



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

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MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Hypertension	BPH
Alpha-Blockers			
alfuzosin ER (Uroxatral®) ¹	generic		X
doxazosin (Cardura®) ²	generic	X	X
doxazosin ER (Cardura XL®) ³	Pfizer		X
silodosin (Rapaflo™) ⁴	Actavis		X
tamsulosin (Flomax®) ⁵	generic		X
terazosin* ⁶	generic	X	X
5-Alpha Reductase (5AR) Inhibitors			
dutasteride (Avodart®) ⁷	generic		Treatment of symptomatic BPH in men with enlarged prostate to improve symptoms, reduce the risk of acute urinary retention, 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		Treatment of symptomatic BPH in men with enlarged prostate to improve symptoms, reduce the risk of acute urinary retention, 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) Inhibitors / Alpha-Blocker Combinations			
dutasteride/ tamsulosin (Jalyn®) ⁹	generic		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	Eli Lilly and Company		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

*Hytrin®, the branded product of terazosin, has been discontinued and is no longer available.

BPH = Benign Prostatic Hyperplasia
ER = extended release

OVERVIEW

Benign prostatic hyperplasia (BPH) is one of the most common conditions in aging men. 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 (urinary frequency, nocturia, urgency, urge incontinence) and/or obstruction (difficulty initiating urination or passing urine, weak stream, involuntary postvoid dripping of urine, and sensation of incomplete bladder emptying).^{11,12} Most men with BPH experience only mild or moderate symptoms of obstruction. Severe BPH, more likely to occur in men over 60 years of age, can lead to urinary retention, renal insufficiency, urinary tract infections, hematuria, and bladder stones. More serious complications, such as uremia and irreversible bladder dysfunction, are uncommon.^{13,14}

Drugs used in the treatment of BPH relieve LUTS and prevent complications and, in some cases, are an alternative to surgical intervention.

As many as 14 million men in the United States have symptoms related to BPH. An estimated 50% of men demonstrate histopathologic BPH by age 60 years. This number increases to 90% by 85 years of age.¹⁵

According to the American Urological Association (AUA) 2010 standards (reaffirmed in 2014), patients with mild symptoms of BPH (AUA Symptom Score ≤ 7) and patients with moderate or severe symptoms (AUA Symptom Score ≥ 8) who are not bothered by their symptoms (e.g., they do not interfere with the daily activities of living) should be managed using a strategy of watchful waiting.¹⁶ Alpha-adrenergic blocker therapy is an appropriate treatment option for patients with moderate to severe LUTS secondary to BPH.

For pharmacological treatment, the 2010 AUA guidelines state that alfuzosin (Uroxatral), doxazosin (Cardura), tamsulosin (Flomax), and terazosin are appropriate treatment options for patients with LUTS secondary to BPH.¹⁷ Although there are slight differences in the adverse event profiles of these agents, the AUA states that all 4 agents have equal clinical effectiveness. Silodosin (Rapaflo) did not have published peer-reviewed studies prior to the deadline for literature evaluation for the guideline update.

The guidelines also state that the 5 α -reductase inhibitors, finasteride (Proscar) and dutasteride (Avodart), are appropriate and effective treatments for patients with LUTS associated with demonstrable prostatic enlargement, but they are not appropriate treatments for men with LUTS who do not have evidence of prostatic enlargement.

The 5 α -reductase inhibitors may be used to prevent progression of LUTS secondary to BPH and to reduce the risk of urinary retention and future prostate-related surgery.¹⁸ The patient should also be advised of the disadvantages of this therapeutic approach (e.g., side effects such as sexual dysfunction) and the need for long-term daily therapy in comparison to a reasonable estimate of his baseline risk of

progression (e.g., retention and the risks associated with BPH-related surgery) so an informed decision may be made.

Finally, according to the 2010 AUA guidelines, combination therapy utilizing an α -adrenergic receptor blocker and a 5 α -reductase inhibitor presents an appropriate and effective treatment for patients who not only exhibit LUTS symptoms, but also have definitive prostatic enlargement.

PHARMACOLOGY

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.¹⁹ 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.²⁰

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.²¹ These agents are more effective at improving obstructive symptoms than irritative symptoms.²² 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.²³

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 5 α -dihydrotestosterone (DHT), which stimulates growth of glandular and stromal cells.^{24,25} Over time, progressive proliferation may lead to increased prostate size and bladder outlet obstruction.²⁶ The intracellular enzyme 5-alpha-reductase (5AR) is responsible for the conversion of testosterone to DHT, and 5 α -reductase (5AR) inhibitors block this action.²⁷ 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.^{28,29}

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.³⁰

PHARMACOKINETICS^{31,32,33,34,35,36,37,38,39,40}

Drug	Bioavailability (%)	Protein Binding (%)	Peak Concentration (hrs)	Half-Life (hrs)	Liver Metabolism	Excretion in Urine (%)
Alpha-Blockers⁴¹						
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		5 weeks	cytochrome P450 (CYP3A4 and CYP 3A5)	<1
finasteride (Proscar)	63			6-8	cytochrome P450 (CYP3A4)	39
5-Alpha Reductase (5AR) Inhibitors / Alpha-Blocker Combinations						
dutasteride/ tamsulosin (Jalyn)	Refer to data on component ingredients					
Phosphodiesterase 5 (PDE5) Inhibitors						
tadalafil (Cialis)	not determined	94	2	17.5	cytochrome P450	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

Alpha-Blockers^{42,43,44,45,46,47}

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 box 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; reactions have included 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 in 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 \leq 30 mL/minute). Clinical studies have shown that the effect of moderate renal impairment (creatinine clearance 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 phacoemulsification cataract 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.⁴⁸

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

5AR Inhibitors^{49,50}

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 in patients 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 Combinations⁵¹

The first alpha-blocker and 5AR inhibitor combination product for the treatment of BPH, Jalyn (dutasteride and tamsulosin), was introduced into the market. As a combination product, adverse reactions, as well as warnings and contraindications for this product, consist of the reactions listed above for the component parts.

Phosphodiesterase 5 (PDE5) Inhibitors⁵²

Tadalafil (Cialis) is contraindicated in patients who are using any form of organic nitrate, either regularly and/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 more than 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.

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

DRUG INTERACTIONS^{53,54,55,56,57,58,59,60,61,62}

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 using caution with concomitant administration of tamsulosin (Flomax) and strong CYP3A4 inhibitors. The effect of moderate CYP3A4 inhibitors (diltiazem, erythromycin, verapamil) on the pharmacokinetics may increase the concentration of alpha-blockers, and, therefore, use caution when administered with a moderate CYP3A4 inhibitor.

The 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 accentuation of the first-dose effect. Based upon the 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 the 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 (PDE5). 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 should be used 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

Similar to adverse reactions, 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.

ADVERSE EFFECTS^{63,64,65,66,67,68,69,70,71,72}

Drug	Asthenia	Headache	Dizziness	Hypotension	Altered libido	Abnormal ejaculation	Impotence
Alpha-Blockers							
alfuzosin ER (Uroxatral)	2.7	3.0	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	nr	<2	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. nr = not reported

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: male infertility and/or poor seminal quality, depression, and erectile dysfunction (ED) and decreased libido that continued after discontinuation of treatment.⁷³

A meta-analysis evaluated the impact on alpha blockers and 5AR inhibitors on ejaculatory dysfunction (23 trials).⁷⁴ Both alpha blockers (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^{75,76,77,78,79,80,81,82,83,84}

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) because of the possibility of fetal anomaly to a male fetus. The 5AR inhibitors, dutasteride and finasteride, are Pregnancy Category X.

Alfuzosin (Uroxatral), tamsulosin (Flomax), silodosin (Rapaflo), and tadalafil (Cialis) are Pregnancy Category B. These products are not indicated for use in women. The remaining products in this class are Pregnancy Category C.

Elderly

The cumulative incidence for 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.

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 (creatinine clearance \leq 30 mL/min).

Due to increased tadalafil (Cialis) exposure (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 creatinine clearance less than 30 mL/min or patients on hemodialysis. In patients with creatinine clearance 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.

DOSAGES^{85,86,87,88,89,90,91,92,93,94}

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, 2, 4, 8 mg tablets
doxazosin ER (Cardura XL)	4 mg daily	4 – 8 mg daily taken with breakfast	4, 8 mg extended-release tablets
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, 2, 5, 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 (0.5 mg dutasteride/ 0.4 mg tamsulosin)	1 capsule daily (0.5 mg dutasteride/ 0.4 mg tamsulosin)	0.5 mg dutasteride/ 0.4 mg tamsulosin per capsule
Phosphodiesterase 5 (PDE5) Inhibitors			
tadalafil (Cialis) [§]	5 mg daily Creatinine clearance 30 – 50 mL/min: 2.5 mg daily	5 mg daily Creatinine clearance 30 – 50 mL/min: may increase to 5 mg daily based on individual response	2.5, 5, 10, 20 mg tablets (the 10 mg and 20 mg strengths are not used in BPH)

* 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.

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.⁹⁵ 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.⁹⁶ 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 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.⁹⁷ 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.⁹⁸ 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.⁹⁹ 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.¹⁰⁰ 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 also 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.¹⁰¹ 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.¹⁰² 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 changes from baseline to the final visit for IPSS 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).¹⁰³ 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 ($p \leq 0.006$). 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 (AUR) or BPH-related surgery.¹⁰⁴ 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 than either monotherapy protocol. Safety and tolerability data at the 4 year period was consistent with previous results from tamsulosin and dutasteride monotherapies.¹⁰⁵

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.¹⁰⁶ 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.¹⁰⁷ 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.¹⁰⁸ 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, $p=0.65$).

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 ($n=6,840$).¹⁰⁹ 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 (Q_{max} , 1.32 mL/min; 95% CI, 1.07 to 1.57).¹¹⁰ 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).¹¹¹ 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.

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). Dutasteride and the alpha-blocker, tamsulosin, are available as the combination product, Jalyn. 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. 5-alpha reductase 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 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 product available has not proven more effective than coadministration of the individual products in treating disease progression and symptom relief.

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