Benign prostatic hyperplasia

By Lynn Gould

Learning objectives
After reading this article you should be able to:

• Identify symptoms suggestive of benign prostatic hyperplasia (BPH).
• Provide advice to customers on medicines used to treat BPH, in particular tamsulosin.
• Discuss complementary and non-drug therapies used in the treatment of BPH.
• Provide advice on lifestyle modifications which may help to alleviate the symptoms BPH.

Competency standards (2010) addressed:
4.2.2, 4.3.3, 7.1.2

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Case study

Mr Edkins, a 73-year-old customer, presents a script for tamsulosin. He has just visited his doctor because he has been getting up to urinate several times during the night and has also started having difficulty urinating. The doctor has diagnosed him with benign prostatic hyperplasia (BPH) and has given him the script for tamsulosin and a referral to a urologist. Mr Edkins has a history of hypertension and depression, for which he takes ramipril 5 mg daily, hydrochlorothiazide 12.5 mg daily and sertraline 50 mg daily.

What is BPH?

Benign prostatic hyperplasia (BPH) is non-malignant enlargement of the prostate gland. The prostate gland is located beneath the bladder and surrounds the top part of the urethra. It produces a fluid that is secreted into the urethra and makes up about half of the volume of seminal fluid, helping to keep the sperm alive and motile. When testosterone levels in boys begin to rise during puberty, the prostate grows about eight times in size. It then continues to grow slowly, doubling in size from ages 21 to 50, and almost doubling again between the ages of 50 and 80.\(^1\)

The causes of BPH are not well understood, but it is thought that hormonal changes associated with ageing may be involved. The hormonal changes that are thought to promote prostate enlargement include an increase in the oestrogen-testosterone ratio that normally occurs as men age and an accumulation of dihydrotestosterone (DHT) in the prostate, which stimulates the growth of cells. Another theory is that BPH may develop as a result of a ‘reawakening’ in adulthood of embryonic induction processes. Although not all men who have BPH are symptomatic, it is estimated that BPH is present in approximately 20%
of men aged 41–50, 50% of men aged 51–60, and 90% of men over the age of 80.1,6

What problems can BPH cause?

For some men, the symptoms of BPH are quite mild or non-existent. There is a range of urinary symptoms associated with BPH which are commonly referred to as lower urinary tract symptoms, or LUTS. These symptoms are thought to occur for two reasons. Firstly, hyperplasia of the prostate can cause compression of the urethra resulting in bladder outlet obstruction (obstructive symptoms). Secondly, prolonged obstruction of the bladder outlet causes the detrusor (the muscle of the bladder wall) to increase in tone in an attempt to compensate, leading to detrusor overactivity (irritative symptoms).1,3,6

Obstructive symptoms include: hesitancy (a longer than usual wait for the stream of urine to begin); a weak and poorly directed stream of urine; straining to urinate; post-urination dribbling or an irregular stream; urinary retention; and overflow or paradoxical incontinence (urine overflows uncontrollably from a full bladder although normal urination cannot be initiated). Irritative symptoms include: urgency (an urgent desire to urinate); frequency (frequently needing to urinate); and nocturia (a need to pass urine more than twice at night). The prevalence and severity of LUTS usually increases with increasing age, although the severity of symptoms is not necessarily related to prostate size.1,3,6

Straining to urinate can cause congestion of superficial veins in the prostatic urethra, which may rupture and produce haematuria. Repeated straining over a prolonged period of time may result in haemorrhoids or inguinal hernias. Sometimes a man may not realise that he has BPH until he suddenly finds himself unable to urinate at all. This is known as acute urinary retention and may be precipitated by long periods of immobility, exposure to cold, or the use of anaesthetics, anticholinergics, sympathomimetics, opioids or alcohol. Other complications that may be caused by BPH include urinary tract infections, bladder stones and renal impairment.2,3,7

Other medical conditions that can cause lower urinary tract symptoms include infections, prostate cancer, neurological disease and renal disease. Men who present with these symptoms should be promptly referred to a doctor for further investigation.2,3,6

How does tamsulosin work?

Tamsulosin works by relaxing the muscles in the bladder neck and prostate, reducing bladder outlet obstruction and improving urine flow. Tamsulosin is a selective alpha,-adrenergic-receptor blocking agent (other drugs in this class are alfuzosin, prazosin and terazosin). It selectively blocks the alpha, receptor subtypes found in the bladder and prostate, producing localised relaxation of smooth muscle. The symptoms associated with BPH may improve within 48 hours of commencing tamsulosin, with full effect usually seen within four to six weeks.3,10

How should I take tamsulosin?

The dose of tamsulosin is one tablet a day. The tablet needs to be swallowed whole, preferably with a glass of water. It should not be not broken, crushed or chewed, as this will compromise its prolonged release properties. It can be taken before, with or after food. If there is no improvement in symptoms after four to six weeks of treatment, it is unlikely that it will be effective and an alternative treatment may need to be prescribed.1,12

Are there any unwanted effects?

Common side effects of tamsulosin include ejaculatory dysfunction (particularly retrograde ejaculation, where the semen flows backwards into the bladder during ejaculation) and dizziness. Less common side effects include weakness, constipation, diarrhoea, nausea, vomiting, headache, pruritus, rhinitis, somnolence and skin peeling-off (desquamation). Tamsulosin may also induce or aggravate stress incontinence due to sphincter relaxation. Current or previous therapy with tamsulosin may increase the risk of intra-operative floppy iris syndrome during cataract surgery. Inhibition of iris dilator smooth muscle has been suggested as a potential mechanism. Tamsulosin has also been associated with increased rates of post-operative ocular complications.6,10

Potentially serious adverse reactions to tamsulosin may occur infrequently. They include palpitations, orthostatic hypotension, urticaria, fainting and angioedema (which may present as hoarseness, large hive-like swellings on eyelids, face, genitals, hands, feet, lips, throat, tongue, and difficulty swallowing or breathing). An extremely rare side effect of tamsulosin is priapism, a persistent, painful penile erection unrelated to sexual activity. If priapism occurs immediate medical attention should be sought as, without treatment, it can lead to permanent erectile dysfunction.6,9

Will it affect any of my other medicines?

There is limited clinical data available on interactions between tamsulosin and other drugs. Tamsulosin may cause orthostatic hypotension, and administration with other drugs that can lower blood pressure may result in additional hypotensive effects. This increases the risk of first-dose hypotension or a sharp drop in blood pressure. As Mr Edkins is taking other blood-pressure lowering medicines, it is important to warn him that he may experience some dizziness when commencing tamsulosin. Concurrent use of a phosphodiesterase 5 [PDE5] inhibitor (sildenafil, tadalafil or vardenafil) with tamsulosin may result in symptomatic hypotension. If Mr Edkins starts taking a PDE5 inhibitor while on tamsulosin therapy, he should begin with a low dose of the PDE5 inhibitor and leave at least a four-hour gap (six hours with vardenafil) between the administration of each medicine. Concurrent administration of tamsulosin with other alpha,-blockers is contraindicated because of the potential for hypotensive effects.7,8

Tamsulosin is metabolised in the liver, primarily by cytochrome P450 (CYP) 3A4 and 2D6. It is therefore theoretically possible that inducers or inhibitors of CYP3A4 or CYP2D6 may affect tamsulosin plasma concentrations. CYP2D6 inhibitors include all selective serotonin reuptake inhibitors, with fluoxetine and paroxetine being
the most potent. CYP3A4 inducers include phenytoin and St John’s wort, and CYP3A4 inhibitors include clarithromycin, diltiazem, verapamil and ketoconazole.\(^7\)--\(^9\)

Tamsulosin also binds extensively to plasma proteins and may displace other protein-bound drugs. However, this is unlikely to be clinically significant, as most drugs which are extensively bound to plasma proteins (e.g. warfarin, phenytoin, sodium valproate, methotrexate) have low-extraction ratios and any increase in the free fraction should be rapidly metabolised and cleared.\(^8\)--\(^11\)

If tamsulosin doesn’t work, are there any other medicines the doctor can prescribe?

If Mr Edkins’ symptoms do not improve with tamsulosin therapy, the use of a 5-alpha-reductase inhibitor (finasteride or dutasteride) may be considered. These medicines inhibit the enzyme 5-alpha-reductase, which converts testosterone to dihydrotestosterone (DHT). 5-alpha-reductase inhibitors are indicated for use in symptomatic BPH when the prostate size is >30-40 cm\(^3\). They reduce prostate size, thereby improving urinary symptoms and urinary flow rate, and reducing the risk of acute urinary retention and the need for surgery. It may take six months or longer for symptoms to improve and 12–18 months before the full effect is seen. Adverse effects may include impotence, decreased libido, ejaculation disorder (including decreased ejaculate volume) and breast tenderness or enlargement.\(^1\)--\(^12\)

Combination treatment with alpha\(^1\)-blockers and 5-alpha-reductase inhibitors medicines may be considered when prostate size is >30–40 cm\(^3\) and rapid relief of troublesome symptoms is required as alpha\(^1\)-blockers relieve symptoms more rapidly than 5-alpha-reductase inhibitors.\(^7\)--\(^12\)

A promising new treatment that is still under investigation is botulinum toxin type-A (BTX-A) which can be injected directly into the prostate. Although the mechanism of action is not yet fully understood, it appears to reduce the size of the prostate as well as relaxing the smooth muscle of the prostate and urethral sphincter. Clinical trials are being carried out to investigate its efficacy and safety.\(^1\)--\(^13\)

Are there any complementary and alternative treatments for BPH?

The herbal medicine most commonly used for BPH is saw palmetto (Serenoa repens). Cochrane reviews carried out in 1998 and 2002 concluded that saw palmetto provided mild improvement of symptoms in BPH. However, a review carried out in 2008 found that saw palmetto did not provide noticeable relief of urinary symptoms and was no better than placebo for the treatment of BPH. The most common adverse effects of saw palmetto are gastrointestinal and include abdominal discomfort, nausea, vomiting and diarrhoea. Headaches, sexual dysfunction and two cases of severe bleeding have also been reported. Based on the proposed anti-androgenic activity of saw palmetto, it is possible that additive effects may occur if it is used concomitantly with 5-alpha-reductase inhibitors. Because there have been reports of bleeding with saw palmetto, it should be used cautiously with anticoagulants.\(^1\)--\(^14\)--\(^16\)

Another herbal medicine which has been used to treat BPH is an extract from the bark of the African prune tree *Pygeum africanum*. A 1998 Cochrane review found that *Pygeum africanum* is well tolerated and provides moderate relief from the symptoms of BPH. However, the authors caution that the reviewed studies were small and of short duration, used varied doses and preparations and rarely reported outcomes using standardised validated measures of efficacy. They conclude that additional well-designed trials are needed before definitive recommendations can be made.\(^1\)--\(^16\)

Are there any non-drug treatments for BPH?

Men with severe BPH symptoms which have not responded to pharmacotherapy may require surgery. The standard surgical therapy is transurethral resection of the prostate (TURP). It involves removing part of the prostate via an endoscope through the urethra. If the prostate is greatly enlarged (>80 cm\(^3\)) an open prostatectomy, via an incision in the lower abdominal area, may be considered. Possible complications of these procedures include TUR syndrome (a dilutional hyponatraemia caused by absorption of irrigating solution into the bloodstream), erectile dysfunction, urinary incontinence, retrograde ejaculation, bladder neck contracture, urinary tract infections and haematuria.\(^1\)--\(^16\)

Alternative, less invasive procedures include:\(^1\)--\(^16\)

- Laser therapy, which uses laser energy to produce a variety of effects within prostate tissue including coagulation necrosis and vapourisation. This treatment causes less bleeding than TURP and is generally recommended for men taking anticoagulants. However, because of the cost of the laser machine, it is not available in all hospitals.
- Transurethral microwave thermotherapy (TUMT), in which the prostate is heated using a microwave antenna mounted on a urethral catheter. Although this treatment has fewer and less serious side-effects than TURP, it is not commonly used as it has lower success rates than TURP.

Can I do anything else to help relieve my symptoms?

Certain lifestyle modifications may help to alleviate symptoms of BPH. These may include:\(^1\)--\(^12\)--\(^17\)

- Limiting daily fluid intake to less than 2,000 mL and avoiding drinking after the evening meal;
- Reducing intake of caffeine, alcohol and spicy foods;
- Avoiding constipation – eat plenty of fruit, vegetables and fibre-containing foods;
- Staying active – immobility may increase the risk of urine retention;
- Avoiding activities that involve vibration or trauma to the perineum (e.g. bike riding, tractor driving, long-distance driving);
- After urinating, waiting for a short time and trying to urinate again (‘double-voiding’);
- Trying to urinate at least once every three hours;
- Avoiding medicines that may worsen urinary incontinence (e.g. decongestants, antihistamines);
- Doing pelvic floor exercises;
- Learning how to do urethral milking, which helps to expel any residual urine by physically pressing the urinary tract. A doctor or continence nurse can show men how to do this.
is taking, or has taken, tamsulosin. Lifestyle modifications which may help to alleviate his symptoms can also be suggested.

Key learning points

- BPH becomes increasingly common as men get older, and is present in approximately 90% of men over the age of 80. For some men the symptoms are quite mild or non-existent, however, many men experience a range of lower urinary tract symptoms (LUTS). These can include hesitancy, urinary retention, overflow incontinence, urgency, frequency and nocturia.

- Drugs used for BPH include selective alpha<sub>1</sub>-adrenergic blockers (tamsulosin, alfuzosin, prazosin and terazosin) and 5-alpha-reductase inhibitors (finasteride and dutasteride).

- Men with severe symptoms which have not responded to drug therapy may require surgical intervention. Non-drug therapies which are available include transurethral resection of the prostate (TURP), laser therapy, transurethral microwave thermotherapy (TUMT) and prostatectomy.

- Men can also try certain lifestyle modifications which may help to alleviate the symptoms of BPH. Because LUTS can also be caused by other disorders, including infections, prostate cancer, neurological disease or renal disease, men with these symptoms should be referred to a doctor for investigation.

References

Combination therapy for BPH approved

*Duodart* (dutasteride/tamsulosin hydrochloride) has been approved for use in Australia as a new, convenient option for men diagnosed with moderate to severe symptomatic benign prostatic hyperplasia (BPH). It combines a 5-alpha reductase inhibitor (dutasteride) and an alpha blocker (tamsulosin) into a single treatment.

A recent study has shown that combination therapy – where dutasteride is used in combination with tamsulosin – provides rapid, superior and sustained symptom improvement in BPH compared to tamsulosin or dutasteride alone (as measured by International Prostate Symptom Score (IPSS), p<0.001 for both comparisons at 4 years). Combination therapy also significantly reduced the relative risk of BPH clinical progression over four years compared to either monotherapy. The primary end point, time to acute urinary retention or BPH related surgery, was also significantly longer with combination therapy versus tamsulosin (p<0.001) but there was no significant difference between combination therapy and dutasteride monotherapy (p=0.18). While the occurrence of drug-related adverse events was significantly greater in those patients receiving combination therapy in this study, withdrawal rates due to drug related adverse events were similar across the treatment groups. Dutasteride/tamsulosin is not PBS listed. According to the Minimum Product Information, dutasteride/tamsulosin is indicated for the management of moderate to severe symptomatic benign prostatic hyperplasia (BPH). Contraindications include: Hypersensitivity to dutasteride, other 5-alpha reductase inhibitors, tamsulosin hydrochloride, or any component of the preparation; use in women and children; pregnancy (Category X); lactation; history of orthostatic hypotension; severe hepatic impairment; severe renal impairment; combination with another alpha-blocker.

GlaxoSmithKline’s registration of *Duodart* follows the PBS listing of Avodart (dutasteride), in combination with an alpha blocker, from February 2011.

Reference