The Medical Management of Symptomatic Benign Prostatic Enlargement

Introduction

Symptomatic Benign Prostatic Enlargement (BPE) is a common problem affecting one third of men over 50 years of age, with prevalence increasing with age.[1] Symptomatic BPE results in bothersome lower urinary tract symptoms (LUTS) that do not only affect the quality of life (QoL) of a man and his family, but also potentially increase the risk of significant and costly long-term health sequelae such as acute urinary retention (AUR), hospitalisation and surgery.[2] The management of BPE has advanced considerably in the past 20 years to include less invasive surgical and pharmaceutical options, when previously the choice was between reassurance with no treatment or transurethral resection of the prostate (TURP).[3] This paper reviews current medical management of BPE.

What is Benign Prostatic Enlargement?

BPE is the term used to describe the benign (noncancerous) enlargement of the prostate gland due to increased cell numbers (hyperplasia).[4] This enlargement restricts the urethra as it passes through the prostate, resulting in bladder outlet obstruction (BOO) and LUTS.[3] Cell proliferation is stimulated by dihydrotestosterone (DHT), a metabolite of testosterone and key androgen responsible for healthy prostate growth, by the action of the enzyme 5-alpha-reductase (5-AR).[5] As men age, homeostasis between cell proliferation and apoptosis is lost in favour of proliferation, resulting in progressive prostate enlargement.

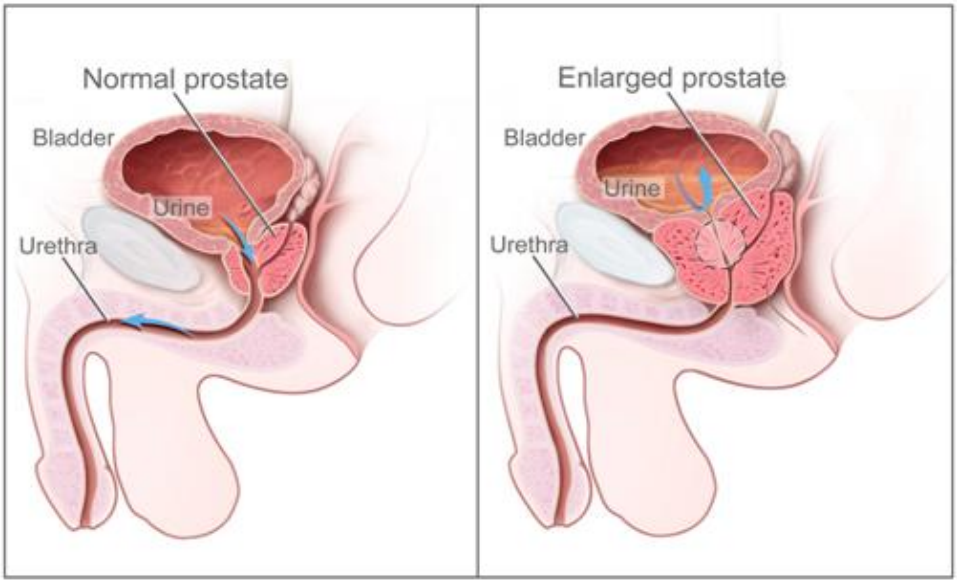

Figure 1: normal (left) and enlarged prostate (right).[6]

Symptoms

BPE presents with a wide variety of LUTS. The International Continence Society has categorised these symptoms into three groups according to the three bladder cycle stages (table 1).[7]

Storage (filling)	Voiding (emptying)	Post Micturition (immediately after voiding)
• Urgency • Increased Daytime Frequency • Nocturia • Urinary Incontinence • Altered Bladder Sensations	• Hesitancy • Intermittency • Slow Stream • Splitting or Spraying • Straining • Terminal Dribble	• Feeling of incomplete emptying • Post micturition dribble

Table 1: Lower Urinary Tract Symptoms. Adapted from reference 7

Symptom severity is quantified using the validated International Prostate Symptom Score (IPSS) (figure 2). Scores of 0-8 are categorised as mild, 8-19 as moderate and 20-35 as severe. Increased severity is linked to increased impact on QoL, including sleep, low mood and sexual dysfunction.[7]

Patient Name _____ Date of Birth_____ Date Completed _____	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Score
Incomplete Emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
Frequency Over the past month, how often have you had to urinate again less than 2 hours? After you finished urinating?	0	1	2	3	4	5	
Intermittency Over the past month, how often have you found you stopped and started again? Several times when you urinated?	0	1	2	3	4	5	
Urgency Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
Weak Stream Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	1-Time	2-Times	3-Times	4-Times	5-Times or more	
Nocturia Over the past month, how many times did you most typically get up to urinate from the time you went to be at night until the time you got up in the morning?	0	1	2	3	4	5	
Your Total I-PSS Score							
Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly Satisfied	Mixed Mostly	Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Figure 2: International Prostate Symptom Score IPSS. The American Urological Association (AUA) [8]

Beyond Quality of Life Improvement

Although BPE is a benign condition, it is progressive and without treatment the prostate continues to enlarge and symptoms become increasingly severe.[9] This may result in complete urethral blockage, causing AUR.[2] AUR is a painful medical emergency, requiring swift catheterisation and sometimes surgical intervention, to

avoid complications of renal failure, urinary tract infections and post-obstructive diaeresis.[2] The risk of AUR increases with increasing age, symptoms severity and poor flow rate. The most important risk factors in AUR are increased age, high IPSS score, prostate size and prostate-specific antigen (PSA) level. Men with prostate sizes >30ml are one-and-a-half times more likely to suffer moderate to severe LUTS and three times more likely to experience AUR than men with prostate sizes <30ml.[10] Men with PSAs >1.4ng/ml have twice the AUR risk compared to men with lower PSAs.[11] It is essential to identify high risk men because appropriate treatment can delay or prevent BPE progression and reduce the associated increased AUR risk.[12]

Medical Management

Watchful waiting

Watchful waiting requires regular monitoring, reassurance that BPE is a benign condition, education about BPE and lifestyle advice.[13] Watchful waiting is most beneficial for mild symptoms or in men who do not feel that their QoL is affected to the extent that they wish to pursue active management.[13]

Alpha-$_1$ receptor antagonists (A_1RAs)

A_1RAs provided the first licensed pharmacological therapy for BPE.[3] Alpha-1 receptors (A_1Rs) are responsible for smooth muscle contraction and smooth muscle cells contribute 40% of the prostatic hyperplasia responsible for BPE. By antagonising A_1Rs and reducing the tone in the smooth muscle of the prostate, bladder neck and urethra, A_1RAs reduce resistance, improve flow rate and bladder emptying thereby reducing BPE symptoms.[14] A_1Rs are subdivided into 1a, 1b and 1c[15] with Alpha-1a predominant in the prostate, bladder neck and urethra.[15] The British Association of Urological Surgeons (BAUS)[10] and the National Institute for Health and Clinical Excellence (NICE)[16] evidence-based-guidelines concur that symptomatic men with relatively small prostates (<30ml) and PSA levels <1.4ng/ml are best treated pharmacologically with an A_1RA, when an anticipated 20-30% improvement in symptoms can be seen within 6-12 weeks.[10,16]

A_1RAs are classified according to selectivity of action. Non-selective A_1RAs may cause vascular smooth muscle relaxation (acting in the alpha$_{1B}$ receptor subunit),

resulting in decreased vascular resistance and thus a decrease in blood pressure which may lead to dizziness or postural hypotension as side-effects.[17] However the antihypertensive action may be desirable in some patients with hypertension requiring medication, treating two conditions with one intervention, thus reducing the medication burden and improving concordance. Preferentially selective A_1RAs for $alpha_{1A}$ receptor (e.g.:tamsulosin) possess fewer non-specific side-effects. All A_1RAs carry a risk of retrograde ejaculation[17] which men should be aware of prior to commencing treatment as it may be a side-effect sexually active men are not willing to accept, and if uninformed may result in reduced concordance and mistrust.

5-alpha-reductase inhibitors (5-ARIs)

5-ARIs, such as finasteride and dutasteride which are of comparable efficacy, are specific inhibitors of 5-AR.[18] 5-AR converts testosterone into the more potent DHT.[5] Since prostate cell proliferation occurs in response to DHT, inhibition of testosterone metabolism leads to a reduction in prostate size, improvement in urinary flow rate and reduction in obstructive symptoms. Men who are relatively asymptomatic, but with an enlarged prostate (>30ml) and a PSA level of >1.4ng/ml and are consequently at risk of progression of BPE, should be considered for treatment with a 5-ARI, because of the prostate size reduction effect.[10,16] This effect of 5-ARI appears to have a more significant long term impact on the natural history of BPE than A_1RAs, reducing the risk of AUR and need for future surgery.[14] 5-ARIs have a three-six month lag time for symptom relief. Side effects include impotence, decreased libido, ejaculation disorders, and breast tenderness and enlargement.[19] 5-ARIs are excreted in semen and use of a condom is recommended if the patient's sexual partner is pregnant or likely to become pregnant.[19]

Combination Therapy

Trials have shown that men with larger prostates (>30ml), PSA levels of >1.4ng/mL and bothersome symptoms are best managed with a combination of A_1RA and 5-ARI, than monotherapy.[10,16,20,21] A_1RAs provide a faster onset, with symptom relief within 6-12 weeks, whilst 5-ARIs require 3-6 months. Such patients have the highest risk of BPE progression and complications and higher associated BPE related health and economic costs. For some patients, A_1RA therapy may be stopped once 5-ARI treatment has had time to induce sufficient shrinkage of the prostate and symptom

reduction without symptom recurrance.[22] In routine primary care follow up, these patients would require regular monitoring to ensure symptom and progression reduction stability.

Anticholinergics

Bladder contraction is mediated via parasympathetic cholinergic nerves. Blockade of these nerves reduces bladder over-activity which underlies storage LUTS.[23] Anticholinergics reduce bothersome LUTS (storage symptoms such as urgency, frequency, nocturia and urgency incontinence) but are not superior to A_1RAs.[23] The predominant side-effect is dry mouth and there is no significant increase of voiding difficulty or AUR. Anticholinergics should be offered in combination with A_1RA or 5-ARI, if insufficient symptom and QoL improvement can be gained.[10,16]

Phosphodiesterase-5 inhibitors (PDE-5Is)

PDE-5Is (e.g.:sildenafil) increase intracellular concentrations of cyclic guanosine monophosphate and are best known as the first-line treatment for erectile dysfunction (ED).[24] More recently, PDE-5Is have been found to regulate smooth muscle tone in the human prostate.[24] Studies have shown promising evidence that PDE-5Is may be an effective and well tolerated treatment option for BPE/LUTS.[24] Combination therapy using PDE-5Is and A_1RAs results in greater improvements in BPE/LUTS than either drug alone.[25] However further well designed studies are required to determine PDE-5I safety, efficacy and cost-effectiveness.

Phytotherapy

A number of plant based treatments have been linked to BPE management. However the evidence to support efficacy for plant use in BPE is currently too weak for their recommendation.[16] Significant concerns also exist regarding side-effects, potential drug interactions and the standardisation of potency.[16]

Monitoring and follow up

NICE recommends that patients on A_1ARs are reviewed at 4-6weeks and then every 6-12 months with 5-ARIs reviewed at 3-6 months then 6-12 months.[16] In the context of poor treatment response it should also be remembered that a benign prostate can undergo malignant change, with repeat digital rectal examination and PSA levels required.[26] Such routine monitoring should be undertaken in primary care, with referral indicated in complicated BPE if failure to reach a sufficient improvement in QoL or malignancy is suspected.

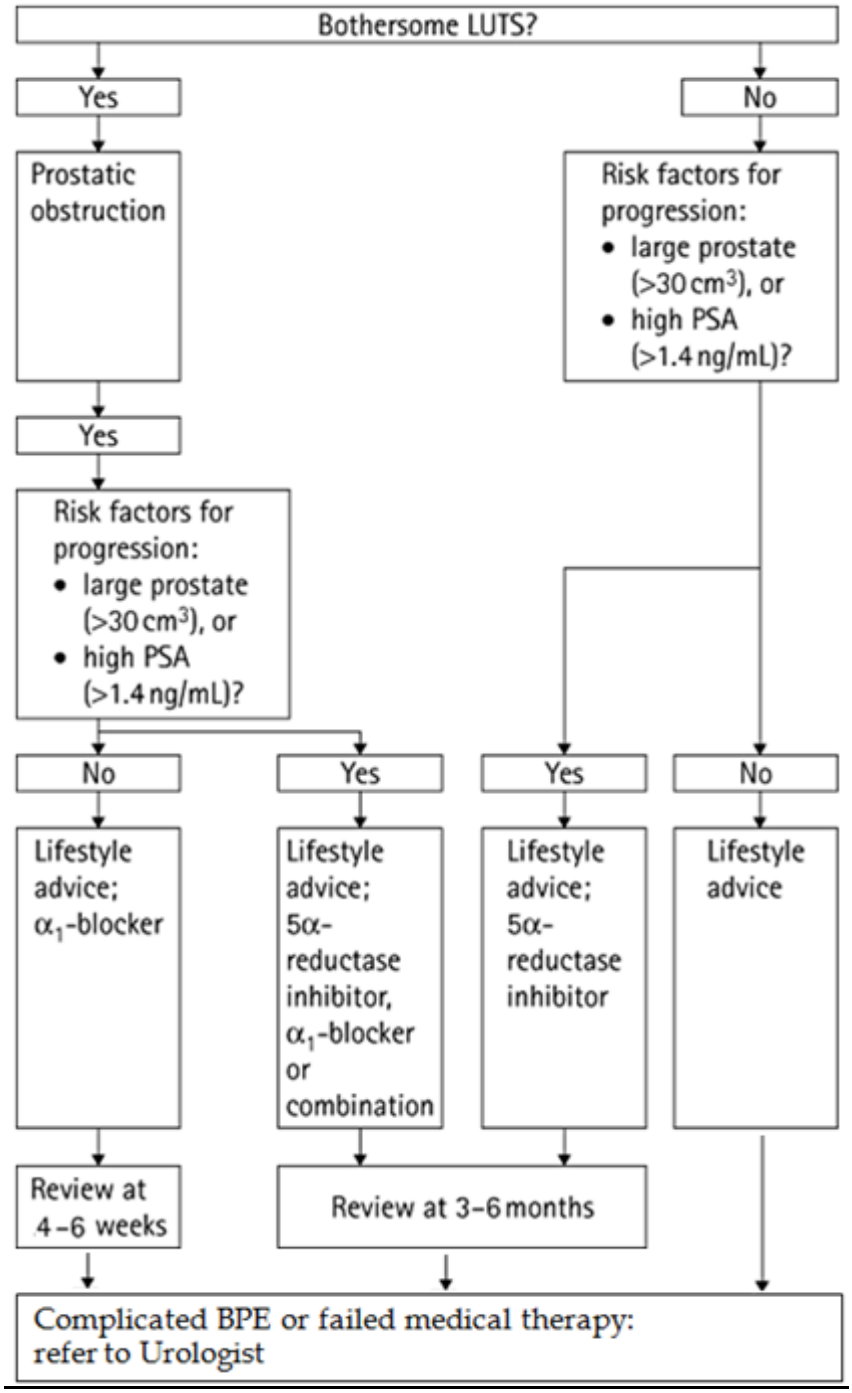

Figure 3: *The medical management of men of BPE. Adapted from the BAUS/NICE guidelines and reference 27*

Conclusion

The decision to opt for a particular treatment of BPE is largely dependent on patient choice, the evidence base for each treatment and clinical considerations, such as symptom severity, degree of prostatic enlargement and response to any previous treatment. The decision must also consider the risks/benefits of alternative treatment options. Surgical intervention carries the greatest possibility of improvement, particularly in patients with severe symptoms but this must be weighed against the risks of surgery, anaesthesia and hospitalisation. Medical management, although not risk-free, provides an effective, lower risk, method to improve patient QoL and reduce BPE progression and associated risk of complications. Due to the ageing population, it is likely that more men will suffer symptomatic BPE, and also be unsuitable for surgical intervention. Medical management offers a treatment option for these men. For men who are fit for surgery, initial drug therapy leaves the option for surgery later if required. Above all treatment should be tailored to the individual.

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