therapeutics letter ©

THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Benign Prostatic Hypertrophy
An update on drug therapy

Benign prostatic hypertrophy (BPH) is relatively common and potentially bothersome to aging men. See Therapeutics Letter # 19 (May/June 1997) for background information.[1] This Letter updates the evidence of benefit and harm from alpha blockers and 5-α-reductase inhibitors.

The goals of drug therapy are symptom relief and prevention of complications. Symptoms are classified as irritative (frequency, nocturia, burning, urgency, or urge incontinence) or obstructive (hesitancy, weak stream, dribbling, incomplete voiding, or retention).

Many trials use the 35-point American Urological Association (AUA) symptom scale.[1] When AUA scores were compared with patient perceptions, men who felt 'slightly improved' averaged a 3-pt reduction; those 'not improved' averaged a 0.7-pt reduction.[8] Over 4 years, mean AUA scores fell by 5 points on placebo.[5] Complications of BPH include infection, acute urinary retention (AUR) requiring catheterization, and urinary obstruction requiring surgery (partial or complete prostatectomy).

Alpha blockers

Five alpha blockers are available in Canada: alfuzosin, doxazosin, prazosin, tamsulosin, and terazosin.

Alpha blockers provide modest symptomatic benefit. Compared with placebo, on average terazosin reduced AUA score by 3 points,[4] tamsulosin by 3 points,[5] doxazosin by 3 points at 1 year [6] and 2 points at 4 years,[2] alfuzosin by 2 points short-term [7] and 1 point at 2 years.[3] Comparable data are not available for prazosin.

Alpha blockers do not prevent BPH complications. Doxazosin was tested over 4 years vs. placebo (n=1493).[2] Incidence of AUR (doxazosin 1%, placebo 2%) and surgery (doxazosin 3%, placebo 5%) did not differ. A 2-year trial of alfuzosin vs. placebo (n=1506) also found no difference in AUR or surgery.[3]

Only 1 trial longer than a year reports on serious adverse events (SAEs): alfuzosin 12%, placebo 11%.[3] In the ALLHAT hypertension trial (no placebo arm), doxazosin increased congestive heart failure, angina and stroke vs. chlorthalidone. (see Therapeutics Letter 36)

The most frequent adverse effects of alpha blockers are dizziness, asthenia and postural hypotension. Tamsulosin's efficacy increases slightly with higher doses, but adverse effects are dose-related: dizziness 17% at 0.8mg, 9% at 0.4mg and 3% at 0.2mg.[5] Average absolute risk increases for alpha blockers versus placebo are: dizziness 3-8%, postural hypotension 3-5%,

and asthenia 5-6%, number needed to harm (NNH) 13-33.[4,5,7,9]

No consistent evidence exists for a therapeutic advantage of one alpha blocker over another.

5-α-reductase inhibitors

Two 5-α-reductase inhibitors are available in Canada: finasteride and dutasteride.

Finasteride

Finasteride did not significantly reduce symptom scores vs. placebo in one 4-year trial.[2] In a second 4-year trial, scores fell by a mean of 1.6 points.[11]

We meta-analyzed 16 randomized controlled trials (RCTs) (n=17,456; max 4 years) with at least one clinically important health outcome (Table 1).[2,6,10-23] Since finasteride reduces AUR and surgery it is surprising that total SAEs are not also reduced. Published reports provide insufficient detail to assess rates of other SAEs.

Table 1: Benefits and Harms of Finasteride vs. Placebo

Outcome	N*	Finasteride	Placebo	RR (95% CI)	ARR/ ARI	NNT/ NNH
Mortality	2,358	1.2%	0.7%	1.7 (0.7-4.1)	-	-
Total SAEs	9,180	11.0%	11.4%	0.9 (0.7-1.1)	-	-
Prostate Surgery	15,398	2.1%	4.8%	0.6 (0.4, 0.8)	2.7%	37
Acute Urinary Retention	14,329	1.1%	3.1%	0.4 (0.3, 0.6)	2.0%	50
Ejaculation Abnormality	14,396	2.7%	0.7%	3.6 (2.6, 5.1)	2.0%	50
Erectile Dysfunction	15,839	8.1%	4.8%	1.8 (1.6, 2.0)	3.3%	30
Decreased Libido	14,626	5.3%	3.4%	1.7 (1.4, 2.0)	1.9%	53

*N = number of patients in trials with this outcome. **RR** = relative risk. **CI** = confidence interval. **ARR** = absolute risk reduction. **ARI** = absolute risk increase. **NNT** = number needed to treat to prevent one event. **NNH** = number needed to treat to cause one harmful event.

Mailing Address: Therapeutics Initiative
The University of British Columbia
Department of Anesthesiology, Pharmacology & Therapeutics
2176 Health Sciences Mall
Vancouver, BC Canada V6T 1Z3

Tel.: 604 822•0700
Fax: 604 822•0701
E-mail: info@ti.ubc.ca
Web: www.ti.ubc.ca

During a 4-year trial, 4/1554 (0.3%) men on finasteride developed breast cancer (~ 200 times expected rate).[2,24] In a 7-year prostate cancer prevention trial (n=18,882) fewer men on finasteride vs. placebo developed tumours, 18.4% vs. 24.4%, but more men on finasteride had high-grade tumours with a worse prognosis: 6.4% vs. 5.1%. Mortality did not differ.[25]

Finasteride versus alpha blockers

Five RCTs (0.5 - 4 yrs) compared finasteride with an alpha blocker.[2,6,10,26,27] Mortality [6,10], SAEs [26,27] and withdrawals due to adverse effects [6,10,26,27] did not differ. Finasteride increased sexual dysfunction; alpha blockers increased dizziness, postural hypotension and asthenia. Surgery rates did not differ: finasteride 1.6%, doxazosin or terazosin 2.2%.[2,6,10] In 4 studies alpha blockers reduced AUA symptom scores by 1-3 points more than finasteride.[2,6,10,27] Alfuzosin affected scores similarly to finasteride.[26]

Adding finasteride to an alpha blocker

Adding finasteride did not reduce mean symptom score as compared with an alpha-blocker alone in 0.5 - 1 year trials: difference = 0.3 points.[6,10,26] In one 4-year RCT the mean symptom score fell by 0.8 points.[2]

Adding an alpha blocker to finasteride

Combination therapy reduced a combined outcome ("clinical progression") largely driven by symptom scores vs. finasteride alone,[2] but did not reduce AUR (0.4% vs. 0.7%)[2, 6, 26] or surgery (1.0% vs. 1.6%).[2, 6,10]

Dutasteride

Dutasteride has been tested less extensively. In 3 double-blind trials (combined n=4325), dutasteride reduced AUA scores by 1.3 points vs. placebo at 1 year. Dutasteride reduced AUR (1.8% vs. 4.2%) and need for surgery (2.2% vs. 4.1%), but increased impotence (7.3% vs. 4.0%), ejaculation disorder, gynecomastia and lowered libido.[28] Mortality and SAE rates did not differ.[29] A 6-month trial (n=399)[30] and an unpublished 1-year trial (n=1630) vs. finasteride found no difference in efficacy or adverse events. Total SAEs and mortality were not reported.[31-33]

Table 2: Usual dose range, half-life and cost of drugs for BPH

Drug	Brand name	Dose range	Half-life	Daily cost
alfuzosin	Xatral®	10 mg/d	5-10 hrs	$1.14♦
doxazosin	Cardura®, generic	1 - 8 mg/d	22 hrs	$0.35 - $1.09*
prazosin	generic	1 - 5 mg BID	2-3 hrs	$0.32 - $0.62*
tamsulosin	Flomax®	0.4 - 0.8 mg/d	5-7 hrs	$1.04 - $2.08*
terazosin	Hytrin®, generic	1 - 10 mg/d	12 hrs	$0.36 - $0.90*
dutasteride	Avodart®	0.5 mg/d	5 weeks	$1.96♦
finasteride	Proscar®	5 mg/d	6 hrs	$1.78*

*Average daily cost for the lowest priced formulation, calculated using 2005 PharmaCare data. ♦Average price at local pharmacy.

Conclusions

- Alpha blockers improve symptoms on average by 2-3 points more than placebo (35 point AUA scale), a difference patients perceive as 'slight benefit'. Alpha blockers do not reduce complications, but increase dizziness, postural hypotension and asthenia (ARI 3-8%, NNH 13-33).
- 5-α-reductase inhibitors reduce acute urinary retention (ARR 2%, NNT 50), and BPH surgery (ARR 2-3%, NNT 33-50), but impair sexual function (ARI 3%, NNH 33).
- There is insufficient evidence that combining the two drug classes provides additional benefit.
- **Most BPH trials do not report total serious adverse events and mortality. This prevents an assessment of the overall clinical impact of drug treatment.**

Clinical implications

Men with bothersome symptoms who wish a trial of alpha blocker therapy should set their own treatment goals and weigh the benefits (e.g. symptom relief) against side effects (e.g. postural hypotension, asthenia). Since all alpha blockers have relatively short half-lives (see Table 2), maximum concentrations and effect will occur within 4 days. A reasonable approach is to start with a low dose and assess for symptoms during a series of 1-week therapeutic trials at several doses. Neither finasteride nor dutasteride provide symptomatic benefit for most men. Patients considering long-term therapy to prevent complications should be informed of the magnitude of potential benefits and harms, as outlined above.

Addendum: saw palmetto extract

Letter #19 discussed saw palmetto (*S.repens*), a commonly used herbal treatment. A Cochrane review suggested a short-term modest reduction in symptoms with saw palmetto.[34] A new 1-year RCT comparing standardized doses (160 mg BID) with placebo showed no differences in symptom scores, urinary flow rates, quality of life measures, adverse effects or SAEs.[35]

The draft of this Therapeutics Letter was submitted for review to 40 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

References

1. Therapeutics Initiative. *Medical Management of Benign Prostatic Hyperplasia.* Therapeutics Letter 19 (May/June 1997). Available at: http://www.ti.ubc.ca/PDF/19.PDF
2. 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.* N Engl J Med 2003; 349:2387-2398.
3. Roehrborn CG; ALTESS Study Group. *Alfuzosin 10 mg once daily prevents overall clinical progression of benign prostatic hyperplasia but not acute urinary retention: results of a 2-year placebo-controlled study.* BJU Int 2006;97:734-741.
4. Wilt TJ, Howe RW, Rutks IR, MacDonald R. *Terazosin for benign prostatic hyperplasia.* The Cochrane Database of Systematic Reviews 2000, Issue 1. Art. No.: CD003851. DOI: 10.1002/14651858.CD003851.
5. Wilt TJ, MacDonald R, Rutks I. *Tamsulosin for benign prostatic hyperplasia.* The Cochrane Database of Systematic Reviews 2002, Issue 4. Art. No.: CD002081. DOI: 10.1002/14651858.CD002081.
6. 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;61:119-126.
7. MacDonald R, Wilt TJ. *Alfuzosin for treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia: a systematic review of efficacy and adverse effects.* Urology 2005; 66:780-788.

References 8-35 can be found in the electronic version of this letter on the TI web site: www.ti.ubc.ca/pages/letter58.htm