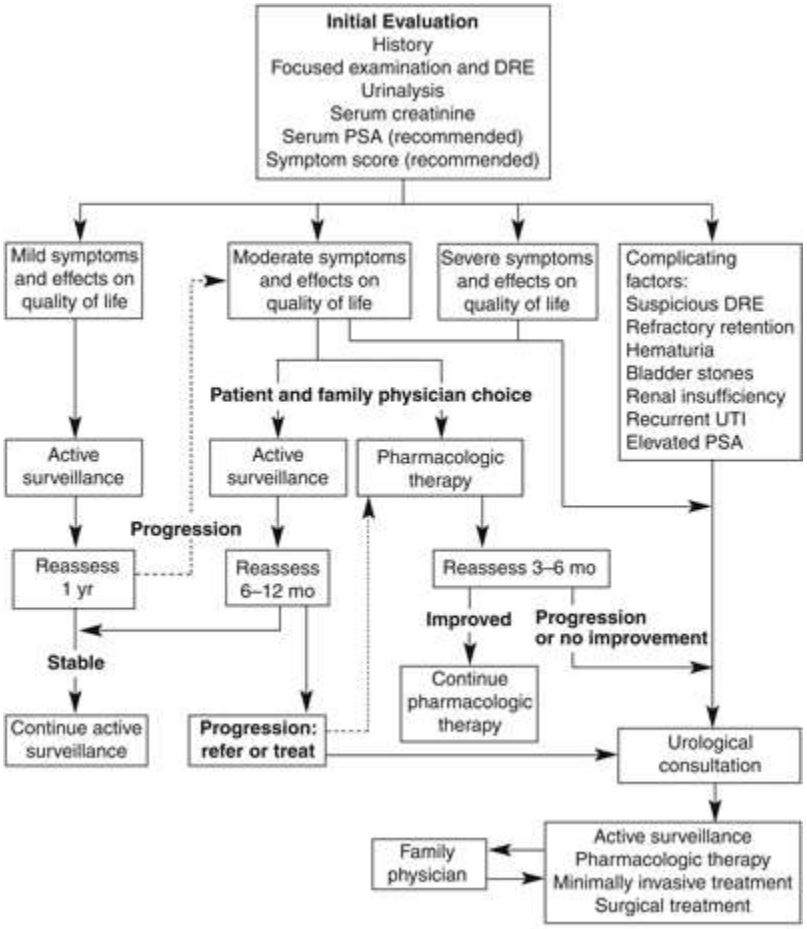
Benign Prostatic Hyperplasia

Management of Benign Prostatic Hyperplasia



Goals of Therapy

- Improve or abolish lower urinary tract symptoms (LUTS)
- Prevent or delay clinical progression of benign prostatic hyperplasia (BPH)
- Reduce the risk of surgical intervention
- Prevent the sequelae of long-term bladder outlet obstruction (urinary tract infections, bladder stones, hydronephrosis)

Investigations

- Thorough history with attention to:
    - voiding (weak/interrupted stream, dribbling, hesitancy, straining) and storage (nocturia, frequency, urgency) symptoms

    - onset and progression of LUTS and degree of inconvenience or bother to the patient
    - episodes of urinary tract infection, hematuria or urinary retention

- Physical examination:
    - abdomen (bladder distention, flank tenderness)
    - digital rectal examination (DRE). Document prostate size, consistency, symmetry and tenderness
- Laboratory tests:
    - urinalysis
    - serum creatinine
    - prostate specific antigen (PSA); recommended in patients who have a life expectancy >10 years and for whom a diagnosis of prostate cancer would change management.

Therapeutic Choices

The alpha$_1$-adrenergic antagonists, **alfuzosin**, **doxazosin**, **silodosin**, **tamsulosin** and **terazosin**, ***and the 5-alpha-reductase inhibitors***, **dutasteride** and **finasteride**, are all useful in improving symptoms

Alpha$_1$-adrenergic Antagonists

Alfuzosin, doxazosin, silodosin, tamsulosin and terazosin are the agents most commonly used to block alpha$_1$-adrenergic receptors that mediate muscular activity in the bladder neck, prostate and prostatic capsule, reducing the dynamic component of bladder outlet obstruction. Over a period of days to weeks, this may improve urinary flow rates by 1–3 mL/sec and symptom scores by 1–3 points. The effectiveness of the alpha$_1$-adrenergic antagonists is not influenced by prostate size.

To avoid first-dose syncope, start doxazosin and terazosin at a low dosage and gradually increase until symptomatic improvement or intolerance occurs. Dose titration is not necessary with alfuzosin, silodosin and tamsulosin because of their greater selectivity for the alpha$_{1A}$-receptor subtype which predominates in the prostate, bladder neck and urethra.

Side effects of alpha-antagonists include dizziness (10–20%), headaches (15%), asthenia (5–15%) and nasal congestion (5–10%). Retrograde ejaculation develops in 28% of men taking silodosin and 5–10% taking tamsulosin. These drugs may potentiate other antihypertensive medications, and caution should be used when they are added to an ongoing regimen, particularly in the elderly. Alfuzosin, silodosin and tamsulosin have fewer systemic side effects because of their greater selectivity for the $alpha_{1A}$-receptor subtype, and because their administration with meals produces more constant serum drug concentrations. Side effects of terazosin and doxazosin may be reduced by taking them at bedtime.

Terazosin and doxazosin may cause a small decrease in total cholesterol and low-density lipoprotein fraction. The clinical importance of this is unknown.

Although there are differences in the adverse event profiles of these agents, all 4 have equal clinical effectiveness. Choice of agent depends upon the side effect profile and on the patient's comorbidities and individual tolerance. Provincial drug coverage may also play a role in this decision. In patients with no significant cardiovascular or cerebrovascular disease and with the ability to understand and carry out dose titration, terazosin and doxazosin are cost-effective $alpha_1$-antagonists.

5-Alpha-reductase Inhibitors

Finasteride inhibits type II and dutasteride types I and II isoenzymes of 5-alpha-reductase, which blocks the metabolism of testosterone to dihydrotestosterone. The net effect is a decrease in intraprostatic dihydrotestosterone and a progressive reduction in prostatic volume. This reduces the static component of bladder outlet obstruction over a period of several months to years and may be accompanied by an improvement in urinary flow rates of 1–2 mL/sec and symptom scores of 1–2 points.

5-alpha-reductase inhibitors work best in men with a large prostate. Because of their site specificity, there is a low incidence of side effects (e.g., 3–4% sexual dysfunction) and little risk of significant drug interactions. Within 6 months of initiation, these drugs decrease serum PSA levels by approximately 50% in men with BPH and may partially suppress serum PSA in men with prostate cancer.

Combination Alpha-adrenergic Antagonist and 5-Alpha-reductase Inhibitor

Therapy

The combination of an alpha$_1$-adrenergic antagonist and a 5-alpha-reductase inhibitor is an appropriate and effective treatment for patients with LUTS associated with demonstrable prostatic enlargement.

Give patients who are successfully treated with combination therapy the option of discontinuing the alpha-antagonist after 6–12 months. If symptoms recur, restart the alpha-antagonist.

Phosphodiesterase Type 5 Inhibitors

Tadalafil is the only phosphodiesterase type 5 inhibitor (PDE5I) indicated for the daily management of erectile dysfunction, LUTS associated with BPH or both. Men taking nitrate-based drugs, such as nitroglycerin, should not take tadalafil as it can lead to a dangerous decrease in blood pressure. Use of a PDE5I and an alpha1-adrenergic antagonist in combination leads to improved LUTS compared to alpha1-adrenergic antagonist monotherapy.

Phytotherapeutic Agents

Saw palmetto is the most popular and studied plant extract used to reduce symptoms related to BPH.

Therapeutic Tips

- Patients with minimal symptoms that do not interfere with their normal activities should be managed by active surveillance and regular follow-up.
- Patients starting to develop progressive symptoms or who are moderately inconvenienced or bothered by them are candidates for pharmacologic intervention.
- Continue drug therapy indefinitely since symptoms recur when medication is stopped.
- Complicating factors or unexpected (or lack of) response to any intervention are indications for urologic consultation.

- Avoid decongestants and other drugs with alpha-adrenergic activity because they can stimulate smooth muscle in the bladder neck and prostate, and increase obstruction.
- Drugs with anticholinergic activity may reduce detrusor contractility. Although they may not be as much of a problem as previously thought in patients with symptoms of bladder outlet obstruction, these agents should be used with caution.

Table 1: Procedures for Benign Prostatic Hyperplasia

Procedure	Description/Efficacy	Adverse Effects	Comments
Laser prostatectomy (various types)	1-day hospital stay; 80% reduction in symptoms.	Little or no bleeding.	Preferred technique for patients requiring anticoagulants or with uncorrected coagulopathies; long-term data awaited.
Retropubic prostatectomy	Open surgery; 3–5 days in hospital; similar efficacy to TURP.	Retrograde ejaculation (80–90%); bladder neck contracture (2–3%).	For very enlarged prostates or when required to correct other bladder pathology.
Transurethral incision of prostate (TUIP)	Outpatient; 80% reduction in symptoms.	Retrograde ejaculation (6–55%).	Useful for smaller prostates.
Transurethral resection of prostate (TURP)	1–2 days in hospital; gold standard for efficacy (85–90% reduction in symptoms).	Retrograde ejaculation (50–95%), urethral strictures (3%), bladder neck contracture (3–10%), re-	For moderately enlarged prostates.

Procedure	Description/Efficacy	Adverse Effects	Comments
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Class	Drug	Dose	Adverse Effects	Drug Interactions	Comments	Cost[a]
5-Alpha-reductase Inhibitors	*dutasteride* Avodart	0.5 mg daily po	Sexual dysfunction (3–4%).	Combination with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir) may increase serum concentration of dutasteride. Monitor for increased adverse reactions, e.g., impotence, decreased libido.	Blocks types I and II isoenzymes. ↓ prostate-specific antigen. Early response seen in 6 mo.	$$$
5-Alpha-reductase Inhibitors	*finasteride* Proscar, generics	5 mg daily po	Sexual dysfunction (3–4%).	No known clinically significant drug interactions.	Blocks type II isoenzyme. ↓ prostate-specific antigen. Early response	$$

Class	Drug	Dose	Adverse Effects	Drug Interactions	Comments	Cost[a]
					seen in 6 mo.	
Alpha$_1$-adrenergic Antagonists, nonselective	*doxazosin* Cardura, generics	1–12 mg QHS po Dose titrated weekly to desired response	Dizziness, headaches, asthenia and nasal congestion (5–20%); syncope (<1%).	Possible additive hypotension when combined with beta-blockers. Monitor blood pressure. May precipitate hypotension in conjunction with phosphodiesterase type 5 inhibitors (e.g., sildenafil).	Maximal response seen in weeks. May rarely cause intraoperative floppy iris syndrome. Patients undergoing cataract surgery should inform their ophthalmologist if they are or were using an α_1-adrenergic antagonist.[5]	$-$$
Alpha$_1$-adrenergic Antagonists, nonselective	*terazosin* Hytrin, generics	1–10 mg QHS po Dose titrated weekly to desired response	Dizziness, headaches, asthenia and nasal congestion (5–20%); syncope (<1%).	Possible additive hypotension when combined with beta-blockers. Monitor blood pressure.	Maximal response seen in weeks. May rarely cause intraoperative floppy iris syndrome.	$-$$

Class	Drug	Dose	Adverse Effects	Drug Interactions	Comments	Cost[a]
				May precipitate hypotension in conjunction with phosphodiesterase type 5 inhibitors (e.g., sildenafil).	Patients undergoing cataract surgery should inform their ophthalmologist if they are or were using an α_1-adrenergic antagonist.[5]	
Alpha$_{1A}$-adrenergic Antagonists, selective	*alfuzosin* Xatral, generics	10 mg daily po after the same meal each day	Vertigo (2%).	Possible additive hypotension when combined with beta blockers. Monitor blood pressure. Avoid combination with potent CYP3A4 inhibitors, e.g., ketoconazole, ritonavir. Excessive hypotension may occur.	Maximal response seen in weeks. May rarely cause intraoperative floppy iris syndrome. Patients undergoing cataract surgery should inform their ophthalmologist if they are or were using an α_1-adrenergic antagonist.[5]	$

Class	Drug	Dose	Adverse Effects	Drug Interactions	Comments	Cost[a]
					Shown to have a role in management of acute urinary retention.	
Alpha$_{1A}$-adrenergic Antagonists, selective	*silodosin* Rapaflo	8 mg daily po after the same meal each day. ↓ to 4 mg daily in patients with moderate renal impairment (ClCr 30–50 mL/min)	Diarrhea (2.6%), dizziness (3.2%), headache (2.4%), nasal congestion (2.1%), orthostatic hypotension (2.6%), retrograde ejaculation (28%).	↑ silodosin blood levels by potent CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, ketoconazole, ritonavir). No dose adjustment is required if combined with moderate CYP3A4 inhibitors (e.g., diltiazem). ↑ silodosin blood levels when combined with P-glycoprotein inhibitors (e.g.,	Maximal response seen in weeks. May rarely cause intraoperative floppy iris syndrome. Patients undergoing cataract surgery should inform their ophthalmologist if they are or were using an α_1-adrenergic antagonist.[5] Contraindicated in patients	$$$

Class	Drug	Dose	Adverse Effects	Drug Interactions	Comments	Cost[a]
				cyclosporine).	with severe renal impairment (ClCr <30 mL/min). Not recommended in severe hepatic insufficiency or if also using potent CYP3A4 inhibitors.	
Alpha$_{1A}$-adrenergic Antagonists, selective	*tamsulosin controlled-release* Flomax CR, generics	0.4 mg daily po at the same time each day, with or without food	Retrograde ejaculation (5–10%).	No known clinically significant drug interactions.	Maximal response seen in weeks. May rarely cause intraoperative floppy iris syndrome. Patients undergoing cataract surgery should inform their ophthalmologist if they are or were using an α_1-adrenergic	$

Class	Drug	Dose	Adverse Effects	Drug Interactions	Comments	Cost[a]
					antagonist.[5] Swallow pills whole; do not crush or chew.	
5-Alpha-reductase Inhibitors and Alpha$_{1A}$-adrenergic Antagonists Combinations	*dutasteride/tamsulosin modified release* Jalyn	0.5 mg dutasteride/ 0.4 mg tamsulosin (1 capsule) po 30 minutes after the same meal each day	Breast disorders (1%), ↓ libido (5%), dizziness (1%), ejaculation disorders (8%), impotence (5%). All are most pronounced within first 6 months of treatment.	Combination with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir) may increase serum concentration of dutasteride. Monitor for increased adverse reactions, e.g., impotence, decreased libido.	Blocks types I and II isoenzymes. ↓ prostate-specific antigen. Early response seen in 6 mo. Maximal response seen in weeks. May rarely cause intraoperative floppy iris syndrome. Patients undergoing cataract surgery	$$$

Class	Drug	Dose	Adverse Effects	Drug Interactions	Comments	Cost[a]
					should inform their ophthalmologist if they are or were using an α_1-adrenergic antagonist.[5]	
					Swallow pills whole; do not crush or chew.	
					Contact with the contents of the dutasteride soft gelatin capsule contained within the hard-shell capsule may irritate the oropharyngeal mucosa.	
					Indicated for the treatment of	

Class	Drug	Dose	Adverse Effects	Drug Interactions	Comments	Cost[a]
					moderate to severe symptomatic benign prostatic hyperplasia in men with enlarged prostates.	
Phosphodiesterase Type 5 Inhibitors	*tadalafil* Cialis	5 mg once daily po	Back pain, dyspepsia, flushing, headache, myalgia, nasal congestion. Rare: visual disturbances, permanent vision loss.	Contraindicated with nitrates (seek emergency care if chest pain presents within 24–48 hours of taking tadalafil; not to be given for 5 days after stopping long-acting nitrates). May cause hypotension if used with nonselective alpha-adrenergic antagonists (e.g., doxazosin).	Not recommended for those with severe renal or hepatic impairment.	