Entry for British Association of Urological Surgeons
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"Medical management of symptomatic benign prostatic enlargement"

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Medical management of symptomatic benign prostatic enlargement

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1. Introduction

Benign prostatic enlargement (BPE) and the development of lower urinary tract symptoms (LUTS) are often related events. LUTS are not classified as a disease, but has a symptom complex characterized by storage and voiding problems[1]. Although the aetiology of LUTS can be multifactorial - including idiopathic detrusor overactivity, age-related smooth muscle dysfunction, neurological disorders (e.g. dementia), longstanding diabetes, etc. it is understood that in many elderly men, LUTS are due to bladder outlet obstruction secondary to BPE[1,2]. This notion is supported by the well-documented findings that the incidence of LUTS and BPE (which is often defined histologically as benign prostatic hyperplasia) both increases with age[3]. Histological disease is present in more than 60% of men above the age of 60 with more than 40% of them becoming symptomatic (Figure 1)[3]. Therefore, during the greater part of the 20th century, the most common treatment for LUTS arising from BPE was resection or enucleation of the prostate adenoma[2]; surgical approaches that were highly effective for treating symptomatic BPE.

However, a fundamental change to the therapeutic approach towards men presenting with symptomatic BPE took place in the 1990s when medical therapy became an accepted standard of care following reports of randomized, double-blind, placebo-controlled studies showing that finasteride[4], a 5α-reductase inhibitor and terazosin[5], an α-blocker both significantly improved LUTS and increased peak urinary flow rates in men with BPE[2]. This, coupled with the landmark Olmsted county study[6], which shed light into the natural history of BPE by showing that men with moderate to severe LUTS are more likely to require surgical treatment, meant that an increasing number of urologists began to adopt medical therapy in lieu of surgical treatment, especially in men presenting with only mild to moderate LUTS.

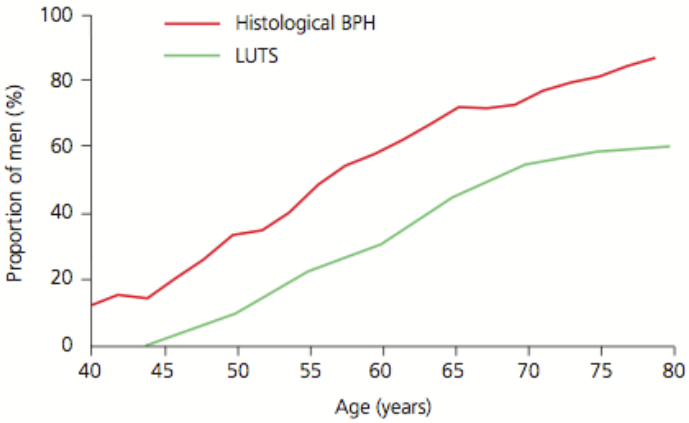

Figure 1: The incidence of both benign prostatic hyperplasia (BPH) and LUTS increases progressively with age. [Taken from: Kirby and Gilling[3], 2010]

2. Single Medications

Alpha-adrenergic receptor blockers

The α-blockers were the first class of medication introduced into clinical practice for symptomatic BPE[7]. Since the 1ate 1980s, 6 different alpha$_1$-selective α-blockers have been introduced and are currently available in the UK market: **alfuzosin**, **doxazosin**, **indoramin**, **prazosin**, **tamsulosin** and **terazosin**. These antagonists block alpha$_1$ adrenoceptors at the bladder neck and in prostatic smooth muscle, relieving the BPE induced bladder outlet obstruction[1] with a rapid onset of action. Quinazolin derivatives such as terazosin and doxazosin have also been shown to drive apoptosis of prostatic epithelium[8], although this effect is not thought to be clinically relevant as α-blockers do not seem to interfere with the natural history of benign prostatic growth[1].

An update to the meta-analysis published in 1999 comparing the efficacy and tolerability of four alpha$_1$-blockers (alfuzosin, terazosin, doxazosin and tamsulosin) in patients with LUTS suggestive of BPE was reported in 2004[9]. The efficacy of alpha$_1$-blockers with the corresponding placebo response was expressed as a percentage improvement in International Prostate Symptoms Score (IPSS). The authors concluded that *"all alpha$_1$-blockers have comparable efficacy in improving symptoms and the maximal urinary flow rate (Q_{max}) when administered at their full therapeutic dose."* Alpha$_1$-blockers that require dose titration (terazosin and doxazosin) have on average a slower onset of action than those that can be initiated at their full therapeutic doses (alfuzosin and tamsulosin). However, the tolerability profile of the drugs varied with alfuzosin and tamsulosin being better tolerated than doxazosin and terazosin. The main adverse effects that have been reported are hypotension (terazosin and doxazosin) and abnormal ejaculation (tamsulosin). Hypotension occurs due to the vasodilatory action mainly observed with alpha$_1$-blockers that require dose titration. This effect is particularly pronounced in elderly patients receiving polypharmacy and patients with cardiovascular co-morbidities[9].

The evolution of alpha$_1$-blockers for use in symptomatic BPE has involved the development of subtype-specific α-blockers with a slow–release formulation, providing sustained plasma concentrations whilst limiting adverse effects[2]. Silodosin is a relatively new drug[10], which exhibits very high selectivity for the α_{1A} versus α_{1B} adrenoceptor subtype and moderate selectivity for the α_{1A} versus α_{1D}. The relative abundance of α_1-adrenoceptor subtypes in body compartments is shown in Figure 2. Clinical data suggests that silodosin is virtually devoid of cardiovascular adverse effects although the incidence of ejaculatory dysfunction is higher than all other α-blockers[11]. Therefore, the utility of silodosin in the treatment of symptomatic BPE is by harmonizing maximum efficacy whilst limiting cardiovascular and sexual adverse effects.

5α-reductase inhibitor (5-ARI)

The observation by Imperato-McGinley et al.[12] that individuals with a congenital deficiency of 5α-reductase do not develop either BPE or prostate cancer provided the basis for development of 5-ARIs for BPE. The theory behind the idea was that mimicking this metabolic effect, which prevents the in vivo conversion of testosterone to dihydrotestosterone (DHT), would limit prostatic growth since DHT is a stronger contributor to prostatic enlargement. **Finasteride**, an azosteroid, was the first 5-ARI available in the market in early 1990s[13]. Since then, it emerged that 2 isoenzymes of 5α-reductase existed. Finasteride only inhibits type II 5α-reductase whilst **dutasteride**, the newer 5-ARI, inhibits both isoenzymes causing a larger

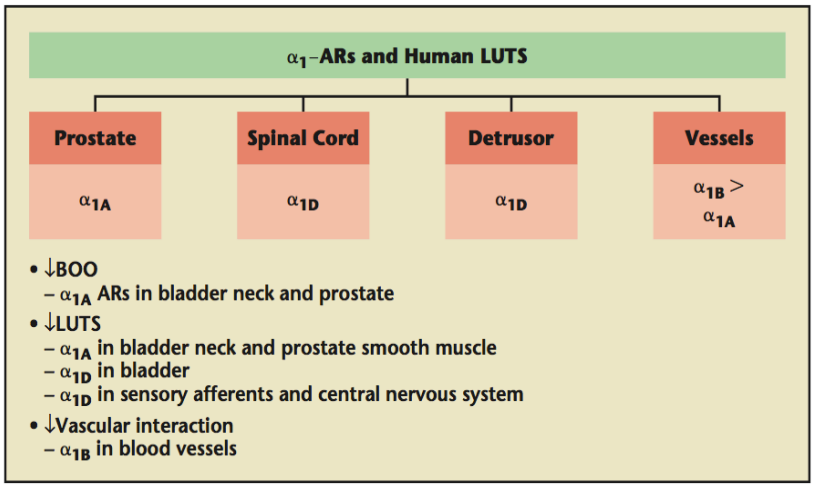

Figure 2: Relative abundance of α_1-adrenoceptor subtype in body compartments. ARs, adrenoceptors; BOO, bladder outlet obstruction; LUTS, lower urinary tract symptoms [Taken from: Lepor[2], 2011]

drop in serum DHT levels[2]. The decrease in intraprostatic DHT seems to alter the natural history of prostatic growth, rendering an average of 18-26% decrease in prostate volume (PV) over time relative to placebo[14,15].

Finasteride has been shown to significantly improve symptom scores (measured on the American Urological Association Symptom Index, AUA-SI) in long term, double blind trials (Figure 3) as well as reducing the risk of symptomatic progression by up to 30% (defined as an increase in the AUA-SI of ≥4 points) compared to placebo[14,16]. The relative risk of acute urinary retention (AUR) and BPE-related surgery was reduced after 4 years of finasteride therapy[14] by 57% and 55% respectively and is thought to be mediated by its effect on PV. The drug is also generally well tolerated with sexual dysfunction being the most commonly reported adverse effect. Interestingly, it is worth noting that there is a relatively high prevelance of sexual dysfunction amongst men with untreated BPE[17]. Furthermore, McConnell et al.[14] reported that the rates of decreased libido and impotence were similar in the finasteride and placebo group after 2 years of treatment. Hence, a clear causal link between treatment and the reported adverse effect is yet to be established.

Finally, a recently published double blind trial[18] comparing the efficacy and safety of dutasteride and finasteride failed to show clinical superiority of dutasteride despite its properties of being a dual inhibitor of type I and type II 5-ARI. Although the reason for this is yet to be understood, it is plausible that the 12-month period of study is not sufficient to discern any long-term superiority that dutasteride may have over finasteride.

3. Combination Therapy

The Veterans Affairs Cooperative Trial[19] and the PREDICT[20] trial were the first two trials to evaluate combination therapy with an α-blocker and 5-ARI in a group of unselected men with symptomatic BPE. Both had unequivocally demonstrated that there is no clinical advantage of combination therapy over monotherapy during the first year. However, these studies were limited

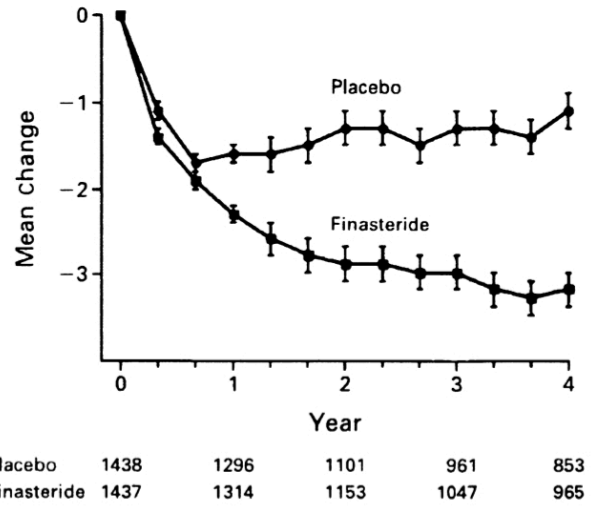

Figure 3: Effect of finasteride or placebo on the American Urological Association Symptom Index. Values shown are average (±SD) changes from baseline.
[Adapted from: McConnell et al.[14], 1998]

by their short duration, during which period a significant response to 5-ARI therapy was unlikely to occur. In contrast, the landmark Medical Therapy of Prostatic Symptoms (MTOPS) trial[16] was the first study to demonstrate the superiority of combination therapy over either finasteride or doxazosin monotherapy (66% reduction in risk vs. 34% or 39% respectively) to prevent overall disease progression (defined as a 4-point increase in IPSS, development of AUR, renal insufficiency or recurrent UTI) in a group of men with symptomatic BPE, **independent of PV**.

In this study, the prevention of LUTS was similar in both monotherapy regimens during the average 4.5 years follow up period whilst the prevention of AUR was superior in the 5-ARI group. However, it is worth putting into perspective that in the placebo group, only 2% of subjects developed AUR. If one adopts an α-blocker as the initial treatment for symptomatic BPE randomly (i.e. without knowing the PV), then the addition of a 5-ARI will only prevent 1 additional case of AUR for every 150 men treated with combination therapy[2]. The Combination of Avodart and Tamsulosin (CombAT) study[21], with its intended bias of recruiting men with large prostates (average PV was 70% greater than MTOPS trial) has demonstrated that combination therapy is in fact, more suited to this group of

patients where only 30 men needed to be treated to prevent one more episode of AUR had treatment been initiated with α-blocker monotherapy.

This view has been supported by an analysis of the MTOPS data that suggests men who are at increased risk of progression (baseline PV ≥ 25 mL and prostate specific antigen (PSA) ≥1.5ng/mL) may benefit from combination therapy[22]. The criticism of combination therapy is that drug related adverse events are more common compared to monotherapy. Also, combination therapy is more costly; hence, this should be reserved for patients who have the highest baseline risk of progression.

4. Other medical therapies

A brief mention of other commonly encountered/novel therapies for BPE will be presented here.

Phytotherapy using extracts from *Serenoa repens* is not used in the UK but has a relatively high prescription index in Belgium[23] and Italy. In a recently published systematic review by the Cochrane Collaboration[24], the authors concluded: "*Serenoa repens* provides mild to moderate improvement in urinary symptoms, although the long term effectiveness, safety and reliability to prevent BPE complications are not known."

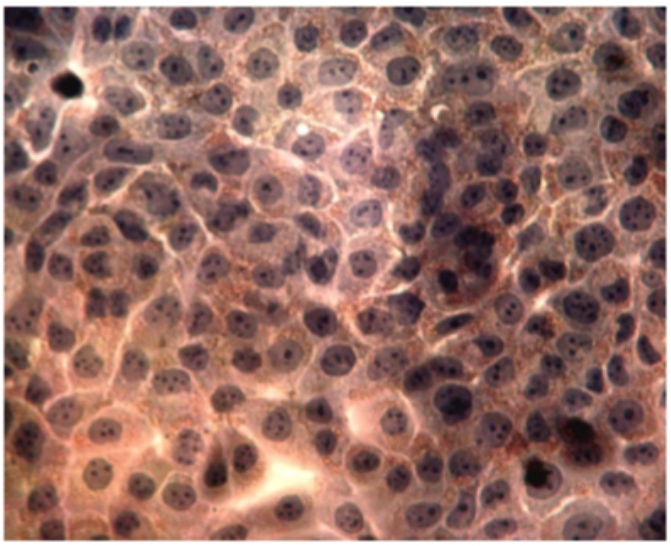

Figure 4: Prostatic epithelial cells observed 1 hour after admixture with *Serenoa repens* extract in culture medium. The lipidosterolic extract concentrates in the cytoplasm of cells. [Taken from: Robert et al.[25], 2009]

The mode of action of *Serenoa repens* remains unclear although it has been suggested that it induces apoptosis by concentrating in the cytoplasm of prostatic epithelial cells[25].

Phosphodiesterase Type 5 Inhibitors (PDE5) (eg. sildenafil, tadalafil) are the primary medical treatment option for erectile dysfunction (ED). The observation that men with ED generally have a greater incidence of symptomatic BPE suggests a common etiology[2]. Data from 4 large trials[26-29] that showed clinical benefit of PDE5 inhibitors for symptomatic BPE however, failed to show improvements in the objective indices of BOO used. Whilst more studies are needed to further establish the utility of PDE5 inhibitors for symptomatic BPE, this observation suggests that future treatments for symptomatic BPE do not necessarily need to be fixated on reducing prostatic smooth muscle tone or decreasing PV.

5. Conclusion

In summary, men with symptomatic BPE are best started initially on α-blocker monotherapy to provide early symptomatic relief. In the subset of men with large prostates (PV ≥ 25 mL, PSA ≥1.5ng/mL), there is a higher risk of symptomatic progression hence, 5-ARI monotherapy or combination therapy with α-blocker and 5-ARI should be considered. Effective allocation of treatment according to risk of progression will result in fewer patients being treated with minimal benefits whilst ensuring efficient management of treatment costs.

References

1. Thorpe A, Neal D. Benign prostatic hyperplasia. Lancet 2003;361:1359-67.

2. Lepor H. Medical treatment of benign prostatic hyperplasia. Reviews in urology 2011;13:20-33.

3. Kirkby R, Gilling P. Fast Facts: Benign Prostatic Hyperplasia. 6 ed. Oxford: Health Press Limited; 2010.

4. Group F. Finasteride (MK-906) in the treatment of benign prostatic hyperplasia. The Finasteride Study Group. The Prostate 1993;22:291-9.

5. Lepor H, Auerbach S, Purasbaez A, et al. A randomized, placebo-controlled multicenter study of the efficacy and safety of terazosin in the treatment of benign prostatic hyperplasia. Journal of Urology 1992;148:1467-74.

6. Jacobsen SJ, Jacobson DJ, Girman CJ, et al. Treatment for benign prostatic hyperplasia among community dwelling men: The Olmsted County study of urinary symptoms and health status. Journal of Urology 1999;162:1301-6.

7. Roehrborn CG. Current medical therapies for men with lower urinary tract symptoms and benign prostatic hyperplasia: achievements and limitations. Reviews in urology 2008;10:14-25.

8. Kyprianou N, Litvak JP, Borkowski A, Alexander R, Jacobs SC. Induction of prostate apoptosis by doxazosin in benign prostatic hyperplasia. Journal of Urology 1998;159:1810-5.

9. Djavan B, Chapple C, Milani S, Marberger M. State of the art on the efficacy and tolerability of alpha(1)-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. Urology 2004;64:1081-8.

10. Lepor H, Hill LA. Silodosin for the Treatment of Benign Prostatic Hyperplasia: Pharmacology and Cardiovascular Tolerability. Pharmacotherapy 2010;30:1303-12.

11. Yu H-J, Lin AT-L, Yang SS-D, et al. Non-inferiority of silodosin to tamsulosin in treating patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). Bju International 2011;108:1843-8.

12. Imperato.J, Guerrero L, Gautier T, Peterson RE. Steroid 5 alpha reductase deficiency in man - Inherited form of male pseduhermaphroditism. Science 1974;186:1213-5.

13. Gormley GJ, Stoner E, Bruskewitz RC, et al. The effect of finasteride in men with benign prostatic hyperplasia. New England Journal of Medicine 1992;327:1185-91.

14. McConnell JD, Bruskewitz R, Walsh P, et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. New England Journal of Medicine 1998;338:557-63.

15. Debruyne F, Barkin J, van Erps P, et al. Efficacy and safety of long-term treatment with the dual 5 alpha-reductase inhibitor dutasteride in men with symptomatic benign prostatic hyperplasia. European Urology 2004;46:488-95.

16. McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. New England Journal of Medicine 2003;349:2387-98.

17. Emberton M, Cornel EB, Bassi PF, Fourcade RO, Gomez JMF, Castro R. Benign prostatic hyperplasia as a progressive disease: a guide to the risk factors and options for medical management. International Journal of Clinical Practice 2008;62:1076-86.

18. Nickel JC, Gilling P, Tammela TL, Morrill B, Wilson TH, Rittmaster RS. Comparison of dutasteride and finasteride for treating benign prostatic hyperplasia: the Enlarged Prostate International Comparator Study (EPICS). Bju International 2011;108:388-94.

19. Lepor H, Williford WO, Barry MJ, et al. The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. New England Journal of Medicine 1996;335:533-9.

20. Kirby RS, Roehrborn C, Boyle P, et al. Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: The Prospective European Doxazosin and Combination Therapy (PREDICT) trial. Urology 2003;61:119-26.

21. Roehrborn CG, Siami P, Barkin J, et al. The Effects of Combination Therapy with Dutasteride and Tamsulosin on Clinical Outcomes in Men with Symptomatic Benign Prostatic Hyperplasia: 4-Year Results from the CombAT Study. European Urology 2010;57:123-31.

22. Kaplan SA, McConnell JD, Roehrborn CG, et al. Combination therapy with doxazosin and finasteride for benign prostatic hyperplasia in patients with lower urinary tract symptoms and a baseline total prostate volume of 25 MI or greater. Journal of Urology 2006;175:217-20.

23. Cornu J-N, Cussenot O, Haab F, Lukacs B. A Widespread Population Study of Actual Medical Management of Lower Urinary Tract Symptoms Related to Benign Prostatic Hyperplasia Across Europe and Beyond Official Clinical Guidelines. European Urology 2010;58:450-6.

24. Tacklind J, MacDonald R, Rutks I, Wilt TJ. Serenoa repens for benign prostatic hyperplasia. Cochrane Database of Systematic Reviews 2009.

25. Robert G, Descazeaud A, Allory Y, Vacherot F, de la Taille A. Should We Investigate Prostatic Inflammation for the Management of Benign Prostatic Hyperplasia? European Urology Supplements 2009;8:879-86.

26. McVary KT, Monnig W, Camps Jr JL, Young JM, Tseng L-J, van den Ende G. Sildenafil Citrate Improves Erectile Function and Urinary Symptoms in Men With Erectile Dysfunction and Lower Urinary Tract Symptoms Associated With Benign Prostatic Hyperplasia: A Randomized, Double-Blind Trial. The Journal of Urology 2007;177:1071-7.

27. McVary KT, Roehrborn CG, Kaminetsky JC, et al. Tadalafil Relieves Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia. The Journal of Urology 2007;177:1401-7.

28. Stief CG, Porst H, Neuser D, Beneke M, Ulbrich E. A Randomised, Placebo-Controlled Study to Assess the Efficacy of Twice-Daily Vardenafil in the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia. European Urology 2008;53:1236-44.

29. Roehrborn CG, McVary KT, Elion-Mboussa A, Viktrup L. Tadalafil Administered Once Daily for Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: A Dose Finding Study. The Journal of Urology 2008;180:1228-34.