Benign prostatic hyperplasia: treatment in primary care
Anand K Patel and Christopher R Chapple

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How do I treat it?
The treatment of lower urinary tract symptoms that are suggestive of bladder outflow obstruction, secondary to benign prostatic hyperplasia, should aim to relieve symptoms and improve quality of life, as well as attempt to prevent progression of clinical disease and the development of complications. These benefits need to be balanced against potential side effects of treatment.

Watchful waiting
Patients with mild symptoms that have little impact on quality of life and who have no evidence of complications can be managed conservatively. They should be advised to reduce fluid intake and avoid caffeinated drinks and alcohol if appropriate. This requires the use of frequency and voiding charts.

It may be helpful to review the drugs they are taking, such as diuretics, and any impairment of mental state, dexterity, or mobility should be optimised to limit the impact on quality of life. Patients selected for watchful waiting should be encouraged to seek medical advice if their symptoms deteriorate, so appropriate treatment can be initiated promptly.

Medical treatment
Options if medical treatment is needed are:

- α Antagonists
- 5α Reductase inhibitors
- Combination therapy.

α Antagonists
Contraction of the prostatic smooth muscle occurs after activation of the α1 adrenoceptors. Inhibition of these receptors relaxes the muscle in the bladder outflow tract; this decreases urinary outflow resistance and helps improve the symptoms. α Antagonists are the first line treatment for benign prostatic hyperplasia.

Summary points
| Benign prostatic hyperplasia leads to progressive clinical disease in a proportion of patients |
|α Antagonists rapidly improve lower urinary tract symptoms, and alfuzosin and tamsulosin (as once daily preparations) are the safest options |
|5α Reductase inhibitors reduce prostatic volume by 20-30% but take up to six months to improve symptoms |
|5α Reductase inhibitors are more effective in patients with larger prostates who are at high risk of progression of disease |
|Long term combination therapy (α antagonist plus 5α reductase inhibitor) decreases progression of disease in patients at high risk |

Benefits
α Antagonists act rapidly (usually within 48 hours), and improvement of symptoms is immediately noticeable to the patient. About 70% of men will respond to this treatment, and non-responders can be identified rapidly and other treatments instigated.

Evidence
Many randomised controlled trials have been performed, and recent systematic reviews have confirmed that all α antagonists have a similar efficacy and that newer longer acting drugs are no more effective than older ones. These drugs tend to improve symptom scores by 30-40% and improve the maximum flow rate by 15-30%. Unlike 5α reductase inhibitors, they do not affect prostate volume and therefore do not alter disease progression.

Side effects
Although all α antagonists have similar efficacies, their side effects differ because they have different actions on α receptors in other organ systems, particularly the
Alfuzosin
Open label studies with alfuzosin have shown that patients with pre-existing cardiovascular disease or those taking other drugs are at increased risk of developing cardiovascular side effects with this drug. This is also the case for patients over 74 years.

However, prolonged release formulations have fewer age related side effects and are associated with only a slightly increased risk of cardiovascular side effects in patients with pre-existing hypertension. The side effects therefore depend on the formulation, and this should be considered carefully when choosing a preparation.

Doxazosin
Four studies have shown an increase in cardiovascular side effects when this drug is used in patients with known or treated hypertension. Data were consistent across all four studies but were not statistically significant, probably because of the low number of patients in the hypertensive subgroups.

Terazosin
Blood pressure was lowered more frequently with this drug than with placebo, but cardiovascular side effects were not significantly different in the hypertensive and non-hypertensive subgroups.

Tamsulosin
Trials have confirmed that tamsulosin is well tolerated and that side effects are not significantly different from placebo in elderly patients and patients with hypertension.

Three randomised controlled trials have studied the effect of concurrent treatment with tamsulosin and antihypertensive drugs (nifedipine, enalapril, and atenolol). They found no alteration in the pharmacodynamic response and no need to adjust the dose of the antihypertensive drugs. Blood pressure is lowered further when a phosphodiesterase type 5 inhibitor (sildenafil, tadalafil, and vardenafil) is added to most α antagonists, although this effect is minimal with tamsulosin.

Recently a new controlled release delivery system for tamsulosin—the oral controlled absorption system (Flomaxtra XL) has been developed to achieve continuous and consistent absorption of tamsulosin throughout the gastrointestinal system. This new preparation maintains consistent 24 hour plasma concentrations of the drug. However, the efficacy is similar to existing preparations.

Doses
- Alfuzosin: 2.5 mg three times a day or 10 mg once a day (once daily preparation)
- Doxazosin: 1-8 mg once a day (usual maintenance dose 2-4 mg once a day)
- Tamsulosin: 0.4 mg once a day (same dose for modified release formulations)
- Terazosin: 1-10 mg once a day (usual maintenance dose 5-10 mg once a day). This drug needs to be titrated to its therapeutic dose to avoid first dose hypotension. It therefore has a slower onset of action than drugs that are started at their therapeutic dose.

Recommendations
α Antagonists are suitable for patients with moderate to severe lower urinary tract symptoms and a low or intermediate risk of progression of disease. Based on systematic reviews, tamsulosin and once daily preparations of extended release alfuzosin have the lowest risk of cardiovascular adverse events and are suitable as first line agents, especially in high risk and elderly patients. The other α antagonists are appropriate for younger patients or those unlikely to have cardiovascular side effects.

Floppy iris syndrome, which may cause technical problems during cataract surgery, has recently been reported as a side effect of α antagonists. This syndrome is seen most often with tamsulosin, and ophthalmologists undertaking cataract surgery need to identify patients who are taking an α antagonist.

5α Reductase inhibitors
Testosterone is converted to dihydrotestosterone by the enzyme 5α reductase within prostate cells. Dihydrotestosterone acts on prostatic tissue to induce

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**Side effects of α antagonists**

- **Cardiovascular system**
  - Postural hypotension
  - Headaches
  - Dizziness

- **Central nervous system**
  - Dizziness
  - Asthenia
  - Somnolence

- **Genitourinary system**
  - Abnormal ejaculation
  
  Abnormal ejaculation is a recognised side effect of treatment with an α antagonist. No α antagonist has been shown definitely to have a better profile for this side effect, although a higher incidence of abnormal ejaculation has been reported for tamsulosin.

Elderly patients are less likely to discontinue treatment because of ejaculatory dysfunction than cardiovascular side effects. The cardiovascular side effects should determine the choice of α antagonist in older patients but not in younger men.

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**GP tips**

Refer all patients with complications of benign prostate hyperplasia (haematuria, retention, renal dysfunction, and recurrent urinary tract infections) to their urologists.

Although all α antagonists have a similar efficacy, the tolerability and side effects are determined by the formulation given.

Make patients aware that 5α reductase inhibitors take about six months before improvements in symptoms are seen.

5α Reductase inhibitors decrease serum prostate specific antigen concentrations by about 50%.
benign prostatic hyperplasia. 5α Reductase inhibitors decrease the production of dihydrotestosterone, thereby arresting prostatic hyperplasia.

Two 5α reductase inhibitors are licensed in the United Kingdom, finasteride and dutasteride (table 1).

Benefits

5α Reductase inhibitors are thought to decrease the progression of disease and the development of acute urinary retention. They are especially beneficial for patients with risk factors for progression of disease (table 2).15

The reduction in risk is a consequence of the decrease in prostate volume with the use of 5α reductase inhibitors. However, shrinkage is slow and symptoms often do not improve in the first six months of treatment.

Side effects

Side effects are:

- Erectile dysfunction
- Reduced libido
- Ejaculatory disorders
- Gynaecomastia
- Breast tenderness.

Evidence

Finasteride

A systematic review of 19 randomised placebo controlled trials showed that symptom scores and flow rates consistently improved and prostate volume decreased by 25% in patients on finasteride.16 However, about a third of men stopped taking finasteride over two years. Only 6% of these men stopped because of lack of benefit and 12% stopped because of side effects, and the number of men who stopped taking finasteride was not significantly different from those who stopped taking placebo.

Dutasteride

Two multicentre randomised placebo controlled trials lasting two years with open label extension for a further two years have been pooled.17 These showed improved symptom scores, a 26% decrease in prostatic volume, and improved urinary flow rates with dutasteride. They also showed a 57% reduction in relative risk of acute urinary retention and a 48% reduction in relative risk of the need for prostatic surgery.

However, a large head to head randomised multicentre comparison trial between finasteride and dutasteride found no significant difference between these drugs with respect to their safety profiles or changes in prostate volume, symptom score, or peak flow rate.11 16 Thus little difference exists between the two drugs, and a dual action 5α reductase inhibitor does not seem to be of additional benefit in the management of benign prostatic hyperplasia.

Table 1 Reduction in dihydrotestosterone by 5α reductase inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type of enzyme inhibited</th>
<th>Reduction of serum dihydrotestosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finasteride</td>
<td>5α reductase type 2</td>
<td>70-75%</td>
</tr>
<tr>
<td>Dutasteride</td>
<td>5α reductase types 1 and 2 (dual action)</td>
<td>90-95%</td>
</tr>
</tbody>
</table>

Doses

- Finasteride: 5 mg once daily
- Dutasteride: 0.5 mg once daily.

Cautions

Both dutasteride and finasteride decrease serum concentrations of prostate specific antigen by about a half, and reference values need to be adjusted if a patient is suspected of having or is being followed up for prostate cancer.

Recommendations

5α Reductase inhibitors are a suitable option in patients with moderate or severe lower urinary tract symptoms with an obviously enlarged prostate or prostate specific antigen concentration greater than 1.4 μg/litre.19 Both currently available agents have similar efficacies and profiles of adverse events. It should be stressed to the patient that there may be no apparent improvement in symptoms for six months and that treatment will need to continue long term.

Combination therapy

The well publicised medical therapy of prostatic symptoms (MTOPS) multicentre randomised controlled trial looked at the long term progress (mean 4.5 years) of patients randomised to either placebo, finasteride, doxazosin, or both (combination therapy).20

The trial showed that finasteride and doxazosin had a similar ability to prevent progression of disease (54-59% compared with placebo), but the combination of both drugs was more effective (66% compared with placebo). However, the end points used to measure progression of disease were controversial.

The risks of progression to acute urinary retention or the necessity for surgery were also significantly reduced by both finasteride and combination therapy, but not by doxazosin alone. However cumulatively more side effects were reported with combination therapy, and it must be borne in mind that the risk of retention in this population is low (0.6/100 person years) and the decision about whether to operate is a subjective end point.

Recommendations

The medical therapy of prostatic symptoms trial presents the first evidence that combination therapy for more than a year is better than monotherapy at preventing progression of disease. It suggests that this approach should be adopted in patients at high risk of progression (high prostate volume, high concentration of prostate specific antigen (where prostate cancer has been excluded), or high post void residual urine volume) who also have symptoms. Unfortunately, these
are the only data from a randomised controlled trial that are available to support this strategy. It is important to realise that patients will need to be on combination therapy indefinitely, with only a small improvement in symptom score compared with monotherapy. A population cost-benefit analysis of improving progression of disease has yet to endorse this approach to treatment, and any therapeutic advantage of combination therapy needs to be balanced against the increased side effects and costs.

Alternative treatments
Several plant extracts have been reported to improve lower urinary tract symptoms due to benign prostatic hyperplasia. These include:

- Extract of *Serenoa repens* (saw palmetto) berry
- Extract of *Curcubita pepo* (pumpkin) seed
- Extract of *Urtica dioica* (stinging nettle) root
- Extract of *Opuntia* (cactus) flower
- Extract of *Hippophae rhamnoides* (South African star grass)
- Extract of *Pygeum africarium* (African plum tree).

Some studies suggest that these extracts are as effective as α antagonists. However, the studies are often poorly designed, and the extracts have not undergone the same scrutiny as conventional drugs for efficacy, purity, and safety. The World Health Organization international consultation on urological disease consensus group does not recommend treatment with these extracts until more robust evidence exists.

Surgical management
Surgery is performed less often now that effective pharmacotherapy is available, but it is an excellent option for improving symptoms and decreasing progression of disease in patients who develop complications or who have inadequately controlled symptoms on medical treatment.

When should I refer my patient?
The National Institute for Health and Clinical Excellence produced guidelines to help doctors decide who to refer to secondary care. It recommends referring patients with:

- Suspected complications
- Haematuria
- Renal impairment
- Hydronephrosis
- Recurrent urinary tract infections
- Suspected prostate cancer
- Large residual volumes of urine (> 200 ml)
- An unclear diagnosis
- No improvement on initial medical treatment.

You should refer your patient urgently if they have:

- Acute or chronic urinary retention
- Renal failure
- Any suspicion of neurological dysfunction.

Contributors: AKP wrote the article with the help of CRC who recently chaired the World Health Organization committee into the medical treatment of benign prostatic hyperplasia. CRC checked the article for accuracy and relevance, and he ensured that it was up to date and agreed with current guidelines. CRC is guarantor.

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Sample questions
1. A 74 year old man attends your surgery with lower urinary tract problems, mainly storage symptoms. What should you do?
   a. Start him on a 5α reductase inhibitor (such as finasteride)
   b. Start him on an α antagonist (such as doxazosin)
   c. Perform urinalysis and tell the patient to keep a voiding diary

2. A 68 year old man presents with a four day history of worsening lower urinary tract symptoms. He now also has suprapubic pain and difficulty voiding. What should you do?
   a. Contact the local urology department and arrange admission
   b. Check his creatinine concentration and then decide whether to refer him or request an ultrasonic scan
   c. Start alfuzosin 10 mg once daily to reduce symptoms quickly

3. A 75 year old man who is taking nifedipine for hypertension presents with mild obstructive lower urinary tract symptoms. What should you do?
   a. Start an α blocker
   b. Manage initially with watchful waiting
   c. Start a 5α reductase inhibitor

Lesson of the week

Acute renal failure induced by contrast medium: steps towards prevention

R Mathew, K Haque, W Woothipoom

Acute renal failure is a well known complication of procedures that involve iodinated contrast media. Despite this, contrast medium induced nephropathy accounts for about 12% of all cases of hospital acquired renal failure. Prevention of this type of nephropathy is crucial as it is associated with prolonged hospital stay, risk of chronic renal impairment, and a more than fivefold increase in mortality. We report a case of acute renal failure in a woman with chronic renal disease who was investigated for metastatic breast cancer with contrast enhanced computed tomography. This case shows the importance of carrying out a risk assessment for contrast medium induced nephropathy before using procedures that involve iodinated contrast media.

Case report

An 81 year old woman with type II diabetes was admitted after a hypoglycaemic episode. She had a four week history of non-productive cough, which failed to resolve with antibiotics. She had been treated with surgery and radiotherapy for breast cancer 13 years previously. She also had stage 3 kidney disease and hypertension.

Breast examination was normal but there were signs of a left sided pleural effusion. Chest x ray showed a possible left sided coin lesion and pleural effusion. Her white blood cell count was 5.6 × 10⁹/litre, C reactive protein was 15 mg/litre, and the pleural aspirate was an exudate containing 38 g/litre protein and 0.5 × 10⁹/litre white blood cells. Plasma creatinine was 224 μmol/litre, which was not very different from her predmission value. In view of the history of breast cancer, contrast enhanced computed tomography of the chest and abdomen was performed. No abnormalities were detected in the lungs, but a lesion, suggestive of metastasis, was detected in the left adrenal.

Over the next two days, the patient became increasingly nauseous and anorexic. Creatinine rose to 392 μmol/litre (figure). Despite supportive treatment for acute renal failure she became anuric, her blood pressure began to drop, and creatinine rose to 664 μmol/litre. She was transferred to the intensive care unit, where haemofiltration was started. Her renal function started to recover over the next few days and her condition began to improve.

Discussion

Nephropathy induced by contrast medium is defined as an impairment in renal function that occurs within 72 hours of giving contrast medium. This impairment is characterised by an increase in serum creatinine of at least 44 μmol/litre or 25% above the baseline. Creatinine typically peaks three to five days after contrast administration and returns to baseline values within two weeks. Renal replacement therapy is needed in a minority of patients, and in-hospital mortality may be as high as 62% in these cases. No specific treatment is available for contrast medium induced nephropathy and management is supportive.