health technology assessment

REPORT

MEDICAL MANAGEMENT OF SYPTOMATIC BENIGN

HEALTH TECHNOLOGY ASSESSMENT UNIT
MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA
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EXECUTIVE SUMMARY

Benign Prostatic Hyperplasia (BPH) is a non-malignant enlargement of the prostate effecting about 50% of men aged 60 years and above. This enlargement is a normal consequence of aging and is rarely life threatening but may produce distressing symptoms.

The prevalence of BPH is said to be high, but patients' only seek treatment when a critical level of bother has been reached. In Malaysia, results from a campaign on health awareness of BPH in Hospital Kuala Lumpur found a prevalence of 35/100 in self referred participants aged 50 years and above.

The terminology associated with BPH has changed from "Prostatism" to lower urinary tract symptoms', whereas traditional symptoms are categorized as irritative or obstructive symptoms.

There are various methods to diagnose BPH, the quantification of symptom severity being recognized as the best diagnostic tool and best predictor of the condition. The most widely used scoring system is the American Urological Association symptom index for BPH, which was later, modified as International Prostate Symptom Score (IPSS). Another method is using uroflometry to measure the peak urinary flow and residual volume by ultrasound or by catheterization.

The treatment options for symptomatic patients with BPH fall into four distinct catagories
- assurance and advice/watchful waiting, pharmacological intervention using alpha receptor blockers, 5 alpha reductase inhibitors and phytotherapy, surgical treatment using endoscopic methods like TURF, TUIP or laser prostatectomy and open prostatectomy, and other treatment methods such as microwave/radiowave, stents and balloon dilation.

The objectives of this assessment are to determine the effectiveness, safety and cost implications of the various modalities of medical management of symptomatic BPH.

There is sufficient evidence that alpha-blockers and 5 alpha reductase inhibitors are effective to treat moderate symptoms of BPH. Alpha blocker are safe for normotensive and controlled hypertensive elderly patients, with Tamsulosin having least side effects compared to other alpha adrenoceptor blocker. 5alpha reductase inhibitors have minimal sexual related side effect, but is otherwise safe and well tolerated. With respect to cost implications there is sufficient evidence to support medical management of BPH in older patients, since it is only cost effective for a short time horizon. Alpha-blocker are more cost effective than alpha reductase inhibitors. There is insufficient evidence to support the effectiveness and safety of phytotherapy.

Medical management is thus recommended for elderly patients with mild to moderate BPH.

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1. INTRODUCTION

1.1 Background

Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate and it affects about 50% of men aged 60 years and over. This enlargement is a normal consequence of aging as has been shown by autopsy studies of histological prevalence of 82% in men aged 71-80 (Berry et al. 1984). This enlargement, though rarely life-threatening, may produce distressing symptoms.

Evidence from studies reveal that the prevalence of BPH is high, but treatment is only sought when a critical level of bother has been reached (Pinnack et al. 1996; Ward and Sladden, 1994; MacFarlane et al. 1995). In Malaysia, the lack of local studies on the epidemiology of BPH, as well as the absence of a registry for BPH, make it difficult to estimate the prevalence of symptomatic BPH. However, it may be a significant problem as indicated by the results of a recent campaign on health awareness on BPH in Kuala Lumpur Hospital, that found a prevalence of symptomatic BPH of 35 per 100 in self-referred participants of the campaign aged 50 years and above.

1.2 Symptoms and Natural History

The terminology associated with BPH has also changed during the last decade. The term "prostatism" was formerly used broadly to describe urinary symptoms in elderly men. Currently, the terminology of " lower urinary tract symptoms" has been proposed as a more adequate expression. Traditionally symptoms of BPH were categorized into irritative or obstructive symptoms. More recently, these symptoms have been classified as voiding or storage symptoms as indicated below.

Storage Symptoms	Voiding Symptoms
• Frequency • Urgency • Nocturia • Urge incontinence	• Hesitancy • Poor flow • Intermittent flow • Post-micturition dribble • Incomplete emptying

The symptoms of frequency, urgency and nocturia are usually cited as the most 'bothersome' (du Beau et al. 1995). Clinically diagnosed but untreated BPH shows a variable pattern of exacerbation and remission, and it is not possible to predict which of these patients will deteriorate if left untreated. However, the reported annual incidence of the progression of symptoms of BPH to urinary retention is in the range of 0.4% - 6% (Roehrborn, 1996). Studies have shown that there is poor correlation between urinary symptoms and the degree of prostatic enlargement (Barry et al. 1993; Girman et al. 1995; Simpson et al. 1996). This makes the issue of who should be treated and when, a difficult one.

1.3 Symptom Assessment and Symptom Scores

1.3.1 Symptom score

In the diagnosis of BPH, the quantification of symptom severity is recognized as the best diagnostic tool and is the best predictor of the condition. It enables the patient and his doctor to determine the nature and severity and the impact they are having on his well-being. The most widely used scoring system is the American Urological Association symptom index for BPH. This has subsequently been modified as the International Prostate Symptom Score (IPSS) with the addition of an extra question relating to the impact of the symptoms on the quality of life. It is a self-administered seven-question instrument (Appendix 1). A classification of mild (0-7), moderate (8-19) or severe (20 to 35) is used to plan and monitor treatment. This score has been shown to have high internal consistency and test-retest reliability (Wernberg, 1995).

1.3.2 *Objective measures*

The peak urinary flow rate, measured by uroflometry, is a non-invasive indicator of bladder outlet obstruction. However, the peak flow rate can be influenced by other factors including impaired detruser function, and hence it may not correlate well with the degree of obstruction. A peak flow rate between 10 to 15 ml/s with a minimal voided volume of 150 ml is regarded as normal. However, for the baseline rate of any patient, the use of flow rates on two separate occasions has been recommended (Roehrbornd et al. 1996). Improvements of greater than 3 ml/second are frequently used as measures of success of treatment in studies analyzing efficiency of surgical or medical treatments (Reynard and Abrams, 1995).

Another measure is that of residual volume, which can be achieved by ultrasound or by catherisation. However, there is a very wide void-to-void variation in post void residual volume, which makes the use of this parameter for treatment decision and evaluation of treatment, difficult to interpret.

1.4 Treatment

The treatment options for symptomatic patients with BPH fall into four distinct categories:

- Reassurance and advice/watchful waiting
- Pharmacological intervention
- Surgical treatment
- Other treatment methods

1.4.1 Reassurance and advice/watchful waiting

A proportion of patients with mild to moderate symptoms of BPH improve spontaneously over time, with no active intervention, a therapeutic option termed watchful waiting (WW). Therefore, in cost-effective analysis of various treatment modalities, WW has often been used as one of the treatment arms in the analysis.

1.4.2 Pharmacological management

The medical treatment of BPH should be regarded as an option in its own right and not only as an interim measure while waiting for surgery. The drugs used in symptomatic BPH can be grouped into three major categories as follows:

α_1 receptor blockers

The alpha-one ($\alpha_{1)}$ blockers have an antagonist effect on the alpha adrenoceptors in the prostate smooth muscle. The resultant relaxation of the smooth muscle decreases the prostate tone on the urethra and hence, reduces the urethral resistance. The α_1 receptor blockers currently available for treatment of BPH in Malaysia include Prazosin, Terazosin, Doxazosin and Alfuzosin. Another α_1 receptor blocker, Tamsulosin, is widely used in Japan and Europe, purportedly with a much better safety profile than the rest.

a) 5α-reductase inhibitors

5α-reductase inhibitors prevent the conversion of testosterone to its active form dihydroxytestosterone, which is important for the growth and differentiation of the prostate. A reduction of dihydroxytestosterone there will reduce the volume of the prostate, leading to a decrease in the urethra flow resistance. The time of onset of action for 5α-reductase inhibitors is reported to be between 3-6 months. The only 5α-reductase inhibitor currently on the market is Finasteride.

b) Phytotherapy

There has been various plant extracts used to treat BPH, but the mechanism of action of phytotherapy is not well understood. Some of the natural remedies available that have been used to treat BPH include Carnilton (a pollen extract), Cubicin (derived from pumpkin seeds), Serenoa repens, certinin and pygemy africanum.

1.4.3 Surgical intervention

Surgery is generally considered for those patients with severe symptoms of BPH.

1. Endoscopic methods

- TURP (Transurethral Resection of Prostate) is considered the gold standard of surgical management. This involves resection/removal of the inner tissue of the gland via the urethra using electro-cautery.

- TUIP (Transurethral Incision of Prostate), also referred to as bladder neck incision, involves making one or two incisions in the prostate to relieve constriction.

- Laser prostatectomy consists of 2 main techniques: TULIP – transurethral ultrasound-guided laser prostatectomy and ELAP/VLAP- visual laser prostatectomy.

2. Open prostatectomy

Open prostatectomy is used for particularly large glands (70-80 gm) and for patients with complicated BPH, urinary retention and patients with hip problems, which prevent the patient from being able to be correctly positioned for TURP.

1.4.4. Other treatment methods

a) Microwaves/Radiowaves

- Microwave involves raising the temperature above body temperatures but less than 45ºC. The may be delivered either transrectally or via the transurethral route, and results in coagulative necrosis of the gland.

- Radiowaves – transurethral needle ablation (TUNA) involves transmission of low frequency radiowaves through needles placed directly into the prostatic lobes. It produces well -defined necrotic lesions, but spares the urethra.

b) Stents

Stents are flexible prostheses inserted into the urethra to hold the prostatic lobes apart. They are used for patients who would need permanent catheter drainage because they are unsuitable for surgery.

c) Balloon Dilatation

Balloon dilation involves stretching the prostatic urethra by the inflation of a balloon. Tears or splits are produced through the stroma along the length of the prostate. This procedure only produces temporary relief of symptoms. This is the least invasive of non-medical therapies.

2. OBJECTIVES

To determine the effectiveness, safety and cost implications of the various modalities of the medical management of symptomatic BPH.

3. METHODOLOGY

An electronic search of the MEDLINE database using the following search criteria was carried

out:

Key words used:	*prostate, costing, cost- effectiveness*
Years searched:	1995- 2001
Number of titles reviewed**:**	56
Relevant full text articles reviewed:	6
Relevant abstracts reviewed:	5

In addition the following journals and reports were searched on- line: Effective Health Care

and Health Technology Assessment Reports. Apart from this, relevant journals were hand-searched from the medical library of the University of Malaya.

Literature was systematically reviewed and the evidence graded according to the modified CAHTA Scale (Appendix 2).

4. RESULTS & DISUSSION

4.1 Effectiveness

4.1.1 Alpha-blockers.

Several randomized placebo controlled trials have demonstrated that alpha one blockers are effective in the treatment of BPH, with the onset of action 2-4 weeks after initiating treatment. (Okada, 2000; Buzelin, 1997; Lee, 1997). The main study outcome was measured by peak urinary flow rates (Q max) and symptom scores in most of the studies. Some studies have used failure of medical treatment, defined as developing acute urinary retention or need for surgical intervention (Clause, 1996). Other studies have used residual volume as a means to measure outcome (Lee 1997). It was noted however that in many of the studies there was lack of standardization, different inclusion criteria were used, different symptom scores were utilized and even different minimal voided volume for the measurement of Q max were used. This makes quantitative comparison between the study groups difficult.

It was demonstrated that α_1- blockers improves the Q max by 20-30%, with an improvement of urine flow up to 2.2 ml/s while the symptom score improved by 25-44% (Lee, 1997; Buzelin, 1997; Kirby, 1997; Claus, 1996; Mostaafa, 1996). There is a reduction in treatment failure in the α_1 blockers treated group as compared to the placebo group (Clause, 1996)

4.1.2 Five alpha reductase inhibitors

The only drug in this group currently available on the market is Finasteride.

A review, (Otten, *1996*), found that the choice of Finasteride was dependent on life expectancy and the severity of symptoms on presentation. There are two main wellconstructed RCT regarding the use of 5α-reductase inhibitors that contradict each other. The study by Lepor et al (1996) showed that there was no significant improvement in the symptom score and Q max in the patients treated with 5α-reductase inhibitors as compared with those treated with a placebo, except for a reduction in the prostate volume. In the study by McConnel et al.(1998) in those patients treated with 5α-reductase inhibitors, there was a reduction in surgery, reduction of acute urinary retention, decrease in the symptom score, increase in Q max, and an overall decrease in the prostate volume. Hudson et al.(1999) also showed that the symptom score improved, Q max increased, with the prostate volume decreasing at 24 months on therapy with 5α-reductase inhibitors. A study by Eri and Tveter, (*1997*) showed that Finasteride was most effective in men with large prostates (> 40 mm). For patients with moderate symptoms and a life expectancy of 3 years or less, Finasteride produced a better quality of life than Watchful Waiting (WW).

4.1.3 Phytotherapy

Two major systematic reviews of phytotherapy by Wilt et al. (1998, 1999) showed that existing studies are limited by short study duration and lack of standardization in the plant extract used. In view of this, the efficacy of phytotherapy in the treatment of BPH at the moment cannot be established, and further studies are needed to determine the role of phytotherapy in the treatment of BPH.

4.2 Safety

4.2.1 Alpha-blockers

The side effects profile for each of the drug can be categorised into two broad groups:-

1) Side effects due to 5α-1 receptor blockade at sites other than the prostate
2) Other side effects unrelated to the above

Safety concerns on the use of α_{1}- receptor blockers in BPH have generally centred around its effect on the vasculature. A randomized control trial of 207 patients followed up for 6 months found that the side effects of **Terazosin** were similar to that of placebo, while a drop in blood pressure was found only in uncontrolled hypertensives, but not in controlled hypertensives or normotensive patients (Kirby 1998). Another prospective non-randomised trial of 36 patients with a follow-up of 6 months found Terazosin and **Doxazosin** to be safe in elderly hypertensives and normotensives, whereby no patients stopped medication due to its vasodilatory effects and only a small non-significant decrease in blood pressure due to aesthenia was noted in 3 patients who stopped medication (Kaplan 1997). In a non- systematic review of alpha adrenoceptor blockade in the treatment of benign prostatic hyperplasia, an estimated 6.7% of patients had vasodilatory side effects but these were rarely troublesome enough to require cessation of treatment. Most patients in clinical trials completed their therapy and withdrawal was frequently for reasons other than side effects or poor efficacy (Kirby, 1997). Another review article found that α_1 blockers are appropriate for elderly patients associated with hypertension and hyperlipidemia. Side effects were minor except for postural hypotension, which decreased with gradual titration. There were no long-term metabolic side effects nor was it affected by renal dysfunction (Cooper, 1995). In another single blind randomised trial of 72 patients with a follow-up for 9 weeks, systolic and diastolic blood pressure decreased significantly in the Terazosin group as compared to the Tamsulosin group, reflecting the better safety profile of Tamsulosin (Lee, 1997). Another review by Chapple (1998) concluded that Tamsulosin had a better or equivalent safety profile compared to Alfuzosin which, in turn, is better than Doxazosin and Terazosin. A case-study of Terazosin resulting in generalised cutaneous rashes that spontaneously resolved on withdrawal of medication has been reported (Hernandez-Cano, 1998).

As for **Alfuzosin**, a non-systematic review found that a twice daily dose has lower side effects compared to a thrice daily dose (Kirby, 1998). A double blind randomised trial of 256 patients with a 12-week follow-up found that the antihypertensive effects of Alfuzosin were not significantly different from that of Tamsulosin. However, statistically significant effects on systolic supine blood pressure, supine and standing blood pressure were observed in the elderly (Buzelin, 1997). Another two randomised controlled trial of Alfuzosin involving 588 patients followed up at 1 and 3 months found that the incidence of drug withdrawal and adverse events related to vasodilatation was similar to placebo. However, a higher incidence of asymptomatic

orthostatic hypotension was noted in the elderly and hypertensives (Buzelin, 1997). A separate randomised controlled trial of 390 patients on Alfuzosin followed up for 12 weeks also found that the drop out rate from side effects and vasodilatory events were similar to placebo (Buzelin, 1997). Further, a non-controlled post marketing surveillence study on 13 389 patients on SR Alfuzosin reported only a rate of 2.7% in vasodilatory events (Lukacs, 1996).

Prazosin has often been linked to syncope and the first dose phenomenon as reported in a non-systematic review of alpha adrenoceptor blockade in the treatment of BPH (Kirby, 1997). Another review article also highlighted the first dose effect and postural hypotension associated with Prazosin (Chapple, 1998). On the other hand, a prospective study of 31 patients awaiting TURP on Prazosin treatment, followed up for 1 to 8 weeks, noted its short-term safety (Ogbonna, 1997). Another review article on the pharmacokinetics of Prazosin found no evidence that it accumulates in renal failure, nor that age-related pharmacokinetic differences is likely to be of major importance. Its first dose effect was said to be unrelated to its pharmacokinetic profile (Vincent, 1985). However, a separate review article on Prazosin found that initial doses of 2 mg or more was more likely to trigger off the first dose phenomenon. It was less likely with starting doses of 1 mg or less and none was reported when diuretic was stopped. Orthostatic hypotension in hypertensives was mild and transient (AIDS Publication 1985).

Tamsulosin, was found not to change blood pressure 1, 2, 4 and 8 hours after the first dose, in a multicentre, double blind randomised placebo-controlled trial of 126 patients followed up for 4 weeks (Abrams, 1997). A double blind randomised controlled trial comparing Alfuzosin and Tamsulosin in 256 patients followed up for 12 weeks found that Tamsulosin caused only an isolated case of retrograde ejaculation (Buzelin, 1997). Another review article concluded that Tamsulosin is the preferred treatment for symptomatic BPH over other α_1 adrenoceptor blockers in the treatment of lower urinary tract symptoms in hypertensive patients treated with other antihypertensive agents (Narayan, 1998).

4.2.2 Five alpha reductase inhibitors

A 4 year follow up of 4 222 patients on Finasteride found that its side effect profile and discontinuation rate similar to placebo with the exception of sexual side effects (decreased libido, ejaculatory disorders and erectile dysfunction). Otherwise, it was safe and well tolerated (Chapple, 1998). An observational cohort study on 14 772 patients on Finasteride for one year, found that impotence was the most common reason for stopping treatment, but it was safe and had good tolerability in long term therapy (Wilton, 1996). A review article also found that the side effects of Finasteride were minor and similar to placebo except for libido, impotence and ejaculatory disorders (Cooper, 1995). A separate review article revealed that only 2% patients ceased treatment due to side effects (Stricker, 1995). Finasteride was found to have minimal side effects and adverse events, which resolved with continued therapy or drug withdrawal, in another review article (Yin, 2000)

4.2.2 Phytotherapy

A systematic review on the use of **beta-sitosterol** on men with symptomatic BPH found that its withdrawal rates were similar to placebo but gastrointestinal symptoms and impotence were higher as compared to placebo (Wilt, 1999).

Another review article on the use of **saw palmetto** for symptomatic BPH found that adverse effects were rare but use in pregnant women and children was not recommended when used for other indications (Wilt, 1998)

4.3 Cost Implications

The evaluation of the cost- effectiveness of the various treatment modalities were dependent on the following factors:

i) Life expectancy of the patient.
ii) Severity of symptoms at presentation.

4.3.1 Surgical vs. Medical Management of BPH

Generally, studies reviewed indicated that men with mild to moderate symptoms were the best candidates for medical treatment, while surgery is usually indicated for patients with severe symptoms (Otten, 1996; Cockrum et al, 1997). All other parameters being equal, surgery appears to be more cost effective at younger patient ages, while medical management has a cost advantage at older ages (Thomas et al. 1996). Finasteride was found to be more costly than TURP if the patient's lifespan was over 14 years (*Effective Health Care, 1995*).

4.3.2 Medical Management of BPH

Alpha Blockers

A randomized controlled trial involving 2084 men followed up for 1 year found that Terazosin was more cost-effective when compared to placebo (Hillman et al. 1996).

A systematic review of 9 randomized control trials (*Effective Health Care, 1995*) demonstrated that Prazosin to be more cost-effective than Terazosin. A study by Cockrum et al (*1997*) demonstrated that alpha- blockers (Prazosin > Terazosin > Doxazosin) were more cost-effective than Finasteride.

5 α Reductase Inhibitors (Finasteride)

A systematic review of 9 randomized control trials (*Effective Health Care, 1995*) found Finasteride was more costly than all the alpha-blockers. A health technology assessment by the Canadian Coordinating Office for Health Technology Assessment Ottawa (1995), involving males with BPH aged > 60 years, found that the cost- effectiveness of initiating Finasteride over Watchful Waiting (WW) and TURP was dependent on the choice of time horizon - Finasteride was more cost-effective than WW if the time horizon was less than 4 years, while it was more cost-effective than TURP if the time horizon was less than 14 years. In a review, (Otten, *1996*), two randomized controlled trials comparing Finasteride with placebo reported that Finasteride produced more Quality Adjusted Life Years (QALYs) than surgery in men suffering from mild symptoms and whose life expectancy was 14 years or less. For patients with moderate symptoms and a life expectancy of 3 years or less, Finasteride produced a better quality of life than WW.

Finasteride demonstrated more cost offsets when compared with WW and Terazosin over 2 years. Finasteride also appeared to be more economical in men with higher Prostatic Specific Antigen (PSA) levels (Albertsen et al. *1999*). A study by Lowe et al., (*1995*) concluded that the

most expensive intervention was surgery, followed by Finasteride and Terazosin at 24 months of therapy.

5. CONCLUSION

There is sufficient evidence to conclude that alpha blockers and five alpha reductase inhibitors are effective to treat moderate symptoms of BPH. Alpha blockers are safe for normotensive and controlled hypertensive elderly patients, with Tamsulosin having the least side effects compared to other α_1 adrenoceptor blockers. Five alpha reductase inhibitors have minimal sexual related side effects such as decreased libido, ejaculatory disorders, erectile dysfunction and impotence, but is otherwise safe and well tolerated. With respect to cost implications, there is sufficient evidence to support medical management of BPH in older patients, since it is only cost effective for short time horizons. There is sufficient evidence to suggest that alpha-blockers are more cost- effective than alpha reductase inhibitors.

There is insufficient evidence to support the effectiveness and safety of phytotherapy.

6. RECOMMENDATION

Medical management is recommended for treatment of elderly patients with mild to moderate BPH.

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8. EVIDENCE TABLE
MEDICAL MANAGEMENT OF BPH - COST BENEFIT/ EFFECTIVENESS

No.	Author/ Title/ Journal	Study Design, Sample Size, Follow- up	Outcome & Characteristics	Comments Grade of Evidence
1.	Hillman A L, Schwartz J S, William M K, Peskin E, Roehrborn C G, Oesterling J E, Mason M F, Maurath C J, Deverka P A, Padley R J. *The Cost- Effectiveness Of Terazosin And Placebo In The Treatment Of Moderate To Severe Benign Prostatic Hyperplasia*. *Urology*, 1996, 47(2), 169-178.	- Prospective, randomized double-blind, placebo-controlled trial - Patients were randomized at 15 regional centres and 141 satellite centres to ensure a sample size of 2084 men (1031- placebo, 1053-terazosin). Follow up 1 year	Terazosin- treated patients had improvement in symptomatology on the 3 AUA indices (AUA symptom score, Bother score and Quality- of Life score). The costs of health care resource utilization were similar for men treated with terazosin and those receiving placebo.	Good -2 A short time horizon is a limitation of this study.
2.	*Benign Prostatic Hyperplasia.* Effective Health care December 1995 Volume 2 Number 2, ISSN: 0965-02888.	Systematic review of randomized control trials.	Watchful waiting is likely to be the least cost option for men with mild or moderate Finasteride is more costly than TURP if the patient's lifespan is over 14 years. Drug therapy costs around $(Pounds) 325 per man-year for Finasteride, $(Pounds) 347 for Terazosin and $(Pounds) 60 for Prazosin. All 3 alpha-blockers are equally effective.	Good - 1 Adequate time horizon, cost and severity of symptoms have been addressed.
3.	Eri L M, Tveter K J. Treatment of benign prostatic hyperplasia: a pharmacoeconomic perspective. *Drugs & Aging*, 1997, 10(2), 107-118.	-	Men with moderate symptoms of BPH are the best candidates for medical treatment, while surgery is usually indicated for patients with severe symptoms. Finasteride is most effective in men with large prostates (> 40 mm). Alpha-blockers work in men with small or large prostates, and their rapid onset of action facilitates the identification of responders.	Original paper not obtained.

No.	Author/ Title/ Journal	Study Design, Sample Size, Follow- up	Outcome & Characteristics	Comments Grade of Evidence
4.	Otten N.*Finasteride: clinical and economic impacts*. Technology overview: pharmaceuticals, 1996, Issue 2.0, 1-8. Canadian Coordinating Office of Health Technology Assessment (CCOHTA), Canada.	- Two randomized controlled trials of finasteride versus placebo in men with BPH. - The time horizon for the analysis was from 1 to 15 years.	For patients with moderate symptoms and a life expectancy of 3 years or less, finasteride produced a better quality of life than watchful waiting. Finasteride produced more QALYs than surgery, for men suffering from mild symptoms and whose life expectancy was 14 years or less. For men with severe symptoms, surgery produced a better quality of life. For moderate symptoms, watchful waiting produced a better quality of life than surgery. The choice of Finasteride is dependent on 2 factors: life expectancy and the severity of symptoms.	Good - 1 No comparison made with alpha blockers
5.	*Cost-effectiveness and cost-utility analyses of finasteride therapy for the treatment of benign prostatic hyperplasia.* Canadian Coordinating Office for Health Technology Assessment Ottawa, Ontario: Canadian Coordinating Office for Health Technology Assessment, 1995.	- Study population: Males, aged above 60 and experiencing symptoms of BPH. - Costs, effects and quality-adjusted-life-years (QALYs) were estimated over time horizons ranging from 2- 15 years.	Cost-effectiveness of initiating treatment for BPH with finasteride, rather than WW or TURP, was dependent on the choice of time horizon. Finasteride was more cost-effective than WW if the time horizon was less than 4 years; finasteride was more cost-effective than TURP if the time horizon was less than 14 years.	It was assumed that if an intervention were effective, then it would remain effective.

No.	Author/ Title/ Journal	Study Design, Sample Size, Follow- up	Outcome & Characteristics	Comments Grade of Evidence
6.	Baladi J F, Menon D, Otten N *An economic evaluation of finasteride for treatment of benign prostatic hyperplasia.* PharmacoEconomics, 1996, 9(5), 443-454.	To assess the cost-effectiveness of using finasteride versus TURP and watchful waiting (WW) in the treatment of older men with BPH.	Treating patients with moderate symptoms using finasteride rather than TURPP leads to savings of Can$32,000 over 4 years. The incremental cost per QALY gained in using finasteride rather than WW, for a 4-year time horizon was can$19,000. Sensitivity analysis showed that the sensitive parameters were effectiveness of WW and time horizon of treatment	Original paper not obtained.
7.	H. Lohgan Holtgrewe *Economic Issues And The Management Of Benign Prostatic Hyperplasia* Urology 46 (Supplement 3A), 1995, 23-25.	- Review article on the guidelines issued by the Agency for Health Care Policy and Research (AHCPR) for the diagnosis and management of BPH in the United States. - Clinical practice guidelines were applied only to men > 55 years with classical symptoms of prostatism with no confounding co-morbidity.	Watchful waiting: US$1,162 (a) US$640 (b) *Finasteride* US$1,326 (a) US$788 (b) *Alpha- blocker* US$1,395 (a) US$845 (b) *Balloon Dilation* US$3,723 (a) US$543 (b) *TURP* US$8,606 (a) US$360 (b) Open prostatectomy US$12,788 (a) US$69 (b) Key: (a): Cost for primary Treatment and 1 Year Follow-up (b) Cost for Second Year of Treatment after Primary Treatment	The costs depicted are enormously influenced by treatment failure rates.

No.	Author/ Title/ Journal	Study Design, Sample Size, Follow- up	Outcome & Characteristics	Comments Grade of Evidence
8.	Thomas N. Chirikos and Edgar Sanford *Cost Consequences Of Surveillance, Medical Management Or Surgery For Benign Prostatic Hyperplasia.* The Journal of Urology Vol. 155, 1311-1316, April 1996.	Synthetic cohort models were constructed to follow men at different ages "analytically" for specific intervals and to calculate the cumulative health care costs for alternative BPH treatment.	Cost- effectiveness of each type of BPH therapy differs by the age of the patient at which it is first initiated. All other parameters being equal, surgery appears to be more cost effective at younger patient ages, while medical management has a cost advantage at older ages.	Original paper not obtained.
9.	Cockrum PC, Finder SF, Riess AJ, Potyk RP. *A pharmacoeconomic analysis of patients with symptoms of benign prostatic hyperplasia.* Pharmacoeconomics 1997 Jun; 11(6): 550-65.	- Review article - Therapies compared were Finasteride and alpha-blockade (doxazosin, prazosin and terazosin).	Men with moderate symptoms are the best candidates for medical treatment, while surgery is usually indicated for patients with severe symptoms. Pharmacological therapy was more cost- effective than surgical intervention, and alpha-blockers (Prazosin> Terazosin> Doxazosin) were more cost effective than Finasteride.	Original paper not obtained.

10.	Albertsen PC, Pellisier JM, Lowe FC, Girman CJ, Roehrborn CG. *Economic analysis of finasteride: a model-based approach using data from the PROSCAR Long- Term Efficacy and Safety Study.* Clinical Therapeutics 1999 Jun; 21(6): 1006-24.		Finasteride shows cost offsets compared with watchful waiting and cost savings compared with terazosin over 2 years. Finasteride appears to be more economical in men with higher PSA levels.	No original paper obtained.

No.	Author/ Title/ Journal	Study Design, Sample Size, Follow- up	Outcome & Characteristics	Comments Grade of Evidence
11.	Lowe FC, McDaniel RL, Chmiel JJ, Hillman AL. *Economic modeling to assess the costs of treatment with finasteride, terazosin and transurethral resection of the prostate for men with moderate to severe symptoms of benign prostatic hyperplasia.* Urology 1995 Oct; 46(4): 477-83.	-	The most expensive intervention was surgery, followed by finasteride and terazosin at 24 months of therapy. Duration of symptom improvement was comparable for the three treatments.	Original article not obtained.

SAFETY

No.	Author/ Title/ Journal	Study Design, Sample Size, Follow- up	Outcome & Characteristics	Comments Grade of Evidence
1.	*The ALLHAT Officers and Co-ordinators for the ALLHAT Collaborative Research Group/ Major Cardiovascular Events in Hypertensive Patients Randomized to Doxazosin vs Chlorthalidone* JAMA, 2000 April 19; 283(15)	Clinical trial on the use of doxazosin vs chlorthalidone as a antihypertensive. N= 42448 F/U: since 1994	Doxazosin treated group has a significantly higher incidence of cardiac failure	Poor-8
2.	Kirby, R.S. *Terazosin in benign prostatic hyperplasia: effects on blood pressure in normotensive and hypertensive men* BJU Sept 1998, l82(3):373-379)	Double blind randomised controlled trial N= 207 patients F/U: 6 months	Side effects profile similar to placebo. Dizziness: 0% (placebo) 3%(terazosin) Headache: 1%(placebo) 2%(terazosin) somnolence:0%(placebo) 2%(terazosin) Clinically significant decrease in BP in untreated and uncontrolled hypertensives with BPH but not in the normotensive and controlled hypertensives group. Clinically significant decrease in SBP and DBP in the normotensive group.	Good - 2 1.20% drop-out in the initial single blind selection study: not analysed in detail in the study. 2. Sample is bias due to the initial selection study
3.	Hernandez-Cano et al *Severe cutaneous reaction due to terazosin* Lancet 1998 July; 352(9123): 202-20	Single case report	Generalised cutaneous rash 3 days after starting treatment on terazosin. Resolved with drug withdrawal	Poor - 9

No.	Author/ Title/ Journal	Study Design, Sample Size, Follow- up	Outcome & Characteristics	Comments Grade of Evidence
5.	Kirby, R.S.; Pool, J.L *Alpha adrenoceptor blockade in the treatment of benign prostatic htperplasia: past, present and future* BJU 1997 Oct, 80(4):521-532	Non systematic review with 63 references	TURP complications: Intra-op: 6.9% Post-op: 18% POM(30d): 0.23% All alpha blockers (prazosin, doxazosin, alfuzosin, terazosin, tamsulosin) are of similar efficacy. Side effects profile due to different pharmacokinetics. Prazosin: syncope and first dose effect. Alfuzosin: lower side effects (twice daily dose better than thrice daily) Tamsulosin: Dizziness 5% Doxazosin: Dizziness 3%, fatigue 2%, headache 1.2%, oedema 1.3% Premature discontinuation: 17% due to adverse events 9% due to insufficient clinical response. Terazosin: Dizziness 6.7%, aesthenia 3.8%, somnolence 2% Premature discontinuation: 19% due to adverse events 11% due to insufficient clinical response. ED side effects: Doxazosin: 1.3% Placebo: 3.8% Beta-blockers: 4.6% Ace-inhibitors:6.1% Calcium channel antagonist: 9.0% Favourable doxazosin side effects: Little or no effects on normotensives Beneficial BP effect for hypertensives Improved serum lipid profile Increased fibrinolysis, inhibition of platelet aggregation, decreased cardiac hypertrophy, increased insulin hypersensitivity. Syncopal attacks: Doxazosin similar to placebo	2 - Good No major side-effects as opposed to TURP

No.	Author/ Title/ Journal	Study Design, Sample Size, Follow- up	Outcome & Characteristics	Comments Grade of Evidence
6.	Abrams, P et al A dose-ranging study of the efficacy and safety of Tamsulosin, the first prostate-selective alpha 1A- adrenoceptor antagonist, in patients with benign prostatic obstruction (symptomatic *BPH* BJU. 1997 Oct, 80(4) :587-596	Multicentre, double blind randomised placebo-controlled N=126 patients F/U: 4 weeks	Report of at least one adverse event: 29% placebo 23% tamsulosin 0.2mg 27% tamsulosin 0.4mg 36% tamsulosin 0.6mg No statistical significant change in BP 1,2 4 and 8 hours after first dose. Mean age group: 65years old	Good - 2
7.	Buzelin, J.M. et al *Comparison of tamsulosin with alfuzosin in the treatment of patients with LUTS suggestive of BOO (symptomatic BPH)* BJU 1997Oct; 80(4):597-605)	Double blind randomised multicentre, parralel group trial N=256 patients F/U: 12 weeks	132 patients on tamsulosin 124 patients on alfuzosin 233 completed trial 14 withdrew due to adverse events Alfuzosin: Adverse events associated with antihypertensive effects not significantly different from tamsulosin Statistical significant effect on systolic supine BP, standing and supine diastolic BP and this is more apparent in the elderly. Tamsulosin: Isolated report of retrograde ejaculation	Good - 2 The group of patients above 75 years of age is small
8.	Lee, E., Lee, C *Clinical comparison of selective and non-selective alpha 1A-adrenoceptor antagonists in benign prostatic hyperplasia: studies on tamsulosin and terazosin in increasing doses*	Single blind randomised trial N= 72 patients F/ U: 9 weeks	Systolic and diastolic BP decreased significantly in the trazosin group as compared to the tamsulosin group 98 patients started the trial but 2 patients withdrew. (10 in the tamsulosin group and 16 in the terazosin group, of which 2 were due to adverse events) Adverse reaction: Terazosin 18 Tamsulosin 1 Tamsulosin has better safety profile. Dizziness 1.2% due to a drop in BP	Good - 3 High withdrawal rate. Tamsulosin dose used was 0.2mg. (fixed dose) whereas terazosin was used on an escalating dose. Tamsulosin dose used might not be in the optimal level.

No.	Author/ Title/ Journal	Study Design, Sample Size, Follow- up	Outcome & Characteristics	Comments *Grade of Evidence*
9.	J.M. Buzelin et al *Clinical Uroselectivity: evidence from patients treated with slow-release alfuzosin for symptomatic benign prostatic obstruction/* BJU 1997 June;- 79(6): 898-904	Two double blind randomised controlled studies N= 588 patients F/U: 1 and 3 months	43% of patients had concomittant cardiovascular disease and/ or on antihypertensive medication Incidence of withdrawal: 3.4% c.f. 5.7% for placebo Adverse events related to vasodilatation similar to placebo: 2.7% Effects on supine minimal. For the elderly and hypertensives: Higher incidence of asymptomatic orthostatic hypertension compared with placebo	Good - 2
10.	Ogbonna, FMCS et al *Alpha-receptor blockade for benign prostatic hyperplasia: uses and problems in a developing country*	Prospective follow-up of 31 patients awaiting: TURP followed up for 1 to 8 weeks	62% benefitted. Only short term safety noted	Poor - 8 No control group Only short term follow-up Selected group of patients awaiting TURP
11.	Quek K.F., et al *The psychological effects of treatments for LUT/* BJU October 2000: Vol 86(6) pp 630-633)	Psychosocial assessment on 123 patients on medical treatment and 52 patients with TURP at baseline and 3 months after treatment	Patients before TURP were significantly more worried and depressed and psychiatrically more morbid than those before medical treatment.	Fair - 4 Both groups being evaluated are at different starting points.
12.	Wilt, T; Macdonald, R.; Ishani, *A beta-sitosterol for the treatment of benign prostatic hyperplasia: a systematic review* BJU June 1999 pp 976-983	Systematic review on the use of beta-sitosterol on men with symptomatic BPH (through Medline Search 1966-1998, EMBAS and Cochrane Library). 4 double blind studies were relevant. F/U: 4-26 weeks	Withdrawal rates: 7.8% c.f. 8% for placebo (n.s.) GIT symptoms: 1.6% c.f. 0 % forPlacebo Impotence: 0.5% c.f. 0% for placebo.	Good - 3 Different types of beta-sitosterol were used. Only short term follow-up

No.	Author/ Title/ Journal	Study Design, Sample Size, Follow- up	Outcome & Characteristics	Comments *Grade of Evidence*
13.	Klepser, Teresa Bailey et al. *Unsafe and potentially safe herbal therapies* American Journal of Health-System Pharmacy 1999 Jan 15; 125-138	Review article on various herbal therapy including saw palmetto for symptomatic BPH	Adverse effects: rare headache Nausea and upset stomach Use in pregnant women and children not recommended	Poor - 8 Type of saw palmetto not standardised Large RCTs still not avaialble Short term follow-up
14.	Chapple, C R *Pharmacotherapy for benign prostatic hyperplasia- the potential for alpha1-adrenoceptor subtype specific treatment (LUTS and HPT: controversies in treatment)/* BJU March 1998 Vol 81 Supp. 1 pp 34-47	Review article with 109 references	4 year follow up of 4222 patients on finasteride: side effect profile and discontinuation rate similar to placebo with the exception of sexual side effects: decreased libido ejaculatory disorders erectile dysfunction Otherwise safe and well tolerated Phenoxybenzamine: 30% had side effects and also mutagenic Prazosin: first dose effect and postural hypotension Side effect profile: Tamsulosin better or equivalent to alfuzosin which in turn is better than Doxazosin/ Terazosin	Good - 2
15.	Narayan, P. ; Man't Veld, A.J. IN *Clinical pharmacology of modern antihypertensive agents and their interaction with alpha-adrenoceptor antagonists (LUTS and HPT: Controversies in treatment* BJU 1998 Mar; 81 (Supp. 1): 6-16	Review article with 78 references	Tamsulosin the preferred treatment for symptomatic BPH over other alpha1 adrenoceptor blockers in the treatment of LUTS in patients with HPT on other antihypertensive agent.	Good - 2

No.	Author/ Title/ Journal	Study Design, Sample Size, Follow- up	Outcome & Characteristics	Comments *Grade of Evidence*
16.	Wilton, L. et al *The safety of finasteride used in benign prostatic hypertrophy: a non-interventional observational cohort study in 14772 patients/* BJU 1996 Sept 78(3):379-384	Observational, cohort study on 14772 patients who were on finasteride for at least 1 year	Finasteride was effective in 60% of patients Impotence/ Ejaculatory failure: 2.1% Decreased libido: 1% Gynaecomastia/ related conditions: 0.4% Impotence: most frequent reason for stopping treatment/ most common adverse reaction Safe and good tolerance in long term therapy.	Fair - 6 Free from selection bias No randomisation 63% response rate GP practice follow-up/ hospital not included
17.	James W. Cooper, Robert W. Piepho *Cost-effective management of benign prostatic hyperplasia/* www.medscape.com/SCP/DBT/1995/v07.n08/d152.cooper/d152.cooper.html	Review article of medline search of relevant articles	Alpha-1 blockers: appropriate for elderly patients associated with hypertension/ hyperlipidaemia Side effects minor except for postural hypotension but decreased with gradual titration No long term metabolic side effects Not affected by renal dysfunction Terazosin: 13% withdrew due to side effects Finasteride: Minor and similar to placebo except for libido, impotence and ejaculatory disorders	Poor - 8
18.	John Vincent, Peter A. Meredith, John L. Reid, Henry L. Elliot and Peter C. Rubin *Pharmacokinetics of Prazosin-* Clinical Pharmacokinetics 1985; 10: 144-154	Clinical pharmacokinetics of prazosin	No evidence to suggest that prazosin accumulates in renal failure. Age related pharmacokinetic differences unlikely to be of major importance. First dose effect not explained pharmacokinetically	Poor - 8
19.	*Prazosin/ Minipress: A summary of fifteen years of clinical experience*	A summary on prazosin after its use for 15 years	Initial doses greater than 2mg more likely to trigger off 'first dose phenomenon. Less likely with starting dose of 1 mg or less. None reported when diuretic was stopped Orthostatic hypotension in hypertensives mild and transient. Other side effects: Headache: 7.8% ; Drowsiness: 7.6%; Lack of energy: 6.9%; Weakness: 6.5% Palpitations: 5.3%; Nausea: 4.9%	Poor - 9 Data was on its used in hypertensive patients

No.	Author/ Title/ Journal	Study Design, Sample Size, Follow- up	Outcome & Characteristics	Comments *Grade of Evidence*
20.	Philip D. Stricker *Drug treatment of benign prostatic hypertrophy* Australian Prescriber 1995; 18(2):30-32	Review article	Finasteride: Only 2% ceased treatment due to side effects	Poor - 9
21.	Ophelia QP Yin *Finasteride: Drug Profile* Medical Progress February 2000 pp 37-40	Review article	Side effects minimal. Adverse events may resolve with continued therapy or drug withdrawal	Poor - 9
22.	J.M. Buzelin et al *Efficacy and safety of Sustained-Release Alfuzosin 5 mg in patients with Benign Prostatic Hyperplasia* European Urology 1997: 31: 190-198	Randomised controlled trial N= 390 patients F/U: 12 weeks	Drop-out rate from side effects: 4.6% (SR Alfuzosin) 7.1%(Placebo) Vasodilatory events(3.1%) similar to placebo(3.6%) Drop in supine BP ,/= 5mmHg	Good - 2
23.	B. Lukacs et al *Safety profile of 3 months' therapy with alfuzosin in 13389 patients suffering from Benign Prostatic Hypertrophy* European Urology 1996; 29: 29-35	Non-controlled post marketing surveilllence studies on 13389 patients on SR alfuzosin	Drop-out rate 10.3% 3.7% for intolerance 2.7% for vasodilatory events:- vertigo/dizziness (1.4%) headache (0.4%) malaise (0.6%) hypotension (0.4%)	Fair - 6

Appendix 1

INTERNATIONAL PROSTATE SYMPTOM SCORE

	Never **0**	Less than once in five 1	Less than half the time 2	About half the time 3	More than half the time 4	Almost always 5	**Your Score**
Incomplete emptying Over the last month how often have you had a sensation of not emptying your bladder completely after you finish urinating?							
Frequency Over the past month how often have you had to urinate again less than two hours after finishing?							
Intermittency Over the past month, how often have you stopped and started again several times when you urinated							
Urgency Over the past month how often have you found it difficult to hold your urine							
Weak Stream Over the past month how often have you had a weak urinary stream							
Straining Over the last month how often have you had to push or strain to begin urination?							
Nocturia Over the past month how many times did you most typically getup to urinate from time you went to bed at night until the time you got up in the morning							
Quality of Life due to Urinary Symptoms If you were to spend the rest of your life with your urinary condition as it is now, how would feel about that.							

Appendix 2

LEVELS OF EVIDENCE SCALE

Level	Strength of Evidence	Study Design
1	Good	Meta-analysis of RCT, Systematic reviews.
2	Good	Large sample of RCT
3	Good to fair	Small sample of RCT
4		Non-randomised controlled prospective trial
5	Fair	Non-randomised controlled prospective trial with historical control
6	Fair	Cohort studies
7	Poor	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi-centre
9	Poor	Expert committees, consensus, case reports, anecdotes

SOURCE: ADAPTED FROM CATALONIAN AGENCY FOR HEALTH TECHNOLOGY ASSESSMENT (CAHTA), SPAIN

THE FOLLOWING HTA REPORTS ARE AVAILABLE ON REQUEST:

REPORT	**YEAR**
1. LOW TEMPERATURE STERILISATION	1998
2. DRY CHEMISTRY	1998
3. DRY LASER IMAGE PROCESSING	1998
4. ROUTINE SKULL RADIOGRAPHS IN HEAD INJURY PATIENTS	2002
5. STROKE REHABILITATION	2002
6. MEDICAL MANAGEMENT OF SYMPTOMATIC BENIGN PROSTATIC HYPERPLASIA	2002