

Benign prostatic hyperplasia. Part 2—Management

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Management of benign prostatic hyperplasia (BPH) is mainly directed at improving bothersome lower urinary tract symptoms. The vast majority of men with these symptoms initially present to primary care seeking information about the risks and benefits of available treatments. Few men require urgent referral to a specialist for additional diagnostic testing or management. This article provides evidence to guide primary care doctors in the treatment of men with lower urinary tract symptoms, with emphasis on BPH. A previous article discussed diagnosis.¹

What treatment options exist?

Treatment goals are to improve bothersome symptoms, prevent symptom progression, and reduce longer term complications (including acute urinary retention, incontinence, recurrent urinary tract infections, renal insufficiency, and the need for surgery).^{2,3} Options include observation (watchful waiting); lifestyle management; modification of existing medications and/or management of coexisting medical conditions; prostate and bladder specific drug treatment; and major surgical and minimally invasive surgical treatments (box). Treatment choices are primarily determined by how severe and bothersome the symptoms are and by patient preferences for types of interventions based on their weighting of established effectiveness and adverse effects. Surgery provides the largest improvement in symptom score (on the American Urological Association's international prostate symptom scale), with minimally invasive surgery producing greater changes in symptom relief than medical treatments.^{2,3}

Lifestyle management

Many men are reassured to be told that lower urinary tract symptoms are common in ageing men, typically progress slowly over time, rarely result in urgent or life threatening complications, are not due to prostate cancer, and do not increase their risk of developing prostate cancer. Simple lifestyle modifications (box) or adjustment of medications that can worsen urinary symptoms (such as diuretics) can result in acceptable

improvement.²⁻⁴ Participation in self help groups may also improve outcomes.^{5,6}

Drug therapy

Monotherapy with α -1 selective adrenergic antagonists or 5 α -reductase inhibitors

For men with moderate or severe symptoms that do not improve satisfactorily with lifestyle management, drug treatments for BPH can be effective (box), with an average reduction in the international prostate symptom score (range 0 to 35) of three to six points from baseline. A four point change in the international prostate symptom score corresponds with a noticeable difference by patients and is used to assess the clinical significance of interventions or symptom progression.⁷ On the basis of this criterion, about 60% of men will notice an improvement of their symptoms with drug treatment.²⁻⁴

Systematic reviews of randomised controlled clinical trials evaluating effectiveness and adverse effects of drug treatments have shown that in the first year of treatment, α -1 selective adrenergic antagonists (α blockers) are more effective than 5 α -reductase inhibitors in improving symptoms.²⁻⁴ All α blockers have similar efficacy in improving symptoms and urinary flow rate, and their effect is generally maximal within a month of treatment starting. In most men who respond to an α blocker and who tolerate it well initially, the drug continues to work and be well tolerated for many years.⁴ Head to head trials of α blockers are few, small, and have serious methodological limitations.^{2-4,8,9} Terazosin and

UNANSWERED QUESTIONS

- Given the chronic nature of benign prostatic hyperplasia, are escalating treatment strategies cost effective compared with one-off treatments (for example, is a single surgical intervention more cost effective than many years of drug treatment)?
- Should surgical ablation be used as a primary treatment or only after failure of drug therapy?
- Do phytotherapeutic compounds improve urinary symptoms and prevent progression?

doxazosin require dose titration to minimise adverse effects at the start (such as dizziness and syncope). Tamsulosin and alfuzosin do not require dose titration, but no convincing evidence exists that they cause fewer cardiovascular adverse effects—such as symptomatic hypotension—than other α blockers.^{2-4,89} Few data exist on the safety of α blockers in men taking drugs for erectile dysfunction; however, there is no absolute contraindication to their concomitant use.

Combination therapy

A combination of an α blocker and a 5 α -reductase inhibitor has similar effects on quality of life to an α blocker alone in the first year and a half of treatment.¹⁰ Long term effectiveness of combination therapy on symptom progression and need for surgery depends on prostate size as assessed by digital rectal examination, ultrasonography, or level of prostate specific antigen. For men with moderate to severe symptoms and a large prostate (>40 g) on digital rectal examination or ultrasonography or a baseline level of prostate specific antigen of >4 ng/ml, combination therapy can prevent about two episodes of clinical progression per 100 men per year over four years of treatment. Effectiveness was considerably less (or non-existent) in men with smaller prostates.

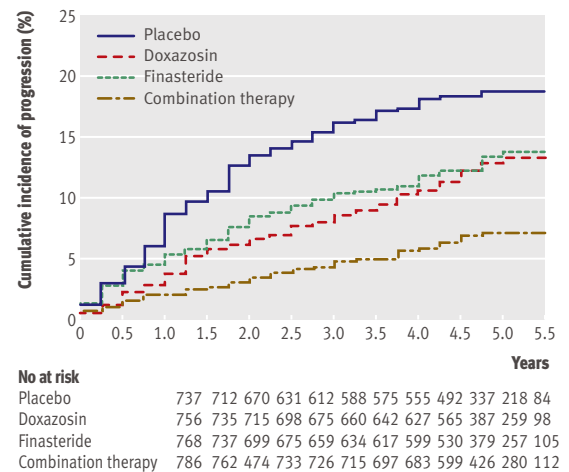


Fig 1 Cumulative incidence of progression of benign prostatic hyperplasia in men with moderate to severe symptoms at baseline. Progression was defined by an increase of at least four points in the international prostate symptom score, acute urinary retention, incontinence renal insufficiency, or recurrent urinary tract infection

Most clinical progression is due to worsening symptoms rather than development of health threatening complications or need for surgery (figs 1 and 2). Disadvantages of the combination therapy described above compared with an α blocker alone include the need for treatment for more than a year before a difference in outcomes is usually noticed; the fact that most men will have no additional benefit; higher medication costs; and sexual side effects (from the 5 α -reductase inhibitors), which occur in about four additional patients per 100.

A possible side benefit of 5 α -reductase inhibitors is their use as primary prevention of prostate cancer—regardless of the presence or severity of lower urinary tract symptoms—in men with levels of prostate specific antigen of <4 ng/ml.¹¹ However, the risk of being diagnosed with high grade prostate cancer is increased. Whether this is a true increased presence of high grade disease or merely a histological or sampling artefact caused by reduction in prostate size owing to 5 α -reductase inhibitors is not certain.¹⁰ If prostate specific antigen is measured with the aim of detecting prostate cancer, thresholds for “abnormal” values should be lowered because 5 α -reductase inhibitors reduce the antigen values by about 50%.^{11,12}

The decision on when to use combination therapy for lower urinary tract symptoms is complex and should ideally be based on informed, shared decision making between patients and providers that incorporates the above information on benefits and harms for the urinary symptoms as well as prevention of prostate cancer.

Phytotherapy

Numerous plant based products (phytotherapy) are commonly used for self treatment of lower urinary tract symptoms and can be prescribed in some European

TREATMENT OPTIONS FOR LOWER URINARY TRACT SYMPTOMS

Observation or watchful waiting

No intervention needed beyond explanation and reassurance

Lifestyle modification

Reduce fluid or diuretic intake and/or modify behaviours to reduce the severity of symptoms and reduce the bothersome nature of the symptoms: avoid excess or night-time fluid intake, caffeine, and alcohol; void the bladder before long trips, meetings, or bed time

Treatment of comorbid contributing conditions

This may improve symptoms and result in reduced diuresis: improve the control of diabetes, adjust diuretic medications

Drug treatments

Use α antagonists to improve bladder and prostate smooth muscle tone; 5 α -reductase inhibitors to reduce prostate volume; combination therapy with α antagonists plus 5 α -reductase inhibitors; and anticholinergics (for symptoms of an overactive bladder) to decrease hypercontractility of the detrusor muscle

Major surgical treatments

- Transurethral resection of the prostate: improves urinary symptoms and flow by “coring out the prostate” through the urethra using instrument with light source
- Transurethral incision of the prostate: for small prostates, relieves urethral narrowing by using special instrument to make incisions in prostate through urethra
- Other ablative surgical treatments use higher energy devices to resect or vaporise prostate tissue: transurethral laser prostatectomy (resection/enucleation); transurethral laser prostatectomy (vaporisation); bipolar transurethral resection of the prostate; transurethral electrovaporisation of the prostate; bipolar transurethral electrovaporisation of the prostate; transurethral vaporessection of the prostate; bipolar transurethral vaporessection of the prostate

Minimally invasive surgical treatments

These destroy prostate tissue using low energy devices through coagulative necrosis: transurethral microwave thermotherapy; transurethral needle ablation of the prostate; high intensity focused ultrasonography; transurethral ethanol ablation of the prostate; transurethral laser coagulation of the prostate; water thermotherapy

countries. Systematic reviews have suggested that both saw palmetto and *Pygeum africanum* provided modest improvement in urinary symptoms and flow.^{13 14} However, a recent high quality randomised trial found that saw palmetto was no more effective than placebo in men with BPH and moderate to severe symptoms.¹⁵ Ongoing trials are assessing long term effectiveness and safety of varying doses of both saw palmetto and *Pygeum africanum*.

Antimuscarinics for storage problems

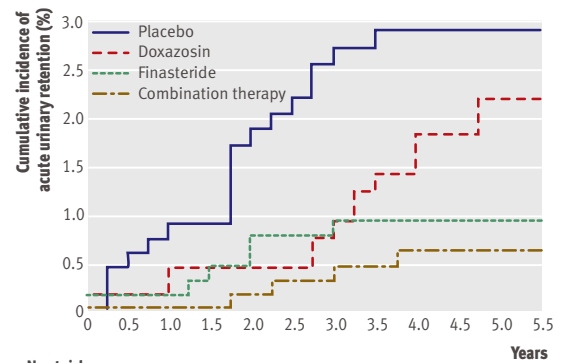
For some men, symptoms of storage problems—such as urinary urgency (with or without urge incontinence), frequency, small urine volumes, and nocturia—in the absence of serious obstructive symptoms are predominant. Recently this symptom complex has been categorised as overactive bladder syndrome. For these men options such as bladder training, biofeedback, and antimuscarinic drugs may be useful either alone or in combination with treatment that is more specifically directed at benign prostatic enlargement.^{16 17} A systematic review of 56 trials found that antimuscarinics (oxybutynin, tolterodine, trospium, solifenacin, and darifenacin) were safe and efficacious in the treatment of overactive bladder syndrome. All antimuscarinics except immediate release oxybutynin were well tolerated.¹⁸ Dry mouth was the most commonly reported adverse event, and no drug was associated with an increase in any serious adverse event.

Antimuscarinics should be used with caution in men with severe obstructive or voiding symptoms as these patients may have high residual urine volumes (more than 150 ml) and antimuscarinics have a theoretical risk of precipitating a deterioration of voiding symptoms including urinary retention. The evidence for this risk, however, is weak.

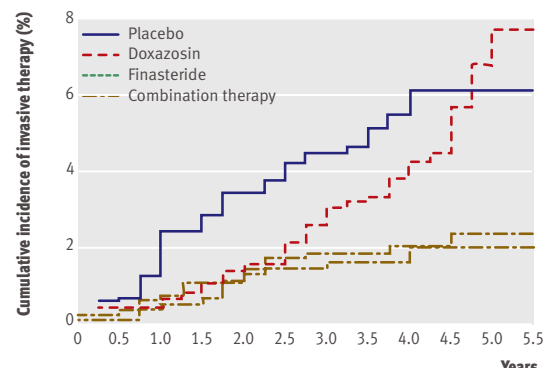
What are the benefits and harms of surgery?

Evidence of effectiveness for minimally invasive surgical treatments comes from case series and randomised trials versus transurethral resection of the prostate, other minimally invasive treatments, sham procedures, and drug interventions.

If conservative management does not give sufficient symptom relief, the standard surgical option is transurethral resection of the prostate. This involves endoscopic removal of the inner (paraurethral) zones of the enlarged prostate using a diathermy loop. Although highly effective (average improvement in score at 16 months is 10 to 18 points from baseline) in relieving both symptoms and urodynamic obstruction, this surgical procedure requires an anaesthetic and a stay in hospital and carries a 5% risk of severe haemorrhage.^{23 19} Because of this, newer procedures using alternative energy sources (such as ultrasound, laser, or microwave) have been developed. Some do not require a general anaesthetic and can be carried out in an outpatient setting with fewer adverse effects. However, uncertainty remains about their long term clinical and cost effectiveness.



No at risk	737	712	670	631	612	588	575	555	492	337	218	84
Placebo	737	712	670	631	612	588	575	555	492	337	218	84
Doxazosin	756	735	715	698	675	660	641	627	565	387	259	98
Finasteride	768	737	699	675	659	634	617	599	530	379	257	105
Combination therapy	786	762	747	733	726	715	697	683	599	426	280	112



No at risk	737	720	698	670	565	643	632	616	543	373	247	96
Placebo	737	720	698	670	565	643	632	616	543	373	247	96
Doxazosin	756	736	728	712	391	675	660	642	584	699	272	105
Finasteride	768	744	724	706	689	670	655	640	562	401	274	110
Combination therapy	786	764	753	727	717	701	687	675	588	420	278	102

Fig 2 Cumulative incidence of acute urinary retention and invasive therapy for BPH. Adapted from McConnell et al

Current standard

Transurethral resection of the prostate has been the standard method of surgical management of clinical BPH for 50 years. In recent times the procedure accounted for more than 90% of prostatectomies for BPH, although now the proportion is only 60-80% because of new minimally invasive procedures.²⁰ Improvements in endoscope design, diathermy units, and bladder irrigation have reduced operating time and risk of major morbidity.²⁰ In respect of symptoms associated with BPH, transurethral resection of the prostate provides a consistent, long lasting, high level of improvement in quality of life and peak urine flow rate.^{2 19}

New technology

Newer surgical options for BPH can be broadly divided into “minimally invasive” and “tissue ablative” treatments. Minimally invasive surgical treatments do not remove tissue but cause in situ coagulative necrosis through low energy heating devices (40-80°C). These include: transurethral microwave therapy,

ONGOING RESEARCH

- Discover and test new drugs to prevent or reduce benign prostatic hyperplasia
- Determine whether phytotherapies including saw palmetto and *Pygeum africanum* used alone or in combination improve urinary symptoms and/or prevent progression
- Determine whether antimuscarinics plus α blockers are safe and more effective for men with urinary symptoms than monotherapy alone
- Determine whether medical treatments (5 α -reductase inhibitors) can reduce incidence and mortality of prostate cancer
- Determine whether drugs typically used to treat erectile dysfunction are also effective for treatment of urinary symptoms
- Determine factors limiting use and outcomes of minimally invasive surgery

radiofrequency transurethral needle ablation, and transurethral or interstitial laser coagulation. Such treatments can be carried out in an ambulatory care environment under simple analgesia or sedation with minimal anaesthesia, but they generally require a prolonged period of bladder catheterisation. Most of these treatments are used in men with smaller prostate volumes (between 30 ml and 100 ml, and levels of prostatic specific antigen <4.0 ng/ml) and no history of urinary retention or previous prostate surgery. Improvement in symptoms and urinary flow rate is slightly poorer with minimally invasive treatments than with transurethral resection of the prostate but better than with α blocker therapy.¹⁶⁻¹⁸ Adverse effects are less common than with transurethral resection of the prostate, but repeat treatment or more invasive treatment is needed for about 30% of men.^{2,3 19-23}

Tissue ablative procedures use similar transurethral instrumentation as transurethral resection of the prostate but differing energy sources that can remove tissue efficiently by vaporisation or resection but cause less bleeding. They include laser resection or vaporisation, monopolar diathermy vaporisation, and bipolar diathermy vaporisation/resection. Procedures such as monopolar diathermy vaporisation and holmium laser enucleation of the prostate give similar improvement in symptoms and quality of life as transurethral resection of the prostate, with less risk of major blood loss. The improved haemostatic properties of these procedures also allow earlier discharge from hospital, saving about one bed-day compared with transurethral resection of the prostate. These procedures may offer particular advantages for men taking anticoagulants and those with cardiac or renal disease as the requirement for

DATA SOURCES

We searched Medline and the Cochrane Library up to November 2007 for randomised trials, systematic reviews, evidence reports, and recent evidence based guidelines from the American Urological Association, European Urological Association, and the National Institute for Health and Clinical Excellence.

irrigation of the bladder during and after surgery is much reduced and haemoglobin concentrations are maintained.

Adverse effects of surgery

Sexual side effects, particularly loss of ejaculation and erectile dysfunction, are of concern to men having prostate surgery. The risk of retrograde ejaculation is significantly lower for minimally invasive procedures. For ablative procedures, the risk is similar to transurethral resection of the prostate.¹⁶⁻¹⁸ Reassuringly, the occurrence of ejaculatory dysfunction does not seem to lower quality of life much after prostate surgery. Rates of erectile dysfunction are similar across all procedures, although lack of baseline data and spontaneous development of erectile dysfunction in this older age group are likely sources of bias.^{2,3 19-23}

Incontinence is similar across all interventions with the exception of transurethral needle ablation of the prostate and laser coagulation (where reported rates were lower), although comparative analysis is hampered by variability in definition. The other most pertinent long term adverse effect is the need for further treatment owing to stricture formation, urinary retention, or disease relapse. Unfortunately, long term follow-up data from randomised controlled trials are not available. The best estimates concern transurethral resection of the prostate, for which long term observational studies suggest a 1% annual risk of requiring further treatment. Shorter term studies suggest further treatment is more frequently required when minimally invasive options such as transurethral microwave thermotherapy are used, which probably reflects the smaller amount of tissue destroyed by these procedures.

Transurethral resection of the prostate remains widely used throughout the world. In communities with ageing populations and access to newer technologies the lower risk of bleeding during laser resection or vaporisation techniques may be advantageous for men with extensive comorbidity or long term anticoagulation. For most healthcare providers, however, the benefits of widespread introduction of new technologies are insufficient to justify the start-up and consumable costs currently associated with these procedures. For the UK NHS minimally invasive options such as transurethral microwave thermotherapy are not approved for use, and the availability of newer methods of ablation such as laser vaporisation or holmium laser enucleation of the prostate currently depends on local enthusiasm and investment.

ADDITIONAL EDUCATIONAL RESOURCES

- PatientPlus (www.patient.co.uk/showdoc/40002437/)—Comprehensive, free, up to date health information as provided by general practitioners to patients during consultations
- Foundation for Informed Medical Decision Making (www.fimdm.org)—Provides information to help patients make sound decisions affecting their health and wellbeing
- Health Dialog (www.healthdialog.com)—Provides care management and analytical services
- Cochrane Library (www.cochrane.org)—Publishes systematic reviews of the effects of healthcare interventions

SUMMARY POINTS

Treatment should improve patients' symptoms and reduce progression and need for surgery while minimising harms and costs

Management includes observation, lifestyle modification, drug treatment, minimally invasive surgery, and surgical removal of prostate tissue

α blockers are the most effective drug for improving lower urinary tract symptoms and short term quality of life

Combination treatment (α blockers and 5α-reductase inhibitors) reduces progression of benign prostatic hyperplasia and need for surgery if the symptoms are moderate or severe and the prostate glands large, if taken for more than a year; adverse events increase

5α-reductase inhibitors may reduce risk of prostate cancer but may increase the risk of high grade disease

Transurethral resection of the prostate results in the greatest improvement in symptoms and flow rate, but adverse effects include the risk of surgery

Minimally invasive surgery can provide benefits comparable to transurethral resection of the prostate, with fewer serious adverse effects. Short term repeat intervention and urinary retention rates are higher than with transurethral resection of the prostate. Long term effect is unclear

When is referral to a urologist indicated?

The vast majority of men can receive appropriate treatment by their primary care provider. In our earlier article we said that referral to a urologist may be indicated on the basis of patient preference or for further assessment of men presenting with atypical lower urinary tract signs or symptoms including new onset urinary incontinence, haematuria, dysuria, recurrent urinary tract infections, urinary obstruction, or raised levels of prostate specific antigen.¹ Referral for potential surgical or minimally invasive interventions is appropriate for men with moderate to severe bothersome symptoms who might prefer surgery to medical treatment or for those in whom medical treatment has not provided adequate symptom improvement or is not well tolerated.

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Health promotion: From clinic to classroom

She was a young primary school teacher who had attended clinic with a history suggesting that her diet needed attention. To alleviate her symptoms, she was advised to increase her fruit and water intake throughout the day. However, she felt that this was incompatible with her lifestyle, citing the classroom as being a difficult place to regularly snack on fruit or indeed drink water.

A letter was duly sent to the headmaster to obtain permission for the patient to eat her “five a day” portions of fruit during class time, and this was permitted. Some months later, we heard that her symptoms had substantially improved. Intriguingly, we were also told that the

children in her classroom, who had watched her eat, picked up the habit of eating fruit on a regular basis and had adopted it as part of their diet.

This shows the power of the classroom in promoting health, particularly in following the philosophy of “prevention is better than cure.” We should all strive to promote health in our workplaces, and perhaps there is no better place to start than with hospital canteens and our own eating habits.

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