



THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

Medical Management of Benign Prostatic Hyperplasia

Benign prostatic hyperplasia (BPH) is a common and bothersome condition of aging men. It is characterized by an increasing cellular growth of both epithelial and stromal elements of the prostate. Symptoms associated with BPH are common and increase in frequency with age.¹ Surgery, most commonly transurethral prostatic resection (TUPR), has been the standard therapy, but carries some morbidity and mortality; utilization varies widely within and between countries. Many other interventional therapies are promoted, but none has been compared with TUPR in adequate randomized controlled trials.

• What are the symptoms of BPH?

BPH symptoms are usually classified as **irritative** (urinary frequency, nocturia, burning, urgency, or urge incontinence) or **obstructive** (hesitancy, weak stream, slow termination/dribbling, sensation of incomplete voiding, and urinary retention). Research studies often refer to the current standard for symptom evaluation, the **American Urological Association (AUA) symptom score**. This tool rates 7 symptoms from 0-5, yielding a combined score of 0-35. Scores from 0-7 are considered "mild", 8-18 "moderate", and 19-35 "severe". The scoring sheet on the last page of this letter allows you to calculate an AUA score for your patients. The "bother index" (part B on the bottom of the last page) is also useful in making management decisions in your practice.²

• What is the natural history of BPH?

While prostatic mass increases with age, an individual man's symptoms may not. Of men with moderate symptoms followed for five years, about 40% improve, 45% remain unchanged, and only 15% deteriorate.¹ When 556 men with moderate symptoms were randomized to TUPR or watchful waiting and followed for 2.8 years, only 7% of the watchful waiting group required surgery for "treatment failure".³ Mean AUA symptom scores decreased from baseline by 5.5 in the watchful waiting group and 9.6 units in the TUPR group. **Thus**



watchful waiting is now recognized as an entirely satisfactory and safe alternative to surgery for many patients, providing there is no evidence of prostatic cancer, obstructive renal damage, hematuria, or recurrent UTI.

• What outcome measures are relevant for our patients?

Drugs are useful if they reduce symptoms, avoid surgery, or prevent complications such as urinary retention, nephropathy, or infection. **Evidence that drugs provide anything more than symptomatic benefit is severely limited.**⁴ Measures reported in many research publications, such as peak flow rate and prostatic volume, do not correlate to the AUA symptom score. Hence they are neither meaningful indicators of need for treatment nor of improvement.³ Intuitively, a high AUA score connotes reduced quality of life, but this measure too is imperfect. For example, men who said they were "not at all bothered" by trouble with urination during the last month had a mean AUA score of 12.4, typical of patients recruited for many studies.⁵ **Even men with relatively high symptom scores may not be particularly bothered by their urinary symptoms.**



• **What is the evidence that medical therapy helps BPH?**

1. ALPHA BLOCKERS

The long acting alpha blocker, phenoxybenzamine, was shown to reduce BPH symptoms as early as 1976. Predictable side effects (dizziness and orthostatic hypotension) limited its popularity. Selective alpha-1 antagonists including prazosin, doxazosin, and terazosin have been shown to reduce symptoms better than placebo in short term studies⁶. Recently, a major US trial demonstrated the superiority of terazosin (10 mg at h.s.) over both finasteride (5 mg at h.s.) and placebo in 1229 men followed for 1 year.⁷ **Adding finasteride provided no additional benefit to terazosin alone.** AUA score dropped within 4 weeks, the effect was maximum by 13 weeks and was maintained for 1 year. **At 1 year the average difference in symptom score between terazosin and placebo was 3.5 units.**

Principal adverse effects of terazosin expressed as absolute risk increase (ARI)* above placebo were: dizziness (ARI = 19%), asthenia (ARI = 7%), and postural hypotension (ARI = 7%). Shorter term controlled trials have demonstrated similar efficacy for prazosin⁸ and doxazosin⁹, but no direct comparison of the drugs exists. A 6-8pm dose of the shorter-acting and less expensive prazosin may be a logical choice for a therapeutic trial in patients whose symptoms are mainly nocturnal. **The lowest dose of alpha-antagonist to achieve symptomatic relief should be determined by starting with the lowest dose and slowly titrating up.**

2. 5-ALPHA REDUCTASE INHIBITORS

Finasteride blocks the conversion of testosterone to active dihydrotestosterone within prostatic cells. **A 1992 study of 895 BPH patients randomized to finasteride 5 mg daily or placebo for 1 year showed a mean 2.7 unit reduction in a 36 point symptom score in men treated with finasteride.**¹⁰ The more recent comparison of finasteride with terazosin and placebo failed to show any benefit from finasteride, even compared with placebo.⁷ A Canadian trial of 472 men followed for 2 years demonstrated a statistically significant but clinically modest difference in symptom scores favouring finasteride (5 mg/d) over placebo. The group difference was 1.4 points on a 54 point scale. **Adverse effects of finasteride were relatively common, notably impotence (ARI = 10%) and ejaculation disorder (ARI = 6%).**¹¹ Finasteride may be more likely to work in men with large prostates.^{12,13} Symptomatic improvement appears to be detectable by 2 months, and 1mg reduces prostate size as effectively as 5 mg, so a lower dose may be more cost-efficient.¹⁰

Recently, a meta-analysis of finasteride trials has provided the first evidence that a drug may prevent surgery or acute urinary retention. Among 4022 men randomized to finasteride or placebo for 2 years, finasteride slightly reduced both. However the absolute risk reduction was only 1.6% for retention (NNT/2 years = 63) and 2.3% for surgery (NNT/2 years = 43).^{4*}

*See Therapeutics Letter 15 for definition and calculation of ARI and NNT.

Table: Drugs for BPH symptoms

Generic Name	Trade Name	Dose Range	Daily Cost*
Prazosin	Minipress®, generic	0.5-10 mg BID •	\$0.16 - \$1.28
Terazosin	Hytrin®	1-20 mg daily •	\$0.58 - \$2.92
Doxazosin	Cardura®	1-16 mg daily •	\$0.58 - \$3.58
Finasteride	Proscar®	5 mg daily	\$1.69

* Average or lowest cost alternative (LCA) price in BC, 1996 (Pharmacare data)

• Start with the lowest dose and slowly titrate

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3.SAW PALMETTO EXTRACT (SERENOA REPENS)

Phytotherapy (herbal therapy) remains popular in the treatment of BPH, especially in Germany. Extracts of saw palmetto berry (dwarf palm, *S. repens*) are the most widely used.¹⁴ A recent RCT provides the first reliable evidence of efficacy for beta-sitosterol, an extract of saw palmetto containing several phytosterols.¹⁵ Two hundred men were randomized to placebo or 20 mg beta-sitosterol daily as "Harzol" (Hoyer, Germany). At 6 months, placebo reduced IPSS score (equivalent to AUA score) by 2.3 points, whereas beta-sitosterol achieved a reduction of 7.4 points. The difference in favour of phytosterol was detectable by 3 months. Adverse effects were reported to be minimal and only 6 of 100 beta-sitosterol treated patients withdrew. **The doses of other saw palmetto extracts equivalent to that used in this trial are unknown.** No evidence is available for long term safety or effectiveness, as regulatory agencies do not require this information for plant products. A typical dose of a representative formulation can be purchased in B.C. for \$25-\$30/month.

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• Conclusions:

- Patients with "mild" symptoms of BPH should be reassured and do not need any treatment. **Many patients with "moderate" to "severe" symptoms will improve spontaneously.**
- Alpha-1-antagonists reduce symptoms in some patients. Their effect is detectable within 2 weeks. If the patient experiences no clear benefit by 1 month, the drug should be discontinued.
- The evidence of a significant benefit to risk ratio for finasteride is less clear. It may be useful for men with large prostates; a therapeutic trial of at least 3 months is required.
- Saw palmetto extracts cannot be recommended because effective doses of available preparations have not been established and evidence of safety and long term efficacy are insufficient.
- Before using any drug to treat BPH, develop a clear treatment goal with the patient. The score sheet (see reverse) may be helpful in symptom evaluation. **If symptoms are not bothersome and there are no indications for urologic evaluation, try "watchful waiting" first.** If this fails, apply the same test to any drug prescribed and evaluate success or failure within the appropriate period of time.

1997

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A SYMPTOM INDEX FOR BENIGN PROSTATIC HYPERPLASIA*

	never	less than 1 time in 5	less than half the time	about half the time	more than half the time	almost always
1. Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. Over the past month or so, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
3. Over the past month or so, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. Over the past month or so, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Over the past month or so, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Over the past month or so, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
7. Over the last month, how many times did you usually get up to urinate from the time you went to bed at night until the time you got up in the morning?	0 never	1 time	2 times	3 times	4 times	5 times or more

*Adapted from the American Urological Association Symptom Index **Symptom Score:**

B "BOTHER" INDEX FOR BENIGN PROSTATIC HYPERPLASIA*

Overall, how bothersome has any trouble with urination been during the past month?*

Not at all Bothersome	Bothers me a little	Bothers me some	Bothers me a lot
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

*From the Benign Prostatic Hyperplasia Impact Index