

## MEDICAL THERAPY

### *Part of "32 - BENIGN PROSTATIC HYPERPLASIA"*

Use of pharmacologically defined and a variety of so-called alternative medications to attempt to improve BPH voiding dysfunction by reducing BPH mass or producing functional alterations of the voiding mechanism is expanding rapidly. Pharmacologic efforts to reduce prostate mass essentially target known androgen-mediated prostate growth induction or maintenance phenomena. Those aimed to produce physiologic alterations essentially target the  $\alpha_1$ -adrenergic agonist modifiable smooth muscle contraction of prostate stroma, bladder, and components of the central nervous system (CNS) affecting voiding symptoms.

### ***Endocrine Approaches***

Endocrine-based approaches to management of BPH have focused on disrupting hormone-mediated growth mechanisms characterized in the normal prostate and persisting in BPH. Consequently, most center on attempting to eliminate testis hormone production directly or indirectly (e.g., castration, pituitary hormone inhibition), altering intraprostatic androgen metabolism (e.g., 5 $\alpha$ -reductase inhibition), interfering with intracellular transcription of androgen-stimulated events (e.g., receptor blockade), or a combination of these mechanisms. Castration and luteinizing hormone–releasing hormone (LH-RH) agonist administration produce marked regression of the epithelial component of BPH in humans (163,320,381). However, these approaches, as well as administration of estrogens (280) or estrogen-androgen combined therapy (181), have yielded equivocal or limited clinical improvement. LH-RH agonist administration produces a 25% to 30% decrease in prostate volume; a 90% and 75% reduction in prostate tissue DHT and T concentration, respectively; and decreased prostate 5 $\alpha$ -reductase activity and androgen receptor levels. With cessation of therapy, prostatic size returns to pretreatment levels (228,285). Flutamide, a nonsteroidal androgen receptor competitor, and cyproterone acetate (323), an inhibitor of gonadotropin release and receptor competitor, have been reported to increase flow rate or to decrease prostate size 23% to 30% (228) in patients with BPH. Other progestational agents, including medrogestone, 17 $\alpha$ -hydroxy progesterone, chlormadinone acetate, and gestonorone caproate, have been used in clinical trials without consistent effects on voiding patterns in patients with BPH voiding dysfunction (109,293). LH-RH antagonists induce a substantial and rapid (less than 12 hours) decrease in serum testosterone and DHT. Preliminary evidence suggests increased flow rates and reduction in symptom score comparable to  $\alpha$ -adrenergic agonist therapy (200). The applicability of these agents to BPH management has not moved beyond the preliminary stages. LH-RH therapy is frequently associated with hot flashes and sexual dysfunction (87). Gynecomastia and diarrhea are recognized complications of single-drug flutamide therapy (344).

Evaluation of purposely altered androgen effect on BPH and BPH voiding dysfunction currently centers on the results of finasteride administration. Finasteride inhibition of 5 $\alpha$ -reductase type 2 activity results in decreased DHT (5.4 to 0.5 ng/g) and increased T (0.3 to 2.2 ng/g) prostate tissue concentrations (266). The following observations of clinical effect seem reasonable based primarily on the results of the 4-year multicenter study of prostate

patients with moderate to severe BPH voiding symptoms and a moderately enlarged prostate.

1. Maximum effect on the prostate is delayed at least 6 to 12 months (121,231).
2. Quasi AUA symptom score improvement in finasteride-treated (F) versus placebo (P) patients is definite but slight (all patients F 2.5 versus P 1.0; completed study patients F 3.3 versus P 1.3) (231).
3. Reduction in prostate volume in men completing the study is limited (18%) but contrasts with an increase of 14% in the placebo group; decreased prostate volume in the finasteride group stabilized at 1 year, whereas the placebo group showed progressively increased volume over 4 years (231).
4. Statistically significant but clinically minimal increased flow rate was seen in finasteride-treated men who completed the study (F 1.9 mL per second versus P 0.2 mL per second) (231).
5. Using intention to treat patients, a quasi bother score (range of 0 to 34) and an approximated activity interference evaluation (range of 0 to 28) of finasteride-treated men demonstrated a statistically significant but clinically limited greater improvement at 4 years in both; bother decreased 3.0 versus 1.2 and activity interference 2.5 versus 1.24 in finasteride compared with placebo patients (39).
6. The study was discontinued by 524 (34%) of finasteride-treated and 633 (42%) of placebo-treated men; most perceived lack of improvement or worsening of BPH

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voiding dysfunction or desired other medical or surgical treatment. Adverse events accounted for the other (F 11.5%; P 10.9%) withdrawals (231).

7. Acute urinary retention (4% F versus 7% P) and BPH-related surgery (5% F versus 10% P) were reduced in finasteride as compared with placebo patients in the 4-year observation period using an intention-to-treat analysis. In absolute numbers, approximately 100 of 1,384 treated patients avoided these events (231). In this study of symptomatic men with enlarged prostates, patients with larger prostate volume as indicated by PSA measurement seemed to be at greater risk for these events (303).
8. Finasteride has had almost universal success in controlling spontaneous BPH-related urinary bleeding promptly and persistently (96). The prompt control of hematuria contrasts with other therapeutic achievements with this drug. Men with bothersome symptoms and no or little enlargement of the prostate are less likely to show comparable improvement (204). Various aspects of sexual dysfunction and possibly gynecomastia may occur with greater frequency in a limited number of finasteride-treated patients. The effects on libido, erection, and volume of ejaculate are slightly increased with finasteride. Overall, results of these studies should be made available to patients, but definite recommendation for finasteride treatment would seem to depend on the patient's general health, his risk/benefit assessment, and the rapidity at which he expects improvement.

Endocrine therapy for the treatment of BPH voiding dysfunction, regardless of method, is accomplished by reduction of prostate mass. This change in gland volume is limited to components of the prostate that are androgen sensitive. Available data indicate that prostate volume decreases by no more and usually appreciably less than 30% with more meager impact on symptoms. Based on this information, it appears that endocrine therapy has a limited utility in patients with symptoms and signs of bladder neck obstruction (BNO) from BPH. Chronic therapy to prevent disease progression may have a role in some patients but is usually not readily accepted by patients who otherwise feel well.

### ***Adrenergic Antagonists***

The most common medical approach to manage effects of BPH voiding dysfunction centers on neuropharmacologic manipulation of the lower urinary tract. Contraction of the autonomically controlled prostate or bladder neck smooth muscle is postulated to be a significant modifiable functional component of BPH-mediated bladder neck obstruction. The predominance of  $\alpha_1$ -adrenergic receptors in the bladder neck or prostate (40 times the bladder concentration) helped focus interest on  $\alpha$ -adrenergic blocking agents in the treatment of symptomatic BPH. Demonstration that administration of phenoxybenzamine, a nonselective  $\alpha$ -adrenergic antagonist, reduced symptoms and improved parameters in patients with BPH voiding dysfunction (43,202) reinforced pursuit of this approach. Efforts to maximize desired physiologic activity and reduce undesirable side effects led to the development and use of selective  $\alpha_1$ -adrenergic antagonists. Of these, drugs that can be given once daily, including terazosin (Hytrin), doxazosin (Cardura), and tamsulosin (Flomax), an  $\alpha$ -adrenergic blocker with more selectivity for the prostate-dominant  $\alpha_{1A}$ - and  $\alpha_{1D}$ -adrenergic receptors, are the most commonly used  $\alpha$ -adrenergic receptor blocking agents. Despite the subtype selectivity of tamsulosin for the  $\alpha_{1A}$ - and  $\alpha_{1D}$ - over that of the  $\alpha_{1B}$ -adrenergic receptor, there is no evidence that this conveys a clinical advantage for the treatment of symptoms (Table 32.5). The  $\alpha$ -adrenergic blocking agents share the characteristic of producing their effects on voiding within hours of administration regardless of prostate size without altering serum PSA or volume. The reported studies of efficacy focus on change in symptom score and peak flow rate. The absolute improvement in maximum flow rate, the clinically important effect, is greater than placebo, yet still relatively small. This increase in maximum flow rate is similar for the various  $\alpha$ -adrenergic blockers (Table 32.6). The maximum flow rate achieved is generally between 11 and 13 mL per second; this may represent an achievable

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maximum for  $\alpha$ -adrenergic blocker pharmacotherapy (50,91,304). In most studies, the decrease in total AUA or comparable symptom score (range of 0 to 35) was approximately  $3 \pm 1$ , and the increase in peak flow rate was usually 1 to 2 mL per second. Both are statistically but clinically marginally significant. Assessments of severity, bother, problem, and global scores tended to reinforce this range of activity (115,205,258).

**TABLE 32.5.  $\alpha$ -ADRENERGIC THERAPY SYMPTOM SCORE CHANGE**

**TABLE 32.6.  $\alpha$ -ADRENERGIC THERAPY FLOW RATE CHANGE**

Potential cardiovascular and other systemic effects of these drugs may limit their use alone and in particular with other vasoactive agents. Postural hypotension, dizziness, headache, syncope, anesthesia or fatigue, rhinitis, and abnormal ejaculation may complicate  $\alpha$ -adrenergic blocker administration. The development of more selectively targeted  $\alpha$ -adrenergic blocking agents, coupled with a better understanding of their effects, has been associated with reduced undesirable reactions. Currently available information suggests that tamsulosin may lessen their occurrence selectively and within dose ranges. Patients with complex medical problems often benefit by a coordinated internist-urologist interaction in guiding  $\alpha$ -adrenergic blocker therapy.

Indication for use of  $\alpha$ -adrenergic blocking agents in patients with BPH voiding dysfunction centers on symptomatic complaints and failure to void satisfactorily. The diagnosis is often not confirmed as objectively as in surgically directed patients. Cystoscopic evaluation of the prostate or the bladder is often omitted despite its use as an exclusionary criterion, and postvoid residual urine is not used regularly to assess therapy. Paradoxically, changes in urinary symptoms and flow rate do not correlate strongly (198,199), leading to questions regarding the role of prostate smooth muscle relaxation in symptom reduction. Effects of  $\alpha$ -adrenergic blocking agents on bladder and CNS function could result in the altered voiding patterns observed (198,340). Despite the predominant pharmacologic role of  $\alpha$ -adrenergic blocker therapy in treating BPH voiding dysfunction, more than 30% of patients discontinue therapy. This *de facto* dissatisfaction demonstrates the incompleteness of understanding of  $\alpha$ -adrenergic blocker effect, as well as an inability to pinpoint the exact cause of BPH voiding dysfunction.

Drug choice depends on primary and secondary (antihypertensive; complications) effects. These drugs are most commonly administered at bedtime to minimize cardiovascular symptoms or hypotension. Terazosin and doxazosin are commonly titrated to establish effective, complication-free dosage levels; most men in the United States receive these drugs at a 5- and 4-mg daily dose, respectively, although limited evidence indicates that double these levels may be optimal. Tamsulosin, commonly given after breakfast, is used at 0.4 mg per day in most men; 0.8 mg daily is slightly more effective but has increased side effects (199). Although many patients have concurrent LUTS and hypertension, treatment for each disease should be optimized individually rather than attempting to treat both simultaneously with a single agent and potentially compromising treatment of both. Most authorities on hypertension suggest that  $\alpha$ -adrenergic blockers are a third- or fourth-line drug after (a) angiotensin-converting enzyme inhibitors and (b) calcium channel blockers and diuretics (6,337).

### **Alternative Therapies**

Increasing attention has been paid to plant extracts (or phytotherapy) use by patients to self-treat medical ailments. Use of these products has grown rapidly to an estimated \$6 billion yearly expenditure despite the frequent lack of a scrutinized demonstration of

efficacy. Saw palmetto, derived from the berry of the American dwarf palm (*Sabal serrulata*), is the most popular of these medications for LUTS. The proposed mechanisms of action for saw palmetto include 5 $\alpha$ -reductase inhibition, intraprostatic androgen receptor blockade, and adrenergic receptor antagonism (111). There is little or no evidence that any of these mechanisms play a role in saw palmetto when used clinically. Clinical evidence suggests that this medication does no harm, is associated with few side effects, and has no effect on PSA (211). Placebo-controlled trials and meta-analyses suggest that saw palmetto leads to only minor subjective and objective improvements in men with LUTS (384). Most studies demonstrating any positive effects of saw palmetto suffer from methodologic flaws, small patient numbers, and short treatment intervals. Clearly, large-scale placebo-controlled trials are needed to assess efficacy of these medications. Their U.S. Food and Drug Administration classification as a food additive allows public promotion of these products without regulated manufacture or demonstrated efficacy. Unfortunately, significant questions persist concerning their use.

## Summary

Current evidence indicates that medical therapies have variable limited effectiveness in altering the symptomatology and pathophysiologic effects of BPH. Use of drugs with established physiologic effects on the prostate or bladder, alone or combined, warrants consideration in selected patients with acute or chronic voiding problems caused by BPH. The long-term effects of  $\alpha$ -adrenergic antagonists and 5 $\alpha$ -reductase inhibitors on BPH and its associated voiding dysfunction are not established. The risk that prolonged exposure to therapies with limited effectiveness may permit conversion of a potentially reversible to a permanent voiding dysfunction should not be overlooked. The most cost-inefficient use of health care expenditure is serial treatment with multiple medications followed by surgical or minimally invasive therapies. Prioritizing of these issues for and with patients remains the urologist's challenge and role.

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