not indicated in women and is contraindicated in women who are pregnant.

Alfuzosin (Uroxatral), silodosin (Rapaflo), tadalafil (Cialis), and tamsulosin (Flomax) were previously Pregnancy Category B, but labeling have been updated to comply with PLLR. These products are not indicated for use in women. The remaining products in this class are Pregnancy Category C. Labeling for doxazosin (Cardura) and doxazosin ER (Cardura XL) have been updated to comply with the PLLR and state that there is not enough information on use in pregnant women to inform of drug-associated risks.

In clinical studies in males taking tadalafil, decreased sperm concentrations were reported after 6 and 9 months of tadalafil 10 mg and 20 mg, respectively; however, clinical significance is unknown.

Elderly

The cumulative incidence of hypotension with doxazosin (Cardura) and doxazosin ER (Cardura XL) appears to be age-related in clinical studies. Caution should be used in the elderly.

No overall differences in safety or effectiveness were observed in the geriatric population when compared to younger subjects for alfuzosin, tamsulosin, and silodosin, although the greater sensitivity of some elderly patients cannot be ruled out.

Hepatic Insufficiency

Because the liver is the primary metabolic pathway for metabolism of drugs in this class, caution should be used when administering any agent to patients with hepatic insufficiency.

Alfuzosin is contraindicated for use in patients with moderate to severe hepatic impairment (Child-Pugh categories B and C). The pharmacokinetics of alfuzosin has not been studied in patients with mild hepatic insufficiency.

Patients with moderate hepatic dysfunction do not require an adjustment in the tamsulosin or silodosin dosage. Tamsulosin and silodosin have not been studied in patients with severe hepatic dysfunction.

Doxazosin ER is also not recommended for use in patients with severe hepatic impairment. Dutasteride and finasteride should be used with caution in patients with severe hepatic insufficiency due to extensive metabolism by the liver. Finasteride/tadalafil (Entadfi) should not be used in patients with severe hepatic impairment (Child-Pugh class C) and should be used with caution in mild to moderate hepatic impairment (Child-Pugh class A or B).

Tadalafil (Cialis) for once daily use has not been extensively evaluated in patients with mild or moderate hepatic impairment. Therefore, caution is advised if tadalafil for once daily use is prescribed to these patients. Because of insufficient information in patients with severe hepatic impairment, use of tadalafil in this group is not recommended.

Renal Insufficiency

Silodosin (Rapaflo) is contraindicated in patients with severe renal impairment (CrCl ≤ 30 mL/min).

Due to increased tadalafil (Cialis) exposure (area under the concentration curve [AUC]), limited clinical experience, and the lack of ability to influence clearance by dialysis, tadalafil for once daily use is not recommended in patients with CrCl < 30 mL/min or patients on hemodialysis. In patients with CrCl of 30 to 50 mL/min, start treatment at 2.5 mg once daily, and increase dose to 5 mg once daily based upon individual response. Finasteride/tadalafil (Entadfi) is not recommended in patients with CrCl < 50 mL/min or on hemodialysis.

DOSAGES[96,97,98,99,100,101,102,103,104,105,106]

Drug	Initial Dose for BPH	Maintenance Dose for BPH	Dosage Forms
Alpha-Blockers			
alfuzosin ER (Uroxatral)	10 mg daily	10 mg daily	10 mg extended-release tablets
doxazosin (Cardura)	1 mg daily	1 – 8 mg daily	1 mg, 2 mg, 4 mg, 8 mg tablets
doxazosin ER (Cardura XL)	4 mg daily	4 – 8 mg daily taken with breakfast	4 mg, 8 mg extended-release tablets

Dosages (continued)

Drug	Initial Dose for BPH	Maintenance Dose for BPH	Dosage Forms
Alpha-Blockers *(continued)*			
silodosin (Rapaflo)*	8 mg daily Moderate renal impairment: 4 mg daily	8 mg daily Moderate renal impairment: 4 mg daily	4 mg, 8 mg capsules
tamsulosin (Flomax)	0.4 mg daily	0.4 – 0.8 mg daily	0.4 mg capsules
terazosin	1 mg daily	2 – 20 mg daily	1 mg, 2 mg, 5 mg, 10 mg capsules
5-Alpha Reductase (5AR) Inhibitors			
dutasteride (Avodart)†	0.5 mg daily	0.5 mg daily	0.5 mg capsules
finasteride (Proscar)‡	5 mg daily	5 mg daily	5 mg tablets
5-Alpha Reductase (5AR) Inhibitors / Alpha-Blocker Combinations			
dutasteride/ tamsulosin (Jalyn)	1 capsule daily	1 capsule daily	0.5 mg dutasteride/0.4 mg tamsulosin per capsule
Phosphodiesterase 5 (PDE5) Inhibitors			
tadalafil (Cialis)§	5 mg daily CrCl 30 – 50 mL/min: 2.5 mg daily	5 mg daily CrCl 30 – 50 mL/min: may increase to 5 mg daily based on individual response	2.5 mg, 5 mg, 10 mg, 20 mg tablets (10 mg and 20 mg strengths are not used in BPH)
5-Alpha Reductase (5AR) Inhibitor / Phosphodiesterase 5 (PDE5) Inhibitor Combinations			
finasteride/tadalafil (Entadfi)¶	1 capsule daily	1 capsule daily	5 mg finasteride/5 mg tadalafil per capsule

* For silodosin, capsules may be opened, and contents sprinkled on a tablespoonful of applesauce. Follow immediately with 8 oz. of cool water to ensure complete swallowing of dose.

† For dutasteride, the same dose of 0.5 mg daily is used in combination therapy with tamsulosin. Also, the capsules should be swallowed whole and not chewed or opened.

‡ For finasteride, the same dose of 5 mg daily is used in combination therapy with doxazosin.

§ For tadalafil, the dose should be taken at approximately the same time every day.

¶ For finasteride/tadalafil, the dose should be taken on an empty stomach at approximately the same time every day for up to 26 weeks.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class and BPH. Randomized, controlled comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including

those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship funding must be considered, the studies in this review have also been evaluated for validity and importance.

There are no double-blind, randomized trials of either terazosin or tadalafil (Cialis) compared to other agents within this class.

alfuzosin (Uroxatral) versus doxazosin (Cardura)

In a 14-week, multicenter, double-blind, baseline-controlled, dose-titration study, 210 men with moderate to severe lower urinary tract symptoms (LUTS) were randomized to receive doxazosin 1 to 8 mg once daily or alfuzosin 5 to 10 mg divided in 2 or 3 daily doses.[107] International Prostate Symptom Score (IPSS) and maximum urinary flow rate were used to assess the efficacy of the treatment. At the end of the study, the mean dose of the 2 drugs (doxazosin 6.1 mg/day, alfuzosin 8.8 mg/day) was not equipotent. The mean change from baseline in total IPSS was statistically significant ($p<0.001$) for both doxazosin and alfuzosin. The mean change from baseline in irritative symptoms was also statistically significant ($p<0.001$ for both). The differences between the treatment groups were statistically significant in favor of doxazosin for both total IPSS ($p=0.036$) and irritative symptoms ($p=0.049$). The improvement between groups was also significantly different for postvoid residual urine volume, at -29.19 mL and + 9.59 mL for doxazosin and alfuzosin, respectively ($p=0.002$). Improvements in mean and maximum urinary flow rates were similar for both treatments, at 1.5 and 1.2, and 2.8 and 2.5 mL/sec, respectively. Doxazosin and alfuzosin were both well tolerated, with most all-cause adverse events reported as mild or moderate.

alfuzosin (Uroxatral) versus tamsulosin (Flomax)

In a randomized, double-blind, multicenter study, 625 patients with BPH were randomized to receive alfuzosin 10 mg, alfuzosin 15 mg, tamsulosin 0.4 mg, or placebo, each given once daily for 12 weeks with no initial dose titration.[108] The study was designed to compare each of the 3 active treatments with the placebo group. Alfuzosin 10 mg and tamsulosin 0.4 mg significantly improved urinary tract symptoms compared with placebo, with a mean change from baseline in IPSS of -6.5 for each of the 2 active treatment groups compared to -4.6 for placebo (adjusted $p=0.007$ and $p=0.014$, respectively). The difference in change between the higher dose of alfuzosin and placebo was not statistically significant. The median change from baseline in maximum urinary flow rate was significantly increased with all 3 active treatment regimens (all adjusted $p=0.02$ versus placebo). Dizziness was the most frequent adverse event, with an incidence of 6%, 7%, and 2% in the alfuzosin 10 mg, alfuzosin 15 mg, and tamsulosin 0.4 mg groups, respectively, compared to a 4% incidence in the placebo group. The respective incidence rates of sexual function adverse events were 3%, 1%, 8%, and 0%.

In a randomized, double-blind, parallel-design trial, efficacy and safety of tamsulosin 0.2 mg daily (n=40) was compared to alfuzosin 10 mg daily (n=36) in 76 men with symptomatic BPH.[109] After 8 weeks of treatment, IPSS, maximum urinary flow rate, Danish prostatic symptom sexual function score, and morbidity rates were compared. Both treatment regimens similarly improved IPSS and maximum urinary flow rate, did not alter sexual function, and were well tolerated. The incidence of adverse events was similar for tamsulosin (25%) and alfuzosin (19.4%).

doxazosin (Cardura) versus finasteride (Proscar) versus combination therapy versus placebo

In the PREDICT trial, over 1,000 patients were randomized to placebo, doxazosin titrated to 1 to 8 mg daily, finasteride 5 mg daily, or a combination of both agents for 52 weeks.[110] Mean reduction in American Urological Association (AUA) Symptom Index was significantly greater in the doxazosin and combination groups than in either the finasteride or placebo groups. Maximum urinary flow rate increased significantly more in the doxazosin monotherapy (3.6 mL/sec) and combination therapy (4.1 mL/sec) groups than in either the finasteride monotherapy (1.9 mL/sec) or placebo (1.9 mL/sec) groups. Finasteride was not significantly different from placebo in either comparison. All treatments were generally well tolerated, with discontinuation rates due to adverse events in the active treatment groups similar to those in the placebo group.

The NIH-funded Medical Therapy of Prostatic Symptoms (MTOPS) study was a large, long-term (mean follow-up 4.5 years), double-blind trial involving 3,047 men with moderate or severe symptomatic BPH.[111] Patients were randomized to receive placebo, doxazosin 4 to 8 mg, finasteride 5 mg, or a combination of both doxazosin and finasteride. The primary outcome of risk of clinical BPH progression (symptom increase, urinary retention, urinary incontinence, renal insufficiency, or recurrent urinary tract infection) occurred in 17% of men treated with placebo, 10% of patients treated with doxazosin ($p<0.001$ versus placebo), 10% of men treated with finasteride ($p=0.002$ versus placebo), and 5.3% of those treated with combination therapy ($p<0.001$ compared to each of the other treatments). The outcomes of acute urinary retention and invasive therapy were significantly reduced by combination therapy by 81% and 67%, respectively ($p<0.001$ for each comparison with placebo). There was also a significant reduction in these risks with finasteride monotherapy ($p<0.001$), but not with doxazosin monotherapy. On average, patients in the study had smaller prostate glands than patients in most other studies; the difference accounts, at least in part, for the overall lower rate of urinary retention and invasive therapy. Discontinuation rates were 27% for doxazosin, 24% for finasteride, and 18% for combination therapy.

A study examined data from the MTOPS study to determine the relationship between baseline total prostate volume (TPV) and the effect of medical therapy in men with lower urinary tract symptoms (LUTS) secondary to BPH.[112] The 3,047 patients had been randomized to placebo, doxazosin 4 to 8 mg, finasteride 5 mg, or the combination of doxazosin and finasteride. In patients with a small prostate (baseline TPV less than 25 mL), combination therapy was no better than doxazosin alone for decreasing the risk of clinical progression of BPH and the need for invasive therapy (a secondary outcome). However, in patients with a moderate size (25 to less than 40 mL) or enlarged (40 mL or greater) prostate gland, combination therapy led to a greater decrease in the risk of clinical progression of BPH than either drug alone.

Another study examined data from the MTOPS study to determine the effect of long-term finasteride treatment on total prostate volume (TPV) regardless of baseline prostate size.[113] The average length of treatment was 4.5 years. Both combination therapy of doxazosin and finasteride and finasteride alone led to reduction of approximately 25% in total prostate volume compared to placebo over the full range of baseline prostate sizes.

doxazosin ER (Cardura XL) versus doxazosin (Cardura)

A randomized, double-blind, multicenter study in 795 men with BPH included a 2-week washout period, 2-week single-blind placebo run-in phase, and 13-week double-blind treatment phase.[114] Doxazosin ER was initiated at 4 mg daily and titrated to 8 mg daily after 7 weeks, if indicated; doxazosin was initiated

at 1 mg daily, titrated to 2 mg after 1 week, to 4 mg at 3 weeks, and to 8 mg at 7 weeks, if indicated, to achieve symptom control. The primary outcome measures were mean change in IPSS from baseline to the final visit and maximum urinary flow rate adjusted for baseline values. Both doxazosin ER and doxazosin significantly improved the symptoms of BPH, as evidenced by reductions in total IPSS of -8 ± 0.3 and -8.4 ± 0.3 from baseline, respectively, compared with a reduction of -6 ± 0.4 in patients on placebo. Doxazosin ER and doxazosin produced clinically comparable improvements in maximum urinary flow rates, with a greater improvement observed earlier following treatment with doxazosin ER than with doxazosin. Both active treatments produced significantly greater increases in maximum urinary flow rate compared with placebo. Overall incidence of adverse events was similar among patients treated with doxazosin ER and placebo and was slightly higher in those on doxazosin.

dutasteride (Avodart) versus tamsulosin (Flomax) versus combination therapy

The CombaT study was a randomized, multicenter, double-blind study which enrolled 4,844 men, ages 50 years and older, with a diagnosis of BPH with mild to moderate LUTS and prostate enlargement (30 mL or greater).[115] Patients received either dutasteride 0.5 mg, tamsulosin 0.4 mg, or the combination, once daily for 4 years. The primary endpoint at 2 years was the change in IPSS from baseline. Combination therapy resulted in significantly greater symptom improvements compared to monotherapy with dutasteride from month three and compared to monotherapy with tamsulosin from month 9 ($p<0.001$ for each comparison). Improvement from baseline in peak urinary flow was significantly greater with combination therapy than with monotherapy with either agent from month 6 ($p\leq0.006$). Combination therapy was associated with a significant increase in drug-related adverse events compared to monotherapy with either agent ($p<0.001$). The results at the completion of the 4-year study continued to demonstrate the superiority of combination to tamsulosin monotherapy, but not dutasteride monotherapy, in reducing the relative risk of acute retention or BPH-related surgery.[116] The 4-year results also continued to show that combination therapy was not superior to dutasteride therapy for surgery risk, but did provide significantly superior symptomatic benefit then either monotherapy protocol. Safety and tolerability data at the 4-year period was consistent with previous results from tamsulosin and dutasteride monotherapies.[117]

Step-Down Therapy – dutasteride (Avodart) and tamsulosin (Flomax)

SMART-1 was a multicenter, randomized, double-blind trial. All patients (n=327) receive dutasteride 0.5 mg and tamsulosin 0.4 mg daily for 24 weeks.[118] At week 24, patients received either combination therapy for an additional 12 weeks or were switched to dutasteride plus placebo. At the 30-week final assessment, 91% of patients treated with combination therapy and 77% of patients treated with dutasteride monotherapy reported feeling better or experiencing no change in urinary symptoms compared to week 24 ($p=0.001$). Among patients with moderate baseline symptoms who switched to dutasteride monotherapy, 84% switched without any obvious deterioration in symptoms. In patients with severe baseline symptoms, 42.5% in the combination group and 14% in the monotherapy group reported worsening of symptoms. Results from the IPSS data correlated with the subjective evaluations.

silodosin (Rapaflo) and tamsulosin (Flomax)

A randomized, double-blind, placebo-controlled study evaluated the safety and efficacy of silodosin 8 mg daily, tamsulosin 0.2 mg daily, or placebo for 12 weeks in 457 patients.[119] The primary endpoint was the change from IPSS from baseline. The change in the total IPSS from baseline in the silodosin, tamsulosin, and placebo groups was -8.3, -6.8, and -5.3, respectively. There was a significant decrease in

the IPSS versus placebo in the silodosin group from week 1. The most common adverse event in the silodosin group was abnormal ejaculation, which occurred more often in the silodosin group than in the tamsulosin group (22.3% versus 1.6%, respectively). However, only 5 men (2.9%) discontinued treatment for abnormal ejaculation.

dutasteride (Avodart) and finasteride (Proscar)

The Enlarged Prostate International Comparator Study (EPICS) was a multicenter, randomized double-blind, 12-month, parallel-group study.[120] Men over 50 years old with a diagnosis of BPH received once daily treatment with dutasteride 0.5 mg (n=813) or finasteride 5 mg (n=817). There was a 4-week placebo run-in period; patients were then randomized to receive dutasteride or finasteride for 48 weeks, followed by an optional 24-month, open-label phase in which patients received dutasteride 0.5 mg once daily. At month 12, a similar reduction in prostate volume, the primary endpoint, was reported in the finasteride group and the dutasteride group (26.7% and 26.3%, respectively, p=0.65).

finasteride (Proscar) and tadalafil (Cialis) versus finasteride (Proscar) and placebo

A 26-week, double-blind, parallel-design study evaluated the efficacy and safety of the combination of finasteride and tadalafil in treating symptoms of BPH in men with an enlarged prostate (> 30 cc).[121] Participants aged 46 to 86 years were randomized to receive finasteride 5 mg with tadalafil 5 mg (n=345) or finasteride 5 mg and placebo (n=350). Change in IPSS score, the primary endpoint, was significantly improved with the combination treatment of finasteride and tadalafil at 12 weeks, compared with finasteride and placebo (-5.2 versus -3.8, treatment difference -1.4, p=0.001). A statistically significant difference in the secondary endpoint, assessing IPSS improvement at week 4, was also observed, and this statistically significant difference favoring the combination therapy was maintained through week 26. However, the magnitude of the benefit decreased during this time, and the benefit of use beyond 26 weeks has not been established.

META-ANALYSES

An early meta-analysis of alpha blockers (alfuzosin, terazosin, doxazosin, and tamsulosin) found that LUTS improved in general by approximately 30% to 40% with all agents (n=6,840).[122] While efficacy among the 4 agents appeared comparable, terazosin and doxazosin led to more dropouts (4% to 10% higher) than alfuzosin and tamsulosin, suggesting possible better tolerability of alfuzosin and tamsulosin. A meta-analysis of 26 studies confirmed efficacy of all alpha blockers in maximum urinary flow rate (Qmax, 1.32 mL/min; 95% CI, 1.07 to 1.57).[123] There was a significant improvement with all 4 agents compared to placebo: alfuzosin (OR, 0.84; 95% CI, 0.55 to 1.13; p<0.0001), terazosin (OR, 1.27; 95% CI, 0.91 to 1.63; p<0.0001), doxazosin (OR, 1.76; 95% CI, 1.13 to 2.39; p<0.0001), and tamsulosin (OR, 1.59; 95% CI, 0.92 to 1.13; p<0.0001). However, this meta-analysis also found a higher risk of developing a vascular-related event (odds ratio [OR], 2.54; 95% CI, 2 to 3.24; p<0.001) with an AB compared to placebo (25 studies). There was a significantly higher risk with alfuzosin (OR, 1.66; 95% CI, 1.17 to 2.36), terazosin (OR, 3.71; 95% CI, 2.48 to 5.53), and doxazosin (OR, 3.32; 95% CI, 2.1 to 5.23), but not with tamsulosin (OR, 1.42; 95% CI, 0.99 to 2.05).

A systematic review and network meta-analysis compared efficacy and safety of monodrug therapies, including alpha blockers, 5AR inhibitors, and PDE5 inhibitors, for LUTS associated with BPH (n=58,548; 124 trials).[124] The analysis found alpha blockers, 5AR inhibitors, and PDE5 inhibitors are all effective (versus placebo) for the treatment BPH (IPSS mean difference [MD]: -1.35 to -3.67 points; peak urinary flow rate [PUF] MD: -0.02 to 1.95 mL/s). Doxazosin (IPSS MD, -3.7 [95% CI, -4.33 to -3.02]; PUF MD, 1.95

mL/s [95% CI, 1.61 to 2.3]) and terazosin (IPSS MD, -3.37 [95% CI, -4.24 to -2.5]; PUF MD, 1.21 mL/s [95% CI, 0.74 to 1.66]) were found to be the most effective agents. Improvements in IPSS were seen with tamsulosin, alfuzosin, silodosin, dutasteride, and tadalafil. No major differences were found in overall side effect profile.

A meta-analysis evaluating the efficacy and safety of tamsulosin plus dutasteride compared to tamsulosin monotherapy identified 5 randomized controlled trials (n=4,348) with a treatment cycle of at least 1 year.[125] Combination therapy demonstrated a significantly greater effect in international prostate symptom score (mean difference, - 1.4; 95% CI, - 2.2 to - 0.7; p=0.0003), prostate volume (mean difference, -10.13; 95% CI, - 12.4 to - 7.9; p< 0.00001), transitional zone volume (mean difference, -3.2; 95% CI, -3.6 to -2.8; p<0.0001), maximum urine flow rate (mean difference, 1.05; 95% CI, 0.8 to 1.3; p< 0.00001), prostate specific antigen (mean difference, -0.5; 95% CI, -0.8 to -0.3; p< 0.0001) and post-void residual volume (mean difference, -3.85; 95% CI, - 5 to -2.8; p< 0.00001) compared with the tamsulosin group. In addition, the combination group significantly reduced the risk of clinical progression than the tamsulosin group especially in incidence of BPH-related symptom progression (OR, 0.6; 95% CI, 0.5 to 0.7; p< 0.00001) and acute urinary retention (OR, 0.6; 95% CI, 0.4 to 1; p= 0.04). Combination therapy was associated with a higher incidence of sexual side effects, including erectile dysfunction (OR, 2.2; 95% CI, 1.7 to 2.9; p< 0.00001), ejaculation disorder (OR, 3.8; 95% CI, 2.0 to 5.8; p< 0.0001), retrograde ejaculation (OR, 2.3; 95% CI, 1.1 to 4.9; p= 0.03), decreased libido (OR, 2.3; 95% CI, 1.5 to 3.3; p< 0.0001), and loss of libido (OR, 3.4; 95% CI, 2 to 5.9; p<0.0001).

SUMMARY

Head-to-head studies have not distinguished any of the alpha-blockers from one another in terms of effectiveness. However, selective alpha-blockers, such as alfuzosin (Uroxatral), tamsulosin (Flomax), and silodosin (Rapaflo), may have a decreased incidence of hypotension-related adverse events.

The Enlarged Prostate International Comparator Study (EPICS) reported a similar reduction in prostate volume for the 5-alpha reductase (5AR) inhibitors, dutasteride (Avodart), and finasteride (Proscar). There are 2 marketed 5AR inhibitor combination products. Dutasteride and the alpha-blocker, tamsulosin, are available as the combination product, Jalyn. Finasteride and the phosphodiesterase 5 (PDE5) inhibitor, tadalafil, are available as the combination product, Entadfi. Two studies have shown that 5AR inhibitors may increase the risk of development of high-grade prostate cancer; however, causal effects have not been established. 5AR inhibitors are not approved for the prevention of prostate cancer.

The phosphodiesterase 5 (PDE5) inhibitor, tadalafil (Cialis), has been approved for the treatment of the signs and symptoms of BPH, given as a once daily dosage.

The NIH-funded Medical Therapy of Prostatic Symptoms (MTOPS) and CombaT studies indicate that combination therapy is likely to be more effective at inhibiting disease progression than monotherapy with either agent. Combination therapy is most appropriate for men at highest risk for disease progression and for those experiencing symptoms of LUTS with demonstrable or indicated prostate enlargement. While combination therapy has demonstrated greater effectiveness than monotherapy, the combination products available have not proven more effective than coadministration of the individual products in treating disease progression and symptom relief.

REFERENCES

1 Uroxatral [package insert]. St. Michael, Barbados; Concordia; May 2020.
2 Cardura [package insert]. New York, NY; Pfizer; June 2021.
3 Cardura XL [package insert]. New York, NY; Pfizer; June 2021.
4 Rapaflo [package insert]. Madison, NJ; Allergan; December 2020.
5 Flomax [package insert]. Bridgewater, NJ; Sanofi; January 2019.
6 Terazosin [package insert]. Chino, CA; Apnar; November 2022.
7 Avodart [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2020.
8 Proscar [package insert]. Whitehouse Station, NJ; Merck; June 2021.
9 Jalyn [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2020.
10 Cialis [package insert] Indianapolis, IN; Eli Lilly and Company; February 2018.
11 Entadfi [package insert]. Miami, FL; Veru; December 2021.
12 Benign prostatic hypertrophy. Updated February 19, 2021. Available at: http://emedicine.medscape.com/article/437359-overview. Accessed December 8, 2022.
13 Benign prostatic hypertrophy. Updated February 19, 2021. Available at: http://emedicine.medscape.com/article/437359-overview. Accessed December 8, 2022.
14 Madersbacher S, Sampson N, Culig Z. Pathophysiology of benign prostatic hyperplasia and benign prostatic enlargement; a mini-review. Gerontology. 2019; 65: 458-464.
15 Benign prostatic hypertrophy. Updated February 19, 2021. Available at: http://emedicine.medscape.com/article/437359-overview. Accessed December 8, 2022.
16 Lerner LB, McVary, KT, Barry MJ et al: Management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: AUA guideline. 2021. Available at: https://www.auanet.org/guidelines-and-quality/guidelines/non-oncology-guidelines. Accessed December 8, 2022.
17 Lerner LB, McVary, KT, Barry MJ et al: Management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: AUA guideline. 2021. Available at: https://www.auanet.org/guidelines-and-quality/guidelines/non-oncology-guidelines. Accessed December 8, 2022.
18 Uroxatral [package insert]. St. Michael, Barbados; Concordia; May 2020.
19 Cardura [package insert]. New York, NY; Pfizer; June 2021.
20 Cardura XL [package insert]. New York, NY; Pfizer; June 2021.
21 Rapaflo [package insert]. Madison, NJ; Allergan; December 2020.
22 Flomax [package insert]. Bridgewater, NJ; Sanofi; January 2019.
23 Terazosin [package insert]. Chino, CA; Apnar; July 2020.
24 Avodart [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2020.
25 Proscar [package insert]. Whitehouse Station, NJ; Merck; June 2021.
26 Jalyn [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2020.
27 Cialis [package insert] Indianapolis, IN; Eli Lilly and Company; February 2018.
28 Entadfi [package insert]. Miami, FL; Veru; December 2021.
29 Cooper KL, McKiernan JM, Kaplan SA. A-adrenoceptor antagonists in the treatment of benign prostatic hyperplasia. Drugs. 1999; 57:9-17.
30 De Mey C. α1 blockers for BPH: are there differences? Eur Urol. 1999; 36(suppl 3): 52-63.
31 Mimata H, Nomura Y, Kasagi Y, et al. Prediction of α-blocker response in men with benign prostatic hyperplasia by magnetic resonance imaging. Urology. 1999; 54:829-833.
32 Drug Facts and Comparisons. St. Louis, MO: Facts and Comparisons. 2000: 498-501.
33 Medical treatment of benign prostatic hyperplasia. Updated August 12, 2022. Available at: https://www.uptodate.com/contents/search. Accessed on December 20, 2022.
34 Randrup E, Baum N. Pharmacologic management of benign prostatic hyperplasia. Hosp Med. 1997; 33: 43-53.
35 Keetch D. Medical therapy for benign prostatic hyperplasia. Infect Urol. 1997; 10: 54-60.
36 Benign prostatic hypertrophy. Updated February 19, 2021. Available at: http://emedicine.medscape.com/article/437359-overview. Accessed December 8, 2022.
37 McConnell J, Wilson J, George F, et al. Finasteride, an inhibitor of 5α-reductase, suppresses prostatic dihydrotestosterone in men with benign prostatic hyperplasia. J Clin Endocrinol Metab. 1992; 74: 505-508.
38 Uroxatral [package insert]. St. Michael, Barbados; Concordia; May 2020.
39 Cardura [package insert]. New York, NY; Pfizer; June 2021.
40 Cardura XL [package insert]. New York, NY; Pfizer; June 2021.
41 Rapaflo [package insert]. Madison, NJ; Allergan; December 2020.
42 Flomax [package insert]. Bridgewater, NJ; Sanofi; January 2019.
43 Terazosin [package insert]. Chino, CA; Apnar; July 2020.
44 Avodart [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2020.
45 Proscar [package insert]. Whitehouse Station, NJ; Merck; June 2021.
46 Jalyn [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2020.
47 Cialis [package insert] Indianapolis, IN; Eli Lilly and Company; February 2018.
48 Entadfi [package insert]. Miami, FL; Veru; December 2021.
49 Lee M. Alfuzosin Hydrochloride for the Treatment of Benign Prostatic Hyperplasia. Am J Health-Syst Pharm. 2003; 60: 1426-1439.
50 Uroxatral [package insert]. St. Michael, Barbados; Concordia; May 2020.
51 Cardura [package insert]. New York, NY; Pfizer; June 2021.
52 Cardura XL [package insert]. New York, NY; Pfizer; June 2021.
53 Rapaflo [package insert]. Madison, NJ; Allergan; December 2020.
54 Flomax [package insert]. Bridgewater, NJ; Sanofi; January 2019.
55 Terazosin [package insert]. Chino, CA; Apnar; July 2020.

56 Avodart [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2020.
57 Proscar [package insert]. Whitehouse Station, NJ; Merck; June 2021.
58 Jalyn [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2020.
59 Cialis [package insert] Indianapolis, IN; Eli Lilly and Company; February 2018.
60 Entadfi [package insert]. Miami, FL; Veru; December 2021.
61 Lerner LB, McVary, KT, Barry MJ et al: Management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: AUA Guideline. 2021. Available at: https://www.auanet.org/guidelines-and-quality/guidelines/non-oncology-guidelines. Accessed December 8, 2022.
62 Uroxatral [package insert]. St. Michael, Barbados; Concordia; May 2020.
63 Cardura [package insert]. New York, NY; Pfizer; June 2021.
64 Cardura XL [package insert]. New York, NY; Pfizer; June 2021.
65 Rapaflo [package insert]. Madison, NJ; Allergan; December 2020.
66 Flomax [package insert]. Bridgewater, NJ; Sanofi; January 2019.
67 Terazosin [package insert]. Chino, CA; Apnar; July 2020.
68 Avodart [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2020.
69 Proscar [package insert]. Whitehouse Station, NJ; Merck; June 2021.
70 Jalyn [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2020.
71 Cialis [package insert] Indianapolis, IN; Eli Lilly and Company; February 2018.
72 Entadfi [package insert]. Miami, FL; Veru; December 2021.
73 Uroxatral [package insert]. St. Michael, Barbados; Concordia; May 2020.
74 Cardura [package insert]. New York, NY; Pfizer; June 2021.
75 Cardura XL [package insert]. New York, NY; Pfizer; June 2021.
76 Rapaflo [package insert]. Madison, NJ; Allergan; December 2020.
77 Flomax [package insert]. Bridgewater, NJ; Sanofi; January 2019.
78 Terazosin [package insert]. Chino, CA; Apnar; July 2020.
79 Avodart [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2020.
80 Proscar [package insert]. Whitehouse Station, NJ; Merck; June 2021.
81 Jalyn [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2020.
82 Cialis [package insert] Indianapolis, IN; Eli Lilly and Company; February 2018.
83 Entadfi [package insert]. Miami, FL; Veru; December 2021.
84 Gacci M, Corona G, Salvi M, et al. A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with α-blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. Eur Urol. 2012; 61(5): 994-1003. DOI: 10.1016/j.eururo.2012.02.033.
85 Uroxatral [package insert]. St. Michael, Barbados; Concordia; May 2020.
86 Cardura [package insert]. New York, NY; Pfizer; June 2021.
87 Cardura XL [package insert]. New York, NY; Pfizer; June 2021.
88 Rapaflo [package insert]. Madison, NJ; Allergan; December 2020.
89 Flomax [package insert]. Bridgewater, NJ; Sanofi; January 2019.
90 Terazosin [package insert]. Chino, CA; Apnar; July 2020.
91 Avodart [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2020.
92 Proscar [package insert]. Whitehouse Station, NJ; Merck; June 2021.
93 Jalyn [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2020.
94 Cialis [package insert] Indianapolis, IN; Eli Lilly and Company; February 2018.
95 Entadfi [package insert]. Miami, FL; Veru; December 2021.
96 Uroxatral [package insert]. St. Michael, Barbados; Concordia; May 2020.
97 Cardura [package insert]. New York, NY; Pfizer; June 2021.
98 Cardura XL [package insert]. New York, NY; Pfizer; June 2021.
99 Rapaflo [package insert]. Madison, NJ; Allergan; December 2020.
100 Flomax [package insert]. Bridgewater, NJ; Sanofi; January 2019.
101 Terazosin [package insert]. Chino, CA; Apnar; July 2020.
102 Avodart [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2020.
103 Proscar [package insert]. Whitehouse Station, NJ; Merck; June 2021.
104 Jalyn [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2020.
105 Cialis [package insert] Indianapolis, IN; Eli Lilly and Company; February 2018.
106 Entadfi [package insert]. Miami, FL; Veru; December 2021.
107 de Reijke TM, Klarskov P. Comparative efficacy of two alpha-adrenoreceptor antagonists, doxazosin and alfuzosin, in patients with lower urinary tract symptoms from benign prostatic enlargement. BJU Int. 2004; 93: 757-762.
108 Nordling J. Efficacy and safety of two doses (10 and 15 mg) of alfuzosin or tamsulosin (0.4 mg) once daily for treating symptomatic benign prostatic hyperplasia. BJU Int. 2005; 95: 1006-12.
109 Lapitan M, Acepcion V, Mangubat J. A comparative study on the safety and efficacy of tamsulosin and alfuzosin in the management of symptomatic benign prostatic hyperplasia: a randomized controlled clinical trial. J Int Med Res. 2005; 33(5): 562-573.
110 Kirby RS, Roehrborn C, Boyle P, et al. Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. Urology. 2003; 61: 119-26.
111 McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med. 2003; 349: 2387-98.
112 Kaplan SA, McConnell JD, Roehrborn CG, et al. Combination therapy with doxazosin and finasteride for benign prostatic hyperplasia in patients with lower urinary tract symptoms and a baseline total prostate volume of 25ml or greater. J Urol. 2006; 175(1): 217-20.
113 Kaplan SA, Roehrborn CG, McConnell JD, et al. Long-term treatment with finasteride results in a clinically significant reduction in total prostate volume compared to placebo over the full range of baseline prostate sizes in med enrolled in the MTOPS trial. J Urol. 2008; 180(3): 1030-2.

114 Andersen M, Dahlstrand C, Hoye K. Double-blind trial of the efficacy and tolerability of doxazosin in the gastrointestinal therapeutic system, doxazosin standard, and placebo in patients with benign prostatic hyperplasia. Eur Urol. 2000; 38(4): 400-9.
115 Roehrborn CG, Siami P, Barkin J, et al. The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombaT study. J Urol. 2008; 179(2): 616-21.
116 Roehrborn CG, Siami P, Barkin J, et al. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign hyperplasia: 4-year results from the CombaT study. Eur Urol. 2010; 57(1): 123-31.
117 Roehrborn CG, Siami P, Barkin J, et al. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign hyperplasia: 4-year results from the CombaT study. Eur Urol. 2010; 57(1): 123-31.
118 Barkin J, Guimaraes M, Jacobi G, et al. Alpha-blocker therapy can be withdrawn in the majority of men following initial combination therapy with the dual 5α-reductase inhibitor dutasteride. Eur Urol. 2003; 44: 461-466.
119 Kawabe K, Yoshida M, Homma Y, et al for the Silodosin Clinical Study Group. Silodosin, a new alpha1A-adrenoceptor-selective antagonist for treating benign prostatic hyperplasia: results of a phase III randomized, placebo-controlled, double-blind study in Japanese men. BJU Int. 2006; 98(5):1019-24.
120 Nickel JC, Gilling P, Tammela TL, et al. Comparison of dutasteride and finasteride for treating benign prostatic hyperplasia: the Enlarged Prostate International Comparator Study (EPICS). BJU Int. 2011; 108(3): 388-94.
121 Entadfi [package insert]. Miami, FL; Veru; December 2021.
122 Djavan B, Marberger M. A meta-analysis on the efficacy and tolerability of alpha1-adrenoreceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. Eur Urol. 1999; 36(1): 1-13.
123 Nickel JC, Sander S, Moon TD. A meta-analysis of the vascular-related safety profile and efficacy of alpha-adrenergic blockers for symptoms related to benign prostatic hyperplasia. Int J Clin Pract. 2008; 62(10): 1547-1559. DOI: 10.1111/j.1742-1241.2008.01880.x.
124 Yuan JQ, Mao C, Wond SY, et al. Comparative effectiveness and safety of monodrug therapies for lower urinary tract symptoms associated with benign prostatic hyperplasia: a network meta-analysis. Medicine. 2015; 94(27): e974. DOI: 10.1097/MD.0000000000000974.
125 Zhou Z, Cui Y, Wu J, et al. Meta-analysis of the efficacy and safety of combination of tamsulosin plus dutasteride compared with tamsulosin monotherapy in treating benign prostatic hyperplasia. BMC Urol. 2019; 19(1): 17. DOI: 10.1186/s12894-019-0446-8.