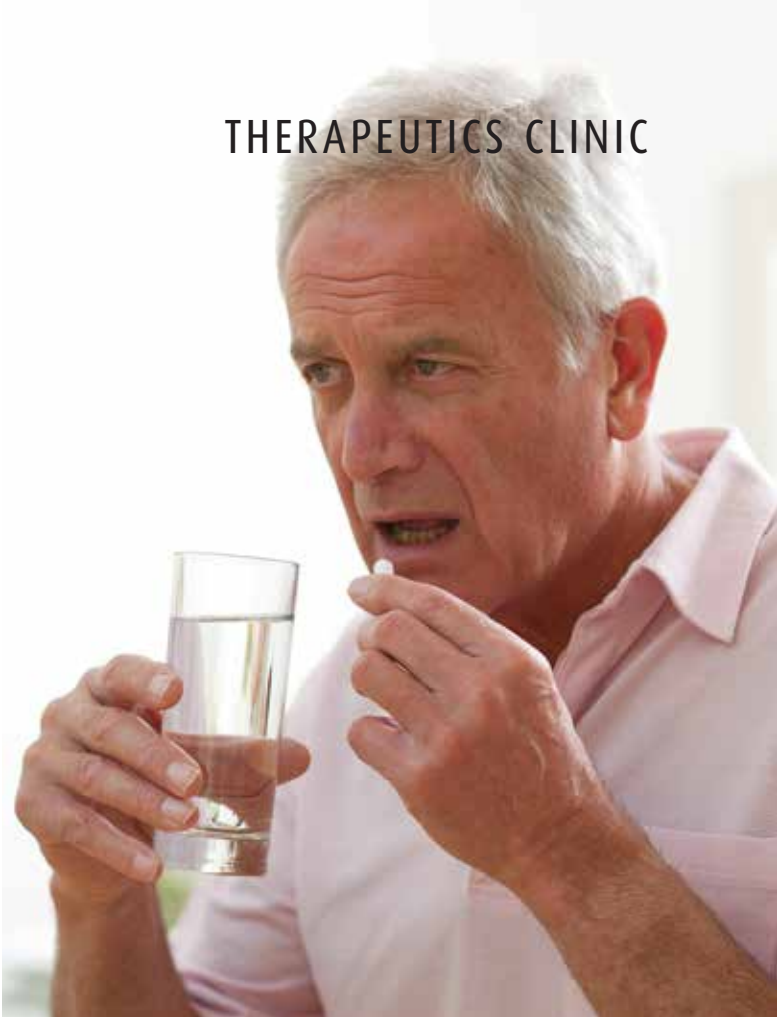
An update on the medical management of benign prostatic hypertrophy



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Medical therapy for men with symptomatic benign prostatic hypertrophy is continuously evolving. The two major classes of medications used in the treatment of affected men are selective α1-adrenergic receptor antagonists and 5α-reductase inhibitors. Depending on the type and severity of urinary symptoms, adjunctive therapies may also be used.

MedicineToday 2014; 15(10): 72-76

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Benign prostatic hypertrophy (BPH) is defined as the proliferation of smooth muscle and epithelial cells within the prostate resulting in an enlarged gland. BPH is a common condition of increasing importance in light of our ageing population, and can have a significant impact on a man's quality of life.

Medical therapy for men with BPH has evolved significantly. It is increasingly being used to improve the quality of life of those with uncomplicated moderate-to-severe lower urinary tract symptoms (LUTS) secondary to BPH, as well as reducing the need for surgery and the long-term risk of complications (Box). Bladder outlet obstruction secondary to BPH is thought to have two components:

- a dynamic component related to the tension of prostatic smooth muscle
- a fixed component related to the enlarged prostate impinging on the urethra.

The two major classes of medications used in the treatment of men with BPH are selective α1-adrenergic receptor antagonists (α1-blockers) and 5α-reductase inhibitors (5-ARIs), which act on the dynamic and fixed components of bladder outlet obstruction, respectively (Table 1). Adjunctive therapies to these two major classes include anticholinergics and mirabegron for men with predominantly storage urinary symptoms (i.e. urgency, frequency, incontinence), desmopressin for men with nocturnal polyuria, and low-dose tadalafil.

COMPLICATIONS OF BENIGN PROSTATIC HYPERTROPHY

- Recurrent infections
- Bladder stones
- Urinary retention
- Renal impairment

TABLE 1. DRUGS USED IN THE TREATMENT OF MEN WITH BENIGN PROSTATIC HYPERTROPHY

Drug class	Drug name
Selective α1-adrenergic receptor antagonists (α1-blockers)	Alfuzosin, tamsulosin, terazosin, prazosin
5α-reductase inhibitors (5-ARIs)	Dutasteride, finasteride
Combination medical therapy (5-ARIs plus α1-blockers)	Dutasteride/tamsulosin
Anticholinergics	Darifinacin, oxybutynin, propantheline, solifenacin, tolterodine
β3-adrenergic agonist	Mirabegron
Antidiuretic hormone analogue	Desmopressin
Phosphodiesterase-5 inhibitor	Tadalafil

SELECTIVE α1-ADRENERGIC RECEPTOR ANTAGONISTS

Selective α1-blockers relax prostatic smooth muscle by blocking α1-receptors, which are abundant in the prostate and bladder neck.[1,2] They have good long-term efficacy in terms of symptom relief but do not alter the progression of prostate growth.[3]

There are four selective α1-blockers available in Australia:

- alfuzosin
- tamsulosin
- terazosin
- prazosin.

Terazosin and prazosin (which are less selective than alfuzosin and terazosin) are also indicated for the treatment of patients with hypertension due to their blockade of postsynaptic α1-receptors, thereby inhibiting catecholamine-mediated vasoconstriction. However, α1-blockers are inferior to other classes of antihypertensives and, as a result, LUTs and hypertension should be treated as two separate disease entities.[4,5]

Due to the lack of large multicentre randomised clinical trials, prazosin is not recommended for the treatment of men with LUTS.[6] Alfuzosin, tamsulosin and terazosin are all listed on the Repatriation Pharmaceutical Benefits Scheme (RPBS) with authority required (where surgery is inappropriate or other drug treatment has failed or is contraindicated).

The recommended dosage for alfuzosin is 10 mg/day and for tamsulosin is 400 µg/day. Terazosin requires dose titration, generally starting at 1 mg/day for seven days then titrating to clinical response up to 5 to 10 mg/day.

Alfuzosin, tamsulosin and terazosin are equally efficacious, but they differ in their side effect profiles. The most common side effects of all α1-blockers are first-dose hypotension, orthostatic hypotension and dizziness. These side effects are more common with the use of terazosin and therefore this drug should be initiated at night-time and used with caution in the elderly.[7] Unlike with alfuzosin and tamsulosin, patients taking terazosin require blood pressure monitoring. Ejaculatory dysfunction is an uncommon reversible side effect that seems restricted to tamsulosin use.[8-10]

An important factor to consider when using α1-blockers is the risk of developing intraoperative floppy iris syndrome, which is most common with tamsulosin use.[11] Cessation of medication does not appear to reduce this risk. There is evidence that the risk of complications from intraoperative floppy iris syndrome during cataract surgery can be nullified if the treating ophthalmologist is aware of a patient's use of α1-blockers and employs a modified surgical technique.[12] Therefore, GPs should delay initiating α1-blockers in men with planned cataract surgery until after surgery is complete. For men already taking α1-blockers who are about to undergo cataract surgery, GPs should not discontinue therapy and should notify the ophthalmologist of α1-blocker use.

5α-REDUCTASE INHIBITORS

5-ARIs act by preventing the conversion of testosterone to dihydrotestosterone, a potent cellular androgen that stimulates prostate growth. They improve LUTS (although they are less effective than α1-blockers)[13] and additionally reduce the risk of acute urinary retention and progression to surgery.[14] However, benefit of the use of 5-ARIs is only evident in men with prostatic sizes of more than 40 mL and they should not be prescribed to men with a prostate smaller than this.

Two 5-ARIs are available in Australia, dutasteride and finasteride, and they are listed on the RPBS with authority required (where surgery is inappropriate or when other drug treatment has failed or is contraindicated). There are two important pharmacological differences between these two 5-ARIs. Firstly, dutasteride inhibits 5α-reductase type 1 and 2 isoenzymes, whereas finasteride inhibits 5α-reductase type 2 isoenzyme only.[15] This leads to a greater reduction of dihydrotestosterone levels in prostate tissues with dutasteride use (94%) compared with finasteride use (80%) in relation to placebo; however, the clinical effect of this greater reduction is unknown.[16-18] Secondly, the half-life of dutasteride (three to five weeks) is much longer than finasteride (six hours) and this may have implications on the persistence of side effects.

TABLE 2. STARTING DOSES AND MAXIMUM DOSES OF ANTICHOLINERGICS

Anticholinergic	Starting dose	Uptitrated dose
Darifenacin	7.5 mg once daily	15 mg once daily
Oxybutynin	2.5 mg twice to three times daily	5 mg four times a day
Propantheline	15 mg twice to three times daily	30 mg four times a day
Solifenacin	5 mg once daily	10 mg once daily
Tolterodine	1 mg twice daily	2 mg twice daily

The dose of dutasteride used is 500 µg/day and of finasteride 5 mg/day. At the time of prescribing, patients need to be counselled that it can take up to six months for benefits of treatment to be seen. Side effects are primarily sexually related, including reduced libido, impotence and reduced ejaculate volume.[19] These side effects are generally reversible on cessation of treatment, but in a small subset of men they can be persistent[20-22] and therefore it is important that sexually active men receive adequate counselling before initiation.

After six months of dutasteride use and one year of finasteride use, prostate specific antigen (PSA) levels should have halved. If this does not occur, the presence of prostate cancer should be suspected. For this reason, it is important to undertake prostate cancer assessment before initiating treatment, including a digital rectal examination and PSA test. Six months after ceasing treatment, PSA levels generally return to baseline levels. It is worth noting that the lower doses of 5-ARIs used off label to treat hair loss (e.g. finasteride 1 mg/day, compared with 5 mg/day for BPH) result in a similar reduction in PSA levels[23] and as a result PSA reference ranges in these men need to be adjusted accordingly.

As testosterone is essential for the growth and proliferation of prostatic tumour cells[24] and 5-ARIs inhibit the formation of the potent androgen dihydrotestosterone, finasteride and dutasteride have been studied as chemopreventive agents for prostate cancer.[25,26] These studies found that although both the 5-ARIs decreased the overall incidence of prostate cancer, there was an increased rate of high-grade prostate cancers.[26,27] For this reason, the US Food and Drug Administration does not recommend the use of 5-ARIs for chemoprevention in healthy men, with an estimate that one additional high-grade cancer would occur for every three to four lower-grade cancers prevented.[28] Warnings appear on the Australian labels of the two drugs to reflect an increased risk of high-grade prostate cancer.

COMBINATION MEDICAL THERAPY

Combination therapy for men with BPH is the use of a 5-ARI plus an α1-blocker. The only combination product available in Australia is dutasteride plus tamsulosin with a recommended dosage of 500/400 µg/day. It is listed on the PBS with authority requiring urologist initiation of treatment. In men with prostate volumes of more than 40 mL, combination therapy is superior to either medication alone in preventing BPH progression and improving symptoms.[29,30] However, the risk of impotence and ejaculatory dysfunction are also increased compared with monotherapy[31] and as a result careful counselling of patients is required on initiation of treatment.

ADJUNCTIVE THERAPIES

Anticholinergics

Anticholinergics used in conjunction with an α1-blocker can be useful for men with predominantly storage urinary symptoms and low postvoid residual volumes.[6] Anticholinergics act by inhibiting bladder contractions that are stimulated by the effects of acetylcholine on muscarinic receptors in the smooth muscle of the bladder. A list of anticholinergics and their recommended starting doses are shown in Table 2. These doses can be slowly uptitrated; however, the benefits need to be balanced with the tolerability of side effects, particularly dry mouth.[32] Oxybutynin is also available as a patch (3.9 mg/day) that needs to be applied twice a week (every three to four days). Common side effects are dose related and include dry mouth, constipation and urinary retention. Only oral oxybutynin and propantheline are listed on the PBS with benefit restricted to men with detrusor overactivity. The oxybutynin patch is PBS listed for men with detrusor overactivity who cannot tolerate or swallow oral oxybutynin. Due to the risk of urinary retention, anticholinergics should be avoided in men with high postvoid residual volumes (>200 mL).

Beta 3-adrenoreceptor agonists

Mirabegron is the first β3-adrenoreceptor agonist, a novel class of drugs, to be approved by the Therapeutics Goods Administration for the management of men with overactive bladder syndrome[33] and has been shown to be safe in men with bladder outlet obstruction.[34] Mirabegron works by selectively acting on β3-adrenoreceptors in the detrusor muscle resulting in relaxation of the smooth muscle facilitating urine storage.[35] Although anticholinergics remain first-line treatment in the management of men with overactive bladder syndrome, mirabegron represents an alternative for those who do not respond to or are unable to tolerate the adverse effects of anticholinergics.

The recommended starting dose of mirabegron is 25 mg/day and the dose may be uptitrated to 50 mg/day depending on clinical response and tolerability. The most common side effects of mirabegron include small increases in blood pressure, nasopharyngitis and urinary tract infections.[36,37] For this reason, blood pressure monitoring is recommended in those patients with hypertension. The incidence of dry mouth, the most intolerable adverse effect of anticholinergics for patients,[32] is similar to that reported with

placebo;[37,38] therefore, this drug is a good option for men unable to tolerate anticholinergics. Like anticholinergics, mirabegron should be avoided in men with high postvoid residual volumes. Mirabegron is not currently listed on the PBS.

Antidiuretic hormone analogues

Although desmopressin is only indicated and PBS listed for patients with central diabetes insipidus and nocturnal enuresis, it may be used off label in men with nocturnal polyuria as a predominant urinary symptom.[39,40] It is a synthetic analogue of vasopressin (an antidiuretic hormone) and acts by increasing tubular reabsorption of water.

The recommended dose for desmopressin is 50 µg/day, which can be increased to 75 µg/day.[39] Due to its mechanism of action, long-term desmopressin therapy gradually reduces serum sodium levels and may result in hyponatraemia. Therefore, serum sodium monitoring is required before treatment is started, one week after and periodically thereafter.[40] Other adverse effects include dry mouth, headache and constipation.

Phosphodiesterase-5 inhibitors

A number of studies have shown that low-dose tadalafil, a long-acting phosphodiesterase-5 (PDE5) inhibitor traditionally indicated for erectile dysfunction, can improve LUTS secondary to BPH.[41-44] It is thought to act by relaxing the smooth muscle in the bladder neck, prostate and urethra and increasing pelvic blood perfusion in these tissues. Although tadalafil seems to improve LUTS, it does not improve uroflowmetry parameters, raising questions about these mechanisms of action. A recent study suggests that PDE5 inhibitors may additionally modulate sensory activity of nerve fibres in an irritated and overextended bladder, thereby improving LUTS secondary to BPH.[45]

The role of tadalafil in the treatment of men with LUTS is currently not established, with selective α1-blockers remaining first-line treatment. Tadalafil is taken at a dose of 5 mg/day for LUTS (off-label use). Side effects are generally well tolerated and include headache, dizziness and flushing. When used in combination with α1-blockers, the blood pressure-lowering effects of tadalafil are increased and this combination should be used with caution.

CONCLUSION

Medical therapy of BPH has evolved significantly and plays an important role in men with uncomplicated moderate to severe symptomatic BPH. The two major classes of drugs used are selective α1-blockers and 5-ARIs. Combination therapy provides maximal benefit over either group of drugs alone in men with large prostates. Adjuncts to these medications include anticholinergics and mirabegron for men with predominantly storage urinary symptoms, desmopressin for men with nocturnal polyuria as the predominant urinary symptom, and low-dose tadalafil. MT

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A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

COMPETING INTERESTS: None.

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