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Volume 23, No.2 **June 2006**

Should combinations of alpha-adrenergic blockers and 5-alpha reductase inhibitors be used to treat benign prostatic hyperplasia ??

Background: Benign prostatic hyperplasia (BPH) is a disorder that affects many men. The incidence increases with age; 40 to 50 percent of men aged 51 to 60 years and over 80 percent of men older than 80 years are affected. Many of these men experience lower urinary tract symptoms (LUTS) including hesitancy, weak urinary stream, terminal dribbling, sensation of incomplete bladder emptying, acute urinary retention, nocturia, urinary frequency and urinary urgency. There are two standard tools used to assess the severity of patients' symptoms: the American Urological Association (AUA) Symptom Index and the seven symptom questions of the International Prostate Symptom Score (IPSS).[1]

Treatment options for BPH

Treatment for BPH is directed at symptomatic relief. The treatment of choice for patients with mild symptoms (AUA score <7) and for patients with moderate to severe symptoms (AUA score >8) in which the symptoms are not bothersome, is watchful waiting.[2] As well, lifestyle changes may be of benefit. These include reducing or avoiding consumption of caffeine and alcohol that could increase the amount of urine produced, reducing fluids in evenings and double voiding.[3]

For patients with bothersome moderate to severe symptoms, surgical treatment or drug therapy may be considered. There are two classes of drugs used: alpha-adrenergic antagonists (non-selective and selective agents) and 5-alpha reductase inhibitors.[4] (Table 1)

Table 1: Drugs for BPH [3,5]

Drug	Dose	Cost *	Side Effects
Nonselective alpha-blockers			
Doxazosin (Cardura®, Generics)	Start at 1mg OD, titrate by doubling dose every 1 to 2 wks. Goal 4-8mg OD. Max 8mg OD.	2 mg = $23 4 mg = $26 8 mg = $46	Dizziness (10-20%), headaches (15%), weakness (5-15%, nasal congestion (5-10%), orthostatic hypotension, first dose syncope
Prazosin ** (Minipress®, Generics)	Start at 0.5mg to 1mg BID; titrate up to 2mg twice BID	2 mg = $23	
Terazosin (Hytrin®, Generics)	Start at 1 mg HS, ⇧ PRN over 4 to 6 wks; most require 10 mg OD. If no response at 10 mg OD, may ⇧ to 20 mg OD	5 mg = $25 10 mg = $39	
Selective alpha-blockers			
Alfuzosin (Xatral®)	10mg OD with the same meal each day	10 mg = $41	⇩ incidence of se's listed above, vertigo (2 %), retrograde ejaculation (tamsulosin 5 – 10 %), interoperative floppy iris syndrome
Tamsulosin (Flomax®)	0.4 mg OD (30 mins after same meal each day), may increase after 2-4 weeks to 0.8 mg OD if not responding.	0.4mg = $42 0.8mg = $77	
5-alpha reductase inhibitors			
Finasteride (Proscar®)	5mg OD	5mg = $68	Sexual dysfunction (3-4 %)
Dutasteride (Avodart®)	0.5mg OD	0.5mg = $65	

* Approximate cost to patient for 30 days supply of medication [6]

** Use for BPH is off-label.

Pharmacology
Alpha-adrenergic antagonists relax the smooth muscle tone of the prostate and bladder neck which contributes to the reduction in urinary flow rates and thereby increases the urinary flow. [4,7] The dose requires titration to a therapeutic dose for some of the drugs and therefore the peak onset is two to three weeks**.** [7] The alpha-adrenergic antagonists are considered first line for reducing the symptoms of LUTS. They are all selective for the alpha-1 adrenergic receptor subtype found in abundance in the bladder neck. Terazosin, doxazosin, alfuzosin and tamsulosin are all considered long acting. They are all considered equally effective in treating the symptoms of BPH. The main difference between the drugs is their side effect profiles. Tamsulosin and alfuzosin are more selective and therefore associated with less dizziness and orthostatic hypotension. This makes tamsulosin and alfuzosin both safer choices for elderly, hypotensive patients or hypertensive patients who have impaired blood pressure regulation. [3]

The 5-alpha reductase inhibitors prevent the conversion of 5-alpha reductase to dihydrotestosterone in the prostate. The dihydrotestosterone is believed to be the male hormone responsible for prostate growth in BPH, so its inhibition can cause the enlarged prostate to shrink. The peak onset of effect is six to twelve months, at which time 30 to 40 percent of patients will show an improvement in their symptoms. [4]

For symptom control the 5-alpha reductase inhibitors have been shown in clinical trials to be less effective than the alpha-adrenergic antagonists; however they had a greater effect on symptoms in men with larger prostates. [3] 5-alpha reductase inhibitors may also be used to prevent progression of BPH. Side effects (sexual dysfunction), cost and the need for long-term treatment need to be weighed on an individual basis against the risk of progression. [2] The 5-alpha reductase inhibitors should not be used for treatment in men who do not have enlarged prostates. [2]

Response: The question of whether or not combination therapy should be used has been asked several times and the latest research leads to the answer yes, but only for certain patients. [7] There have been three large randomised control trials that evaluated the use of combination therapy.

Table 2: Randomized Control Trials

Trial	Drugs	Final doses	Outcomes	Comments
Veterans' Affairs [9]	Terazosin Finasteride	5 to 10mg 5mg	Terazosin was effective in treating BPH symptoms. Combination no better than terazosin alone. Finasteride was no better than placebo.	Both the Veterans' Affairs and PREDICT trials had some limitations which were: only 12 months duration, only looked at the change in symptom score (IPSS) and flow rate (Qmax) as indicators for success and they did not differentiate between patients with enlarged prostates and those without. [8]
PREDICT [10]	Doxazosin Finasteride	4 to 8 mg 5mg	Doxazosin effective in treating BPH symptoms. Combination no better than doxazosin alone. Finasteride was no better than placebo.	
MTOPS [11]	Doxazosin Finasteride	4 to 8 mg 5mg	Combination reduced progression and improved symptoms more than either drug alone. Doxazosin and finasteride both reduced symptoms. Doxazosin alone did not reduce risk of progression.	This trial was 4.5 years and primary outcome was reducing progression of BPH. The risk of progression was decreased more significantly in men with PSA >4ng/mL and prostate volume >40mL.

*All studies had patients randomised to four study groups: either drug alone, combination or placebo.

Conclusion
Combination therapy should not be used in all patients, especially those who do not have an enlarged prostate. [8] The side effects and costs are increased in combination therapy and these need to be weighed against the benefits for each individual patient. Doxazosin and finasteride used together is the only combination therapy shown to be effective. [9] It cannot be assumed that this applies to all the drugs in these classes until it is known if there is a class effect. The American Urological Association guidelines say that combination treatment is appropriate and effective for patients with LUTS associated with a demonstrable prostatic enlargement. [2]

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