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# Outcomes and quality of life issues in the pharmacological management of benign prostatic hyperplasia (BPH)

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**Background:** Benign prostatic hyperplasia (BPH) is a common disease of the aging male population. BPH treatment includes a variety of pharmacological and surgical interventions. The goal of this paper is to review the natural history of BPH, outcomes of pharmacological management, effects on quality of life (QoL), future pharmacotherapies, and associated patient-focused perspectives.

**Materials and methods:** Medline searches for the keywords benign prostatic hyperplasia, BPH, alpha blockers, 5 alpha-reductase, and quality of life were performed. Relevant literature was reviewed and analyzed.

**Results:** Alpha blockers, 5 alpha-reductase inhibitors, and phytotherapy are the three categories of pharmaceutical interventions currently available for BPH. Various clinical trials have shown that alpha blockers and 5 alpha-reductase inhibitors are safe, efficacious, and improve QoL in patients with BPH. The evidence for phytotherapeutics is not as convincing. The current armamentarium of pharmaceutical interventions are encompassed in these three classes of medications. New pharmacotherapies based on novel mechanisms are on the horizon.

**Conclusion:** There are a variety of safe and efficacious medical therapies available for the management of BPH and it is important for the practicing physician to have an understanding of these pharmacotherapies and their potential impact on the patient. There is not enough evidence to make a recommendation regarding phytotherapy use. New classes of drugs for BPH will likely find their way into routine use.

**Keywords:** Benign prostatic hyperplasia, benign prostatic hypertrophy, BPH, alpha blockers, 5 alpha-reductase inhibitor, quality of life.

## Introduction

Benign prostatic hyperplasia (BPH) is the most common benign neoplasm in US males. Seventy-five percent of men in their seventh decade of life are affected (Wei et al 2005). In 2000, approximately 8 million office visits were accounted for by a primary or secondary diagnosis of BPH (Wei et al 2005). The number of office visits for BPH has recently increased, while the number of surgical interventions has decreased. This shift reflects the increased selection and availability of effective pharmacologic therapies (Wei et al 2005).

## BPH: Assessing quality of life Validated symptom scoring questionnaires

Lower urinary tract symptoms (LUTS) can be related to BPH, and the degree of symptom severity dictates the impact on quality of life (QoL). Consistent and reliable evaluation of patient symptoms is necessary to quantify symptoms and determine treatment efficacy. To achieve this, various validated symptom scoring questionnaires have been designed

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and tested for consistency and reliability. These symptom scores are useful for both clinical and research assessments of medication efficacy.

Clinical research, some of which utilizes validated questionnaires, is the foundation for evidence-based medicine. The type of trial design contributes to the quality of the data it yields (Ok et al 2005). Listed from most reliable to least reliable, systematic reviews and meta-analyses of randomized controlled trials (RCTs), nonrandomized controlled trials, case reports, clinical examples, and consensus meetings, are the different types of available evidence (McAlister et al 1999). Although evidence in the published literature has differing levels of importance, it can all play a role in patient management (Smith and Somerfield 1997).

The most widely used and extensively validated symptom score assessment is the American Urological Association Symptom Index (AUASI) (Barry et al 1992; MacDonald and McNicholas 2003). The AUASI is composed of seven questions regarding incomplete emptying, frequency, intermittency, urgency, weakness of the urinary stream, straining, and nocturia. The test-retest correlation for this questionnaire is 0.92 (Barry et al 1992).

Various questionnaires have been developed to quantitatively assess symptoms and QoL issues in BPH. Examples of validated questionnaires include: the Maine Medical Assessment Program score (Fowler et al 1988), the Boyarsky score (Boyarsky et al 1976), the Madsen-Iversen Score (Madsen and Iversen 1983), International Prostate Symptom Score (IPSS) (AUASI plus one question regarding QoL) (Cockett et al 1991) and the Danish Prostatic Symptom Score (Hald et al 1991; Meyhoff et al 1993).

## BPH: Natural history

Defining the natural history of BPH improves management and risk stratification. Community-based longitudinal studies and placebo arms of clinical trials have been used to define the natural history of BPH. Both study types have inherent limitations; however, the latter generally provides less reliable data than a community-based longitudinal study (Fong et al 2005a; Roberts et al 2005).

Surrogate endpoints of clinical progression are used to define natural history. Urinary symptom score, prostate volume, urinary flow rate, episodes of acute urinary retention (AUR), prostate-specific antigen (PSA), post-void residual (PVR), and surgery have been utilized as surrogate endpoints of disease progression.

## American Urological Association Symptom Index

The Olmsted County trial is a community-based, prospective cohort study initiated to define the natural history of BPH. The study included 2115 randomly selected men between the ages of 40 to 79 years from Olmsted County, Minnesota (Sarma et al 2002). An age-associated worsening AUASI and bother score was noted at baseline and last follow-up. The greatest increase in symptom and bother scores occurred during the seventh decade of life. Specifically, nocturia and weak stream demonstrated the strongest association with aging. All seven AUASI symptoms demonstrated significant progression with time and age. Symptoms related to voiding or obstruction were the most common, while symptoms related to storage, irritation, or social embarrassment were the most bothersome. These findings suggest a slowly progressive natural history of BPH with acceleration in symptom severity among individuals in their seventh decade of life (Sarma et al 2002).

## Prostate volume

The Olmsted County study also investigated prostate growth. Prostate volume was determined in 631 men by transrectal ultrasound. After seven years of follow-up, the annual change in volume was 1.6% across all age groups (Rhodes, Girman, et al 1999). Increasing growth rate was observed with increasing age and baseline prostate volume (Rhodes, Girman, et al 1999).

Berry and colleagues (1984) reported the prevalence and growth rate of BPH with age by collecting data from 10 studies accounting for over 1000 cadaveric prostate samples. Men between the ages of 21 and 30 had an average prostate mass of 20g. In the absence of BPH, the prostate remained at this size. Prostates that develop BPH had a greater growth velocity in men between 31 and 50 years of age (doubling time 4.5 years), while men between the ages of 51 and 70 had a slower doubling time of 10 years, and men over 70 had doubling times greater than 100 years. Eight percent of men in their fifth decade of life were shown to have pathological BPH, while half of men in their sixth decade of life were shown to have the condition.

## Peak urinary flow rate

Peak urinary flow rate is another surrogate endpoint for clinical progression of BPH. The Olmsted County trial data demonstrated an annual median peak urinary flow rate slope of  $-2.1\%$  (Roberts et al 2000). Rapid decline in peak urinary

flow rate was associated with decreasing baseline flow rate, and increasing baseline age, prostate volume and symptom severity ( $p = 0.001$ ).

### Acute urinary retention

The Olmsted County trial data demonstrated increasing incidence of AUR associated with age and severity of symptoms. Decreased peak urinary flow rates indicated a four-fold increased risk of AUR, and men with prostates greater than 30 cc experienced a three-fold increase in risk. Risk of AUR, within a five-year period, was 1.6% and 10% for men aged 40–49 and 70–79 years, respectively (Jacobsen et al 1997). AUR is a painful episode with proven negative impact on QoL. Risk factors for AUR and proven efficacy in minimizing this risk are important patient and pharmaceutical factors.

### Prostate-specific antigen

Increasing PSA (Roehrborn et al 2001; Wright et al 2002) is a risk factor for prostate enlargement and may be predictive of risk of developing BPH (Roehrborn et al 2001; Fong et al 2005a). PSA alone (sensitivity 75%, specificity 64%) has been shown to be comparable with both expanded models (PSA, urinary frequency and hesitancy, flow rate parameters, and symptom problem index, sensitivity 72%, specificity 67%) and a scoring algorithm as a predictor of disease progression defined by AUR episode (Roehrborn et al 2001). Although both PSA and prostate volume can be assessed for risk of progression, PSA is more reliable and cheaper than assessing prostate volume with digital rectal exam, transrectal ultrasound, or magnetic resonance imaging (Fong et al 2005a).

### Post-void residual

The Olmsted County Study data has also been used to describe the natural history of PVR and voided volume in 529 community dwelling men between the ages of 40 to 79 (Rule et al 2005). Median annual change in PVR was 2.2% and voided volume was –2.1%. These data suggest gradually increasing PVR and decreasing voided volume; however a clear association has not yet been established between PVR, voided volume, and lower urinary tract symptoms (LUTS).

Degree of LUTS and impact on QoL drive the management of BPH. These measures of BPH aid in quantifying such symptoms and associating them with impact on QoL. Table 1 summarizes the natural history of BPH as defined by measures of BPH.

## BPH: Pharmacological therapy

Available pharmacotherapies for BPH fall under two general categories—pha blockers and 5 alpha-reductase inhibitors. Herbal remedies, while not regulated by the Food and Drug Administration (FDA), are widely available and commonly used.

### Alpha adrenergic blockers: Mechanism of action

Alpha blockers are adrenergic receptor antagonists. In the lower urinary tract, these receptors are found in the smooth muscle of the prostate, urethra, and bladder neck (Caine 1986). Adrenergic blockade results in relaxation of smooth muscle at these anatomic locations, thereby allowing a wider caliber outlet for the passage of urine.

There are two subtypes of alpha adrenergic receptor associated with prostatic smooth muscle, alpha-1 and alpha-2 (Berthelson S 1977). Antagonism of the alpha-1 subtype has shown clinical advantages in treating BPH and has thus been the focus of subsequent study. Adrenoceptor research led to the discovery, classification, and subdivision of type-1 alpha receptors into the subtypes  $1_A$ ,  $1_B$ , and  $1_D$  (Andersson et al 1997; Roehrborn and Schwinn 2004).

Phenoxybenzamine, prazosin, terazosin, doxazosin, alfuzosin, and tamsulosin are alpha blockers currently available for the treatment of BPH. Alpha blocker receptor subtype selectivity, dose, and duration of action are summarized in Table 2.

Phenoxybenzamine is not selective for alpha-1 versus alpha-2 adrenergic receptor. Prazosin, terazosin, doxazosin, and alfuzosin are selective for the alpha-1 receptor, but are not subtype selective (Forray et al 1994; Andersson et al 1997; Roehrborn and Schwinn 2004). Tamsulosin has a relatively greater affinity for the alpha- $1_A$  adrenergic receptor in comparison with the  $1_B$ , and no selectivity for the alpha- $1_A$  versus  $1_D$  receptor subtype (Forray et al 1994; Foglar et al 1995; Richardson et al 1997; Roehrborn and Schwinn 2004).

### Alpha adrenergic blockers: safety and efficacy

Multiple, large, randomized, placebo-controlled trials have supported the safety and efficacy of alpha adrenergic blockers for the treatment of BPH (Abrams et al 1995; Gillenwater et al 1995; Chapple et al 1996; Lepor et al 1996; Roehrborn et al 1996; Abrams et al 1997; Narayan and Tewari 1998; Djavan and Marberger 1999; Narayan et al 2003; Roehrborn

**Table 1** Natural history of BPH as measured by surrogate endpoints of AUASI, prostate volume, peak urinary flow, AUR, PSA, PVR, and voided volume

Reference	No Patients	Surrogate endpoint													
Sarma et al 2002	2115	AUASI	Annual change in symptom score 40–79 years of age: +0.29 points per year 40–49 years of age: +0.13 points per year 60–69 years of age: +0.60 points per year 70–79 years of age: +0.38 points per year												
Rhodes, Girman, et al 1999	631	Prostate volume	% Annual change in prostate volume Overall: +1.6%												
Roberts et al 2000	492	Peak urinary flow	% Annual change in peak urinary flow 40–79 years of age: –2.14% 40–49 years of age: –1.1% >70 years of age: –6.2% Prostate volume ≤30ml: –1.7% Prostate volume >30ml: –3.0%												
Jacobsen et al 1997	2115	AUR	Risk of AUR within 5 years 40–49 years of age: 1.6% 70–79 years of age: 10%												
Wright et al 2002	529	PSA	Relative risk of prostate enlargement <table border="1"> <thead> <tr> <th>Age</th> <th>Baseline PSA</th> <th>RR</th> </tr> </thead> <tbody> <tr> <td>40–49</td> <td>≥0.31 ng/mL</td> <td>3–6-fold increase</td> </tr> <tr> <td>50–59</td> <td>≥0.80 ng/mL</td> <td>5–9-fold increase</td> </tr> <tr> <td>60–69</td> <td>≥1.70 ng/mL</td> <td>11-fold increase</td> </tr> </tbody> </table>	Age	Baseline PSA	RR	40–49	≥0.31 ng/mL	3–6-fold increase	50–59	≥0.80 ng/mL	5–9-fold increase	60–69	≥1.70 ng/mL	11-fold increase
Age	Baseline PSA	RR													
40–49	≥0.31 ng/mL	3–6-fold increase													
50–59	≥0.80 ng/mL	5–9-fold increase													
60–69	≥1.70 ng/mL	11-fold increase													
Rule et al 2005	529	PVR	Median annual % change PVR 40–79 years of age: 2.2 40–49 years of age: 1.8 50–59 years of age: 4.3 60–69 years of age: 2.6 70–79 years of age: –2.6												
Rule 2005	529	Voided volume	Median annual % change voided volume 40–79 years of age: –2.1 40–49 years of age: –1.3 50–59 years of age: –1.1 60–69 years of age: –4.3 70–79 years of age: –4.6												

**Abbreviations:** AUASI, American Urological Association Symptom Index; AUR, acute urinary retention; BPH, benign prostatic hypertrophy; PSA, prostate-specific antigen; PVR, post-void residual.

et al 2003). Table 3 summarizes clinical outcomes for some of the large clinical trials of alpha blockers.

Phenoxybenzamine has proven efficacy in relieving symptoms of BPH, but its use is limited by severe side-effects (Caine et al 1976; Caine et al 1978). Approximately 30% of patients experience side-effects related to phenoxybenzamine (Lepor 1990). Orthostatic hypotension is the main adverse effect; however reflex tachycardia, nasal congestion, diarrhea, miosis, sedation, nausea, and vomiting are also associated (Walsh 2002). Interactions between phenoxybenzamine and other antihypertensive and/or vasodilatory agents can cause additive hypotensive effects. Due to the

availability of alpha-1 selective agents, it is infrequently prescribed for BPH.

Prazosin, an alpha-1 selective blocker, demonstrated efficacy comparable with phenoxybenzamine without as severe a side-effect profile (Hedlund et al 1983). However, a first-dose phenomenon in which patients experience faintness, dizziness, palpitation, and even syncope is associated with prazosin use. The incidence of this side-effect can be minimized with dose titration, as well as dosing before bed (Walsh 2002).

Terazosin has proven safety and efficacy in the treatment of BPH. Large placebo-controlled trials have demonstrated increased peak urinary flow, improved QoL and AUASI scores

**Table 2** Alpha adrenergic receptor antagonists: subtype-selectivity, dosing, and duration of action

Medication	Receptor subtype	Tablet/capsule size (mg)	Dosing schedule	Duration of action
<i>Nonselective</i>				
Phenoxybenzamine	$\alpha_1$ and $\alpha_2$	10	10 mg bid	Long-acting
<i>AI selective</i>				
Alfuzosin	$\alpha_{1A}, \alpha_{1B}, \alpha_{1D}$	2.5	2.5 mg tid	Short-acting
Alfuzosin XL	$\alpha_{1A}, \alpha_{1B}, \alpha_{1D}$	10	10 mg qd	Long-acting
Prazosin	$\alpha_{1A}, \alpha_{1B}, \alpha_{1D}$	2	2 mg bid	Short-acting
Doxazosin	$\alpha_{1A}, \alpha_{1B}, \alpha_{1D}$	1, 2, 4, 8	1, 2, 4, 8 mg qd	Long-acting
Doxazosin GITS	$\alpha_{1A}, \alpha_{1B}, \alpha_{1D}$	4, 8	4, 8 mg qd	Long-acting
Terazosin	$\alpha_{1A}, \alpha_{1B}, \alpha_{1D}$	1, 2, 5, 10	1, 2, 5, 10 mg qd	Long-acting
<i>AI subtype-selective</i>				
Tamsulosin	$\alpha_{1A}, \alpha_{1D}$	0.4	0.4, 0.8	Long-acting

**Abbreviations:** bid, twice daily; GITS, gastrointestinal therapeutic system; qd, once-daily; tid, three times daily; XL, extended-release.

versus placebo (Lepor 1995; Elhilali et al 1996; Roehrborn et al 1996; Rhodes, Krogh et al 1999) The most common adverse events are dizziness and asthenia with respective occurrence rates of 6.7% to 19.8% and 3.8% to 12.3% (Lepor 1995; Elhilali et al 1996; Roehrborn et al 1996). Sixteen percent of patients on terazosin versus 11% on placebo ( $p < 0.05$ ) withdrew from the Hytrin Community Assessment Trial ( $n = 2084$ ) because of treatment emergent adverse events (Roehrborn et al 1996). Overall, placebo-controlled trials suggest that terazosin is effective in reducing symptoms of BPH and improving QoL in patients with LUTS. However, some patients will not tolerate terazosin and may benefit from alternate pharmacotherapy.

Doxazosin has proven safety and efficacy in the treatment of BPH (Chapple et al 1994; Fawzy et al 1995; Lepor et al 1997; de Reijke and Klarskov 2004). It has also been shown to decrease blood pressure in hypertensive patients, while not effecting normotensive patients (Kirby 1995). However, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (ALLHAT 2000) was a large, randomized, double-blind, active-controlled trial designed to detect differences in major cardiovascular events in hypertensive patients randomized to chlorthalidone, doxazosin, amlodipine, or lisinopril. The doxazosin arm of this trial was closed early due to a significantly higher incidence of combined cardiovascular disease events, particularly congestive heart failure (CHF) (ALLHAT 2000). Prior to this study, alpha blockers were commonly an initial drug choice for treating hypertension, particularly in patients with coexisting BPH (JNC 1997); however, the ALLHAT trial results demonstrated that the doxazosin group had an

increased risk of CHF and was less effective than chlorthalidone at treating hypertension, resulting in multiple medication use to control blood pressure. Also, more patients discontinued doxazosin than chlorthalidone reflecting a higher incidence of adverse events.

Alfuzosin has established short term safety and efficacy. A systematic review included 11 trials and 3901 men, particularly eight trials ( $n = 2381$ ) compared alfuzosin with placebo (mean duration 13 weeks, range 4 to 26 weeks) (MacDonald and Wilt 2005). Six trials reported statistically significant improvement in symptom scores in men receiving alfuzosin versus placebo. Five trials reported significant improvement in peak urinary flow over placebo. Two smaller trials ( $n < 50$ ) failed to show significant improvement in symptoms or peak urinary flow. Dizziness was the most commonly reported adverse event. Six percent of patients withdrew from the study due to treatment-emergent adverse events. Withdrawal rate was identical to placebo (MacDonald and Wilt 2005). Results of this systematic review suggest that alfuzosin is significantly efficacious in the treatment of LUTS attributable to BPH. The identical rate of withdrawal due to adverse events between alfuzosin and placebo suggest that alfuzosin is safe and well tolerated by patients.

Tamsulosin has proven long-term safety and efficacy. Narayan and colleagues (Narayan et al 2003) studied safety and efficacy in 609 patients in a four-year multicenter study. One hundred and nine patients in this trial had been on tamsulosin for six years. Significant improvement from baseline was maintained for as long as six years for total AUASI score, QoL improvement, and peak urinary flow rate. Adverse events accounted for 16% of patients discontinuing

**Table 3** Summary of clinical trial outcomes of alpha blockers for BPH

Reference	Agent	No. Patients	Study length	Dose	SI	Significant changes in BPH measurements				TEAE	
						SI change	QoL change	Peak flow (mL/s)	Mean flow (mL/s)	% patients discontinuing <sup>‡</sup> medication	Most common TEAEs (%)
Roehrborn et al 1996	Terazosin	2084	12 mo	2–10mg	AJASI	-7.6	-1.3	2.2	1.2	16	Dizziness (12) Asthenia (8) Periph. edema (4) Chest pain (4) Hernia (2)
MacDonald and Wilt 2005 <sup>†</sup>	Alfuzosin	3901	4 to 26 weeks (mean 13)	7.5–10mg	IPSS	-5.4	-1	2.6	NA	6	Dizziness (5) Post. hypotens. (<2) Syncope (<2) Somnolence (<2)
De Reijke 2004	Doxazosin	210	14 weeks	1–8mg daily	IPSS	-9.23	NA	1.5	2.8	12	Dizziness (14) Asthenia (5) Periph. edema (6) Headache (5) Post. hypotens. (2)
Chung et al 1999	Doxazosin GITS	475	12 mo	4–8mg	IPSS	-9	-1.6	3.2	NA	0	Dizziness(3) ED (1) Dry mouth (1) Prostatic disorder (1) Post. hypotens. (0.4)
Narayan et al 2003	Tamsulosin	609	72 mo	0.4–0.8mg	AJASI	-8 to -11	-2	1.01 to 2.3	1.2	15.7	Abn. ejaculation (0.8) Dizziness (0.2) Post. hypotens. (0.2) Syncope (0.2)

**Note:** <sup>†</sup>systematic review of 11 trials, 8 of which were placebo controlled; <sup>‡</sup>percentage of patients discontinuing drug due to TEAE.

**Abbreviations:** AJASI, American Urological Association Symptom Index; ED, erectile dysfunction; GITS, gastrointestinal therapeutic system; IPSS, International Prostate Symptom Score; mo, month; NA, not available; NS, not significant versus placebo; SI, symptom index; TEAE, treatment-emergent adverse events.

tamsulosin. Dizziness, postural hypotension, and syncope were exceedingly rare with only 0.2% of patients discontinuing tamsulosin for any one of these reasons. Less than 1% of patients discontinued tamsulosin due to abnormal ejaculation. Palacio and colleagues (Palacio et al 2004) confirmed the safety and efficacy of tamsulosin in a prospective multicenter trial including 2921 men with LUTS suggestive of BPH and twelve months of follow-up. Six and twelve month assessments demonstrated significant improvement in the IPSS score, QoL, peak urinary flow, irritative symptoms, and obstructive symptoms.

### Prolonged release agents

Doxazosin use for BPH is limited by its first-dose side-effect of hypotension. It requires a titration regimen that can require up to four steps (Chung et al 1999). In response to this, doxazosin gastrointestinal therapeutic system (GITS) was developed. This controlled-release formulation has a more gradual absorption and once-daily dosing that minimizes adverse effects and may improve compliance (Chung et al 1999). Doxazosin GITS preserves efficacy, simplifies titration and has a slightly better side-effect profile than the standard titration (Kirby et al 2001).

Alfuzosin is currently available in an immediate-, sustained-, and extended-release formulation with three times, twice-, and once-daily dosage, respectively. The extended-release preparation is equally effective as the immediate release and has not been compared with the sustained release formulation (Guay 2004). Food can effect bioavailability of the extended-release formulation and patients should be advised to take the medication on a full stomach (Guay 2004). Also, hepatic impairment delays elimination of alfuzosin, and therefore extended-release formulations should be avoided in patients with this condition (Guay 2004). Systematic review of clinical trials for alfuzosin extended-release demonstrated a 4% discontinuation rate. Treatment emergent adverse events included dizziness (5.7%), headache (3%), and fatigue (2.7%) (Guay 2004).

A new formulation of tamsulosin, oral-controlled absorption system (OCAS), is expected to be available in the near future. The current formulation is based on a controlled release formulation and is prescribed as once-daily dosing (Wyllie 2005). Tamsulosin should be taken 30 minutes after the same meal each day to achieve steady serum levels over a 24-hour period. The new OCAS formulation will likely have altered bioavailability, onset of action and duration of

action relative to the current formulation (Wyllie 2005). However, the active agent is the same and improved efficacy should not be expected (Wyllie 2005). Given the already convenient dosing and low incidence of adverse events with the current formulation of tamsulosin, the motivation for designing an extended-release formulation is unclear (Wyllie 2005).

### Alpha adrenergic blockers: sexual side-effects

Alpha blockers have a low incidence of sexual side-effects. However, they can cause reversible ejaculatory dysfunction (Höfner et al 1999), in particular retrograde ejaculation. The mechanism for sexual dysfunction relates to the antagonism of the alpha receptors, located in the smooth muscle of the bladder neck, preventing closure of the bladder neck, allowing for retrograde ejaculation during climax (Carbone and Hodges 2003).

In a review of 73 studies, sexual dysfunction associated with BPH therapy was reported (Carbone and Hodges 2003). The risk of retrograde ejaculation with transurethral resection of the prostate (TURP) for BPH ranges from 25% to 99%. The risk is 1% with alpha blockers, but can be higher with tamsulosin (Carbone and Hodges 2003). This may be due to alpha-1<sub>A</sub> receptors in the seminal vesicles that are blocked by tamsulosin and thereby decrease the volume of ejaculate. Tamsulosin has been reported to have an incidence of ejaculatory disorder ranging from 4.5% (Chapple et al 1996) to 30% (Narayan and Tewari 1998), however less than 1% of patients discontinued tamsulosin for this reason (Lepor 1998; Narayan and Tewari 1998; Höfner et al 1999; Schulman et al 2001; Narayan et al 2003). There is concern regarding the QoL effects of ejaculatory dysfunction. Ejaculatory disorders are viewed as a mild side-effect by patients and infrequently result in discontinuation of therapy (Höfner et al 1999; Narayan et al 2003; Lowe 2005).

Improved overall sexual function has been reported with alpha blocker use (Lukacs et al 1996; Höfner et al 1999; van Moorselaar et al 2005). This effect may be attributed to an improved overall QoL, or possibly through a direct effect of the alpha receptor antagonism (Lowe 2005). Urinary symptoms associated with BPH are an independent risk factor for sexual life dissatisfaction and severe symptoms have a greater associated risk than moderate symptoms (Macfarlane et al 1996; Vallancien et al 2003). Forty-six percent of patients seen in urologic practice report that LUTS has a negative impact on their sex lives (Frankel et al 1998).



A direct relationship between alpha blockers and improved sexual function has also been theorized. Alpha receptor antagonism in the penis causes smooth muscle relaxation resulting in relaxation of the lacunar spaces of the corpora cavernosa, thereby potentially decreasing blood flow resistance to erectile tissues and increasing erectile rigidity (Andersson and Stief 1997; Höfner et al 1999; Lowe 2005). Comparison of intracavernosal blood samples of healthy men with those of patients with sexual dysfunction suggest that somatic deregulation in sympathetic transmission, or changes of catecholamine reuptake mechanisms, may play a role in erectile dysfunction (Becker et al 2002). This mechanism suggests another explanation regarding the efficacy of alpha blockers in erectile dysfunction (Gwinup 1988; Becker et al 1998).

## 5 alpha-reductase inhibitors: mechanism of action

Androgen suppression results in decreased prostate volume and improvement in LUTS (McConnell 1990). Dihydrotestosterone (DHT), a product of testosterone conversion by the enzyme 5 alpha-reductase, has been shown to play a role in the development of BPH (Coffey and Walsh 1990).

Finasteride is a 5 alpha-reductase inhibitor that effectively inhibits DHT production. (Vermeulen et al 1989). There are two isozymes of the 5 alpha-reductase enzyme, types I and II (Jenkins et al 1992). Finasteride selectively inhibits only the type II isozyme and it does not reduce DHT levels to those seen in castration (Thigpen et al 1993).

Dutasteride, another 5 alpha-reductase inhibitor, differs from finasteride in that it inhibits isozymes (Roehrborn et al 2002). Table 4 summarizes mechanism, dose, and adverse effects associated with 5 alpha-reductase inhibitors.

**Table 4** 5 Alpha-reductase inhibitors: mechanism, dose, and associated adverse effects

Drug Name	Mechanism	Dose	Adverse effects
Finasteride	Inhibits type II isozyme	5mg qd	decreased libido, impotence, decreased ejaculate, ejaculation disorder, breast enlargement, breast tenderness, and rash
Dutasteride	Inhibits type I and type II isozyme	0.5mg qd	impotence, decreased libido, gynecomastia, and ejaculation disorder

**Abbreviations:** qd, once-daily.

## 5 alpha-reductase inhibitors: safety and efficacy

The Proscar (Merck & Co., Inc., Whitehouse Station, NJ, USA) Long-Term Efficacy and Safety Study (PLESS) (McConnell et al 1998) included 3040 men with prostates greater than 50g and BPH. After four years of finasteride treatment, significantly reduced symptoms and prostate volume, increased urinary flow rate, and reduced probability of surgery and AUR were reported. There was a significant difference noted in drug-related adverse events of decreased ejaculate, ejaculation disorder, breast enlargement, breast tenderness, and rash. Decreased libido and impotence only retained significance versus placebo during the first year of the trial.

Roehrborn and colleagues (Roehrborn et al 2002) reported safety and efficacy results on 4325 men randomized to either dutasteride or placebo in a multicenter, double-blind trial with multiple interval assessments. Significant results at 24 months of follow-up included: serum DHT reduction by 90%, prostate volume reduction by 26%, and maximal flow rate improvement of 2.2mL/s. Risk of AUR and surgical intervention was reduced 57% and 48% versus placebo, respectively. Two year open-label extension of this trial suggests sustained and continued improvements in symptoms and flow rate (Roehrborn et al 2005). Significant adverse events included impotence, decreased libido, gynecomastia, and ejaculation disorder. Only gynecomastia retained significance, versus the placebo group, at 24 months. Table 5 summarizes safety and efficacy outcomes for 5 alpha-reductase inhibitors.

Unlike alpha adrenergic blockers, the maximum efficacy of 5 alpha-reductase inhibitors is not quickly achieved. Three to six months of therapy is necessary to see maximum decrease in prostate size and resultant improvement in LUTS (Peters and Walsh 1987; Gormley et al 1992; McConnell et al 1998; Bruskewitz et al 1999).

## 5 alpha-reductase inhibitors: QoL and sexual side-effects

As part of the PLESS trial, Bruskewitz and colleagues (Bruskewitz et al 1999) investigated the long-term effects of finasteride on QoL in men with moderate-to-severe LUTS secondary to BPH. This trial utilized a questionnaire focused on degree of bother, lifestyle interference, and sexual issues. After 4 years of follow-up, men receiving finasteride were significantly ( $p < 0.01$ ) less bothered by LUTS and had

**Table 5** Summary of 5 alpha-reductase inhibitor clinical trial outcomes for BPH

Reference	Agent	No. patients	Study length	Dose	Significant changes in BPH measurements				TEAE	
					SI	SI change	Peak flow (mL/s)	% volume change*	% patients discontinuing <sup>‡</sup> medication	Most common TEAEs (%)
McConnell et al 1998	Finasteride	3040	48 mo	5mg	AUASI**	-2.6	1.9	-18	12	ED (8) Decreased libido (6) Decreased ejaculate volume (4) Ejaculation dysfct (1)
Roehrborn et al 2002	Dutasteride	2951	24 mo	0.5mg	AUASI	-4.5	2.2	-26	9	ED (7) Decreased libido (4) Gynecomastia (2) Ejaculation dysfct (2)

**Note:** \*% change in volume at one year; <sup>‡</sup>percentage of patients discontinuing drug due to TEAE; \*\* "quasi-AUA score" was constructed from seven questions that were part of a larger series of questions constructed before use of AUASI.

**Abbreviations:** AUASI, American Urological Association Symptom Index; ED, erectile dysfunction; mo, month; NS, not significant versus placebo; SI, symptom index; TEAE, treatment-emergent adverse events.

significantly less activity interference and worry about urinary function secondary to LUTS. Effects became evident after 4 months of treatment. Domains of sexual satisfaction and sexual drive were worse for the finasteride group than the placebo group, while no differences were found for the question regarding erectile difficulty.

O'Leary and colleagues (O'Leary et al 2003) investigated the effect of dutasteride on BPH-specific health status. This randomized, double-blind, placebo-controlled study utilized the BPH Impact Index (BII) validated questionnaire (Barry et al 1995) in 4325 men with LUTS due to BPH to assess quality of life. The BII is composed of four questions addressing physical discomfort, worry, degree of bother, and time away from regular activities due to urinary problems. Dutasteride versus placebo resulted in significant improvements in mean BII score after 6 months of therapy with continued improvements from six months to two years. This finding suggests that dutasteride, despite its known sexual side-effects, improves QoL in patients with BPH.

The negative impact on sexual health is greater with 5 alpha-reductase inhibitors than alpha blockers (Lowe 2005). The anti-androgen effects of finasteride and dutasteride should be considered when choosing a pharmacologic therapy for patients with BPH.

## Combination therapy

As the two classes of drugs suggest, BPH symptoms respond to both inhibition of sympathetic smooth muscle tone and gland volume reduction. The distinct mechanisms of action associated with the two drug classes suggest that combination

therapy may have added benefit when compared to either of the two therapies alone.

Two trials, the Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study (Lepor et al 1996), which compared terazosin, finasteride, and combination therapy with placebo, and the Prospective European Doxazosin and Combination Therapy (PREDICT) (Kirby et al 2003) trial which compared doxazosin, finasteride, and combination therapy with placebo, failed to show any benefit of combination therapy.

The Medical Therapy of Prostate Symptoms (MTOPS) trial (McConnell et al 2003) was a multi-center, double-blind, placebo-controlled clinical trial developed to compare the efficacy of combination therapy with doxazosin and finasteride with that of either therapy alone. 3047 men were enrolled in the trial and follow-up was reported for an average of 4.5 years (McConnell et al 2003). The results demonstrated a significantly reduced risk of overall clinical progression with combination therapy. This risk was defined as "An increase above baseline of at least 4 points in the American Urological Association Symptom Score, acute urinary retention, urinary incontinence, renal insufficiency, or recurrent urinary tract infection." (McConnell et al 2003). The reduction in risk of BPH progression associated with combination therapy (66% for the combination vs placebo,  $p < 0.001$ ) was significantly greater than that associated with doxazosin ( $p < 0.001$ ) or finasteride ( $p < 0.001$ ) alone (McConnell et al 2003). The risks of AUR and the need for invasive therapy were significantly reduced by combination therapy and finasteride alone, but not by doxazosin alone.

**Table 6** Summary of clinical trial outcomes for combination therapy for BPH

Reference	Agent	No. patients	Study length	Dose	Significant changes in BPH measurements				TEAE		
					SI	SI change	QoL change	Peak flow (mL/s)	Mean flow (mL/s)	% patients discontinuing medication	Most common TEAEs (%)
McConnell et al 2003	Doxazosin and Finasteride	3047	54 mo	Finasteride 5mg; Doxazosin 4–8mg	AUASI	–6	NA	3.6	NA	18 <sup>†</sup>	Dizziness(5) ED(5) Post.hypotension(4) Asthenia(4) Abn.ejaculation(3) Decreased libido(3)

**Note:** <sup>†</sup>percentage of patients discontinuing both drugs for any reason, *not* only TEAE; <sup>‡</sup>percentage of patients discontinuing drug due to TEAE.

**Abbreviations:** AUASI,American Urological Association Symptom Index; ED,erectile dysfunction; mo, month; NA, not available; NS, not significant versus placebo; SI, symptom index; TEAE, treatment-emergent adverse events.

Combination therapy was superior to both doxazosin and finasteride alone (McConnell et al 2003). Table 6 summarizes clinical outcomes reported by the MTOPTS trial. Discontinuation rates were 27% for doxazosin, 24% for finasteride, and 18% for men who were receiving combination therapy (McConnell et al 2003). Adverse events were the most common reason for stopping treatment. The numbers of statistically significant side-effects were 5, 3, and 9 for doxazosin, finasteride, and combination therapy, respectively. Adverse events that occurred more frequently with combination therapy versus either drug alone included: abnormal ejaculation, peripheral edema, and dyspnea (McConnell et al 2003). The definition of discontinuation in the combined arm was discontinuation of both drugs, and as such more patients in the combination arm may have been on at least one drug as opposed to nothing. The intention to treat design combined with drug tolerability and definition of discontinuation could be contributing to the outcomes reported (Ok et al 2005).

### Phytotherapeutics

The annual prevalence of dietary supplement use in the US increased from 14.2% in 1988–1999 to 18.8% in 2002 (Kelly et al 2005). Dietary supplement use doubled for those age 65 years and older. Saw Palmetto is the second most commonly used dietary supplement in men between the ages of 45 and 64, and fourth most commonly used in men aged 65 and older (Kelly et al 2005).

### Saw Palmetto

Saw palmetto (*Serenoa repens*) is derived from the American dwarf palm tree berry, which naturally grows in the southeastern US (Fong et al 2005b). It has been used as a natural remedy for BPH. Although the mechanism of action has not been completely defined, the most accepted mechanism is 5 alpha-reductase inhibition (Fong et al 2005b). Saw palmetto has been investigated in large, randomized, placebo-controlled trials utilizing validated questionnaires (Carraro et al 1996; Gerber et al 2001; Debruyne et al 2002; Debruyne et al 2004). It has also been compared with finasteride and tamsulosin (Carraro et al 1996; Debruyne et al 2002). In a recent review of the literature regarding saw palmetto, Fong and colleagues (Fong et al 2005b) concluded that this phytotherapeutic significantly improves symptom score (assessed with IPSS score) (Carraro et al 1996; Gerber et al 2001; Debruyne et al 2002; Debruyne et al 2004), QoL (Carraro et al 1996), and urinary flow rate (Carraro et al 1996;

**Table 7** Summary of clinical trial outcomes for combination therapy for BPH

Reference	Agent	No. patients	Study length	Dose	Significant changes in BPH measurements				TEAE		
					SI	SI change	QoL change	Peak flow (mL/s)	Mean flow (mL/s)	% patients discontinuing <sup>‡</sup> medication	Most common TEAEs (%)
Bent et al 2003	Saw Palmetto	225	12 mo	160mg twice daily	AUASI	NS	NS	NS	NA	NS	NS

Note: <sup>‡</sup>percentage of patients discontinuing drug due to TEAE.

Abbreviations: AUASI, American Urological Association Symptom Index; ED, erectile dysfunction; NS, not significant versus placebo; SI, symptom index; TEAE, treatment-emergent adverse events.

Debruyne et al 2002). Saw palmetto has been shown to have a lower incidence of sexual dysfunction and ejaculatory disorders than both alpha blockers and 5 alpha-reductase inhibitors (Carraro et al 1996; Debruyne et al 2002).

Despite previous reports, results from a recent randomized, placebo-controlled trial have called into question the efficacy of saw palmetto. Bent and colleagues (Bent et al 2006) randomized 225 men with moderate to severe BPH to one year of treatment with saw palmetto extract or placebo. They reported no significant difference between the groups in change in AUASI score, maximal urinary flow rate, prostate size, residual volume after voiding, QoL, or PSA during the one-year study. The incidence of side-effects was similar between the two groups. Table 7 summarizes the clinical outcomes reported by Bent and colleagues (Bent et al 2006). Unlike previous studies, this trial used a placebo that was similar in appearance and smell to the pungent active agent. Furthermore, the adequacy of blinding was validated. Inadequate blinding may decrease response in a placebo group, thereby artificially increasing the response in the experimental group. Although this trial challenges current belief that saw palmetto is somewhat efficacious in treating BPH symptoms, reproduction of these results with a similar well designed trial is necessary to confirm these findings. Also, supplemental “prostate-health” preparations include various herbal extracts other than saw palmetto. The other extracts and the combined use of them may, or may not, alter efficacy of such products. We feel that patients should be made aware of the results of this trial so that they can make informed decisions regarding the use of saw palmetto for BPH symptoms.

### Pygeum africanum

*P. africanum* is a plant extract derived from the African plum tree that is widely used in Europe (Lowe and Fagelman 1999). A systematic review and quantitative meta-analysis was conducted to investigate the efficacy and tolerability of this phytotherapeutic in men with BPH (Ishani et al 2000). Eighteen RCTs accounting for 1562 subjects were analyzed. Mean follow-up was 64 days. Six studies involving 474 subjects compared *P. africanum* with placebo. Men were twice as likely to report an overall improvement of symptoms when taking *P. africanum* extract versus placebo. Nocturia and residual urine volume were reduced by 19% and 24%, respectively. Peak urine flow was increased by 23%. Similar to placebo (11%), 12% of patients dropped out of respective studies. Adverse events were generally mild. Gastrointestinal

side-effects were the most common. Although this report is a meta-analysis, most of the included trials did not provide clinically relevant baseline and outcomes data, none were conducted in the US, no standardized validated symptom scales were used, studies were of short duration, and outcomes of acute urinary retention, renal insufficiency, or surgical intervention were not considered (Ishani et al 2000).

A randomized, double blind study comparing once and twice daily dosing of *P. africanum* investigated the safety, efficacy, and QoL outcomes in the BPH patient (Chatelain et al 1999). 174 patients completed the open phase of the trial (100mg once daily) with follow-up of 12 months. IPSS score improved 46% after 12 months. Thirty-two percent of patients scored a 5 (unhappy) or a 6 (terrible) at baseline, and only 11% indicated these poor QoL scores after 12 months. After one year, 58% of patients indicated a QoL score of “mostly satisfied, pleased, or delighted.” After two months, peak urinary flow significantly improved and was maintained. Prostate volume was significantly reduced by 7% after one year. Similar to the meta-analysis, gastrointestinal side-effects were the most common. Less than five percent of patients withdrew from the trial secondary to side-effects. There were no significant changes to PSA levels or sexual activity. This trial suggests safety and efficacy for once a day dosing of *P. africanum* for patients with BPH.

Less studied phytotherapies include *Urtica dioica* (stinging nettle), *Cucurbita pepo* (pumpkin seed), *opuntia* (cactus flower), *Pinus* (pine flower), *Picea* (spruce), and *Secale cereale* (rye pollen). These agents are often part of combination preparations formulated for “prostate health.” Due to the lack of consistency of active agent dose and knowledge regarding pharmacokinetic information and possible drug interactions, we do not feel that there is enough evidence to recommend these products; however in our opinion it is important to be aware of the information that is available regarding herbal remedies as their use is quite common.

## Differential review of agents used in BPH therapy

In a meta-analysis, Djavan and Marberger (Djavan and Marberger 1999) assessed whether or not alpha blockers could be distinguished based on efficacy and/or tolerability. Both placebo-controlled and comparison studies involving alfuzosin, terazosin, doxazosin, and tamsulosin were analyzed. Overall, the various alpha blockers produced similar improvements in symptom scores and urinary flow

rates. Significant differences were found in side-effect profiles. Based on study withdrawal rates due to adverse events and incidence of vasodilatory adverse events, alfuzosin and tamsulosin were better tolerated than terazosin or doxazosin. Withdrawal rates for alfuzosin and tamsulosin were similar to placebo at 4% to 10%. Fourteen percent to 20% of patients taking terazosin or doxazosin withdrew from studies because they could not tolerate related adverse effects. Also, tamsulosin had less effect on blood pressure than alfuzosin or terazosin.

The safety and efficacy of alfuzosin and tamsulosin versus placebo has been studied. In a randomized, double-blind, placebo-controlled study, 625 patients were randomized to alfuzosin (10mg or 15mg), tamsulosin 0.4mg, or placebo for twelve weeks (Nordling 2005). Results demonstrated significant improvement in IPSS score for alfuzosin 10mg and tamsulosin versus placebo ( $p = 0.007$ ,  $p = 0.014$ , respectively), while alfuzosin 15mg demonstrated a trend toward an improvement ( $p = 0.05$ ). Both doses of alfuzosin and tamsulosin produced a significant increase in peak urinary flow relative to placebo ( $p = 0.02$ ). Alfuzosin and tamsulosin were well tolerated. Dizziness was the most common adverse event with 4%, 6%, 7%, and 2% of patients reporting this adverse event for placebo, alfuzosin 10mg, alfuzosin 15mg, and tamsulosin, respectively. Sexual function adverse events were also low with 0%, 3%, 1%, and 8% incidence for placebo, alfuzosin 10mg, alfuzosin 15mg, and tamsulosin, respectively. Discontinuation rate (8%) was greatest with alfuzosin 15mg. This study suggests that the greatest benefit with minimized side-effects can be achieved with the use of alfuzosin 10mg or tamsulosin.

## BPH treatment strategies

The Triumph Project investigated treatment strategies, patterns of drug use and treatment discontinuation in men with BPH (Verhamme et al 2003). Nine percent of patients newly diagnosed with BPH undergo surgery, while 45% are treated pharmacologically within the first year after diagnosis (Verhamme et al 2003). Age, type of complaint, and co-morbidity are factors associated with receiving pharmacologic therapy versus watchful waiting or surgery. Alpha blockers are the most commonly prescribed first line therapy (Verhamme et al 2003). Adherence rates of alpha blockers (67% at one year) are similar to 5 alpha-reductase inhibitors (73% at one year) and combination therapy (71% at one year) (Verhamme et al 2003). Adherence rates do not

vary within a class of medication (Verhamme et al 2003). Patients with voiding symptoms (versus storage or post micturition syndromes), younger age, normal PSA, and less co-morbidity are more likely to discontinue medication (Verhamme et al 2003). These treatment strategies reflect the conservative nature of BPH management, safety of alpha blockers and 5 alpha-reductase inhibitors, and risk stratification for progressive disease.

One-quarter of patients discontinue pharmacologic treatment early after starting (adherence time <20% of total follow-up). Overall, the most common reasons for discontinuing a medication are adverse events or persistence of complaints despite therapy or resolution of complaint (Verhamme et al 2003). Interestingly, adherence of once-daily dosing preparations is not significantly better than multiple dosing regimens (Verhamme et al 2003).

In practice, BPH treatment is largely based on patient symptoms. Typically, we start with pharmacologic therapies and advance to minimally invasive and ultimately surgical options. Alpha blockers, particularly tamsulosin, are first line agents for BPH treatment because they are effective with limited side-effects and convenient once-daily dosing. If a patient is unable to tolerate an alpha blocker or if the medication is not efficacious we would offer a 5 alpha reductase inhibitor or a minimally invasive therapy. 5 alpha-reductase inhibitors are especially helpful in patients with large prostate glands (>50 g) and/or symptomatic bleeding. Long-term use of 5 alpha-reductase inhibitors is somewhat controversial because of the associated increased rate of higher grade prostate cancers. As discussed earlier, the evidence for combination therapy is unclear and we do not routinely recommend it due to a 2-fold increase in side-effects and costs. Patients not desiring to take a medication are offered minimally invasive or surgical options.

## Discussion

### Major events in the development and progression of BPH

Patients suffering from LUTS secondary to BPH typically experience the gradual onset of symptoms that can prompt seeking of medical treatment. Also, AUR can rarely be the presenting event. Without treatment, patients are at risk for disease progression including AUR, recurrent urinary tract infection, hydronephrosis, gross hematuria, bladder stones, bladder decompensation, overflow incontinence, renal

impairment, and even renal failure can result. The impending impact these events have on QoL justifies the need for appropriate therapeutic intervention.

### Critical issues in QoL

Critical issues in QoL management with these agents relate to the subjective experience of the patient. Symptoms attributed to BPH have been shown to negatively impact QoL, therefore it is reasonable to treat these patients. However, patients with low-to-moderate symptoms may not be bothered enough to warrant medical intervention. These patients may be best served by watchful waiting because treatment side-effects may negate benefits of therapy.

Patients desiring medical treatment are at risk for adverse events. Although the risk of side-effects with the current agents is quite low, this risk can be minimized by starting with alpha adrenergic antagonists, particularly tamsulosin, and advancing to 5 alpha-reductase inhibitors.

Patients having persistent symptoms, despite alpha blocker therapy, carry the combined risk of medication side-effect and LUTS. These patients can be offered an alternate alpha blocker, trial of a 5 alpha-reductase inhibitor or a minimally invasive/surgical option.

### Future directions and experimental therapy

Outside of alpha adrenergic antagonism, 5 alpha-reductase inhibition and phytotherapeutics there has not been alternate drug classes for treatment of BPH. However, new forms of monotherapy, as well as combination therapy with alpha adrenergic antagonists, are on the horizon. Further improvement of alpha adrenergic receptor subtype selectivity (Barrow et al 2000), endothelin receptor antagonists (Stachon et al 2004), phosphodiesterase inhibitors, nitric oxide, cyclic guanosine monophosphate, L-arginine, vanilloid receptor modulation, and purine receptor modulation are future therapies for the treatment of BPH (Andersson et al 2002).

### Pharmacogenomics and BPH

The efficacy and tolerability of pharmaceutical agents vary from person to person. This variability is believed to result in part from the unique interaction of a pharmaceutical agent with the genetic makeup of the individual. Pharmacogenomics is the study of this interaction. The science of pharmacogenomics is intended to produce

medications individualized for one's genetic makeup thereby maximizing efficacy and tolerability.

While this line of research is still in its infancy, investigation is underway to define the association of BPH and polymorphisms of genes involved in sex hormone metabolism, growth factors, cytokine and Vitamin D receptors (Mullan et al 2006; Roberts et al 2006). Highly selective, efficacious therapies with low side-effect profiles are anticipated to result from pharmacogenomic research.

## Conclusion

There are a variety of safe and efficacious medical therapies available for the management of BPH and it is important for the practicing physician to have an understanding of these pharmacotherapies and their potential impact on the patient. Due to the widespread use of phytotherapies, despite adequate evidence of efficacy and safety, physicians must be aware of existing evidence for these products. Particular patient characteristics; of which age, symptom severity, co-morbidities, and sexual function are only a few, should be considered when devising a treatment plan for patients with BPH.

## References

- Abrams P, Schulman CC, Vaage S. 1995. Tamsulosin, a selective alpha 1c-adrenoceptor antagonist: a randomized, controlled trial in patients with benign prostatic 'obstruction' (symptomatic BPH). The European Tamsulosin Study Group. *Br J Urol*, 76:325–36.
- Abrams P, Speakman M, Stott M, et al. 1997. 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 benign prostatic hyperplasia). *Br J Urol*, 80:587–96.
- [ALLHAT] ALLHAT Collaborative Research Group. 2000. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). ALLHAT Collaborative Research Group. *JAMA*, 283:1967–75.
- Andersson KE, Chapple CR, Hofner K. 2002. Future drugs for the treatment of benign prostatic hyperplasia. *World J Urol*, 19:436–42.
- Andersson KE, Lepor H, Wyllie MG. 1997. Prostatic alpha 1-adrenoceptors and uroselectivity. *Prostate*, 30:202–15.
- Andersson KE, Stief CG. 1997. Neurotransmission and the contraction and relaxation of penile erectile tissues. *World J Urol*, 15:14–20.
- Barrow JC, Nantermet PG, Selnick HG, et al. 2000. In vitro and in vivo evaluation of dihydropyrimidinone c-5 amides as potent and selective receptor antagonists for the treatment of benign prostatic hyperplasia. *J Med Chem*, 43:2703–18.
- Barry MJ, Fowler FJ Jr., O'Leary MP, et al. 1992. The American Urological Association symptom index for benign prostatic hyperplasia. *J Urol*, 148:1549–57.
- Barry MJ, Fowler FJ Jr., O'Leary MP, et al. 1995. Measuring disease-specific health status in men with benign prostatic hyperplasia. Measurement Committee of The American Urological Association. *Med Care*, 33:AS145–55.
- Becker AJ, Stief CG, Machtens S, et al. 1998. Oral phentolamine as treatment for erectile dysfunction. *J Urol*, 159:1214–16.
- Becker AJ, Uckert S, Stief CG, et al. 2002. Cavernous and systemic plasma levels of norepinephrine and epinephrine during different penile conditions in healthy men and patients with erectile dysfunction. *Urology*, 59:281–6.
- Bent S, Kane C, Shinohara K, et al. 2006. Saw palmetto for benign prostatic hyperplasia. *N Engl J Med*, 354:557–66.
- Berry SJ, Coffey DS, Walsh PC, et al. 1984. The development of human benign prostatic hyperplasia with age. *J Urol*, 132:474–9.
- Berthelson SPW. 1977. A functional basis for the classification of alpha adrenergic receptor. *Life Sci*, 21:595–600.
- Boyarsky S, Jones G, Paulson DF, et al. 1976. A new look at bladder neck obstruction by the food and drug administration regulators: guide lines for investigation of benign prostatic hypertrophy. *Trans Am Assoc Genitourin Surg*, 68:29–32.
- Bruskewitz R, Girman CJ, Fowler J, et al. 1999. Effect of finasteride on bother and other health-related quality of life aspects associated with benign prostatic hyperplasia. *Urology*, 54:670–8.
- Caine M. 1986. The present role of alpha-adrenergic blockers in the treatment of benign prostatic hypertrophy. *J Urol*, 136:1–4.
- Caine M, Perlberg S, Meretyk S. 1978. A placebo-controlled double-blind study of the effect of phenoxybenzamine in benign prostatic obstruction. *Br J Urol*, 50:551–4.
- Caine M, Pfau A, Perlberg S. 1976. The use of alpha-adrenergic blockers in benign prostatic obstruction. *Br J Urol*, 48:255–63.
- Carbone DJ Jr., Hodges S. 2003. Medical therapy for benign prostatic hyperplasia: sexual dysfunction and impact on quality of life. *Int J Impot Res*, 15:299–306.
- Carraro JC, Raynaud JP, Koch G, et al. 1996. Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostate hyperplasia: a randomized international study of 1,098 patients. *Prostate*, 29:231–40, discussion 241–2.
- Chapple CR, Carter P, Christmas TJ, et al. 1994. A three month double-blind study of doxazosin as treatment for benign prostatic bladder outlet obstruction. *Br J Urol*, 74:50–6.
- Chapple CR, Wyndaele JJ, Nordling J, et al. 1996. Tamsulosin, the first prostate-selective alpha 1A-adrenoceptor antagonist. A meta-analysis of two randomized, placebo-controlled, multicentre studies in patients with benign prostatic obstruction (symptomatic BPH). European Tamsulosin Study Group. *Eur Urol*, 29:155–67.
- Chatelain C, Autet W, Brackman F. 1999. Comparison of once and twice daily dosage forms of P extract in patients with benign prostatic hyperplasia: a randomized, double-blind study, with long-term open label extension. *Urology*, 54:473–8.
- Chung M, Vashi V, Puente J, et al. 1999. Clinical pharmacokinetics of doxazosin in a controlled-release gastrointestinal therapeutic system (GITS) formulation. *Br J Clin Pharmacol*, 48:678–87.
- Cockett AT, Aso Y, Denis L, et al. 1991. World Health Organization Consensus Committee recommendations concerning the diagnosis of BPH. *Prog Urol*, 1:957–72.
- Coffey DS, Walsh PC. 1990. Clinical and experimental studies of benign prostatic hyperplasia. *Urol Clin North Am*, 17:461–75.
- de Reijke TM, Klarskov P. 2004. Comparative efficacy of two alpha-1 adrenoceptor antagonists, doxazosin and alfuzosin, in patients with lower urinary tract symptoms from benign prostatic enlargement. *BJU International*, 93:757–62.
- Debruyne F, Boyle P, Calais Da Silva F, et al. 2004. Evaluation of the clinical benefit of permixon and tamsulosin in severe BPH patients-PERMA study subset analysis. *Eur Urol*, 45:773–9, discussion 779–80.
- Debruyne F, Koch G, Boyle P, et al. 2002. Comparison of a phytotherapeutic agent (Permixon) with an alpha-blocker (Tamsulosin) in the treatment of benign prostatic hyperplasia: a 1-year randomized international study. *Eur Urol*, 41:497–506, discussion 506–7.
- Djavan B, Marberger M. 1999. A meta-analysis on the efficacy and tolerability of alpha-1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. *Eur Urol*, 36:1–13.

- Elhilali MM, Ramsey EW, Barkin J, et al. 1996. A multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of terazosin in the treatment of benign prostatic hyperplasia. *Urology*, 47:335–42.
- Fawzy A, Braun K, Lewis GP, et al. 1995. Doxazosin in the treatment of benign prostatic hyperplasia in normotensive patients: a multicenter study. *J Urol*, 154:105–9.
- Foglar R, Shibata K, Horie K, et al. 1995. Use of recombinant alpha 1-adrenoceptors to characterize subtype selectivity of drugs for the treatment of prostatic hypertrophy. *Eur J Pharmacol*, 288:201–7.
- Fong YK, Milani S, Djavan B. 2005a. Natural history and clinical predictors of clinical progression in benign prostatic hyperplasia. *Curr Opin Urol*, 15:35–8.
- Fong YK, Milani S, Djavan B. 2005b. Role of phytotherapy in men with lower urinary tract symptoms. *Curr Opin Urol*, 15:45–8.
- Forray C, Bard JA, Wetzel JM, et al. 1994. The alpha 1-adrenergic receptor that mediates smooth muscle contraction in human prostate has the pharmacological properties of the cloned human alpha 1c subtype. *Mol Pharmacol*, 45:703–8.
- Fowler FJ Jr, Wennberg JE, Timothy RP, et al. 1988. Symptom status and quality of life following prostatectomy. *JAMA*, 259:3018–22.
- Frankel SJ, Donovan JL, Peters TI, et al. 1998. Sexual dysfunction in men with lower urinary tract symptoms. *J Clin Epidemiol*, 51:677–85.
- Gerber GS, Kuznetsov D, Johnson BC, et al. 2001. Randomized, double-blind, placebo-controlled trial of saw palmetto in men with lower urinary tract symptoms. *Urology*, 58:960–4, discussion 964–5.
- Gillenwater JY, Conn RL, Chrysant SG, et al. 1995. Doxazosin for the treatment of benign prostatic hyperplasia in patients with mild to moderate essential hypertension: a double-blind, placebo-controlled, dose-response multicenter study. *J Urol*, 154:110–15.
- Gormley GJ, Stoner E, Bruskevitz RC, et al. 1992. The effect of finasteride in men with benign prostatic hyperplasia. The Finasteride Study Group. *N Engl J Med*, 327:1185–91.
- Guay DRP. 2004. Extended-release alfuzosin hydrochloride: A new alpha-adrenergic receptor antagonist for symptomatic benign prostatic hyperplasia. *Am J Geriatr Pharmacother*, 2:14–23.
- Gwinup G. 1988. Oral phentolamine in nonspecific erectile insufficiency. *Ann Intern Med*, 109:162–3.
- Hald T, Nordling J, Andersen JT, et al. 1991. A patient weighted symptom score system in the evaluation of uncomplicated benign prostatic hyperplasia. *Scand J Urol Nephrol Suppl*, 138:59–62.
- Hedlund H, Andersson KE, Ek A. 1983. Effects of prazosin in patients with benign prostatic obstruction. *J Urol*, 130:275–8.
- Höfner K, Claes H, De Reijke TM, et al. 1999. Tamsulosin 0.4 mg once daily: effect on sexual function in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. *Eur Urol*, 36:335–41.
- Ishani A, MacDonald R, Nelson D, et al. 2000. Pygeum africanum for the treatment of patients with benign prostatic hyperplasia: a systematic review and quantitative meta-analysis. *Am J Med*, 109:654–64.
- Jacobsen SJ, Jacobson DJ, Girman CJ, et al. 1997. Natural history of prostatism: risk factors for acute urinary retention. *J Urol*, 158:481–7.
- Jenkins EP, Andersson S, Imperato-McGinley J, et al. 1992. Genetic and pharmacological evidence for more than one human steroid 5 alpha-reductase. *J Clin Invest*, 89:293–300.
- [JNC] Joint National Committee. 1997. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med*, 157:2413–46.
- Kelly JP, Kaufman DW, Kelley K, et al. 2005. Recent trends in use of herbal and other natural products. *Arch Intern Med*, 165:281–6.
- Kirby RS. 1995. Efficacy of doxazosin in normotensive and hypertensive patients with benign prostatic hyperplasia. *Scand J Urol Nephrol Suppl*, 168:29–33.
- Kirby RS, Andersen M, Gratzke P, et al. 2001. A combined analysis of double-blind trials of the efficacy and tolerability of doxazosin-gastrointestinal therapeutic system, doxazosin standard and placebo in patients with benign prostatic hyperplasia. *BJU Int*, 87:192–200.
- Kirby RS, Roehrborn C, Boyle P, et al. 2003. 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*, 61:119–26.
- Lepor H. 1990. Role of long-acting selective alpha-1 blockers in the treatment of benign prostatic hyperplasia. *Urol Clin North Am*, 17:651–9.
- Lepor H. 1995. Long-term efficacy and safety of terazosin in patients with benign prostatic hyperplasia. *Urology*, 45:406–13.
- Lepor H. 1998. Phase III multicenter placebo-controlled study of tamsulosin in benign prostatic hyperplasia. *Urology*, 51:892–900.
- Lepor H, Kaplan SA, Klimberg I, et al. 1997. Doxazosin for benign prostatic hyperplasia: long-term efficacy and safety in hypertensive and normotensive patients. The Multicenter Study Group. *J Urol*, 157:525–30.
- Lepor H, Williford WO, Barry MJ, et al. 1996. The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. *N Engl J Med*, 335:533–40.
- Lowe FC. 2005. Treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: sexual function. *BJU International*, 95:12–18.
- Lowe FC, Fagelman E. 1999. Phytotherapy in the treatment of benign prostatic hyperplasia: an update. *Urology*, 53:671–8.
- Lukacs B, Leplege A, Thibault P, et al. 1996. Prospective study of men with clinical benign prostatic hyperplasia treated with alfuzosin by general practitioners: 1-year results. *Urology*, 48:731–40.
- MacDonald D, McNicholas TA. 2003. Drug treatments for lower urinary tract symptoms secondary to bladder outflow obstruction: focus on quality of life. *Drugs*, 63:1947–62.
- MacDonald R, Wilt TJ. 2005. Alfuzosin for treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia: A systematic review of efficacy and adverse effects. *Urology*, 66:780–8.
- Macfarlane GJ, Botto H, Sagnier PP, et al. 1996. The relationship between sexual life and urinary condition in the French community. *J Clin Epidemiol*, 49:1171–6.
- Madsen P, Iversen P. 1983. A point system for selecting operative candidates. New York, Springer-Verlag.
- McAlister FA, Laupacis A, Wells GA, et al. 1999. Users' Guides to the Medical Literature: XIX. Applying clinical trial results B. Guidelines for determining whether a drug is exerting (more than) a class effect. *JAMA*, 282:1371–7.
- McConnell JD. 1990. Medical management of benign prostatic hyperplasia with androgen suppression. *Prostate Suppl*, 3:49–59.
- McConnell JD, Bruskevitz R, Walsh P, et al. 1998. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. *N Engl J Med*, 338:557–63.
- McConnell JD, Roehrborn CG, Bautista OM, et al. 2003. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med*, 349:2387–98.
- Meyhoff HH, Hald T, Nordling J, et al. 1993. A new patient weighted symptom score system (DAN-PSS-1). Clinical assessment of indications and outcomes of transurethral prostatectomy for uncomplicated benign prostatic hyperplasia. *Scand J Urol Nephrol*, 27:493–9.



- Mullan RJ, Bergstralh EJ, Farmer SA, et al. 2006. Growth factor, cytokine, and vitamin D receptor polymorphisms and risk of benign prostatic hyperplasia in a community-based cohort of men. *Urology*, 67:300–5.
- Narayan P, Evans CP, Moon T. 2003. Long-term safety and efficacy of tamsulosin for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia. *J Urol*, 170:498–502.
- Narayan P, Tewari A. 1998. A second phase III multicenter placebo controlled study of 2 dosages of modified release tamsulosin in patients with symptoms of benign prostatic hyperplasia. United States 93-01 Study Group. *J Urol*, 160:1701–6.
- Nordling J. 2005. Efficacy and safety of two doses (10 and 15mg) of alfuzosin or tamsulosin (0.4mg) once daily for treating symptomatic benign prostatic hyperplasia. *BJU Int*, 95:1006–12.
- O'Leary MP, Roehrborn C, Andriole G, et al. 2003. Improvements in benign prostatic hyperplasia-specific quality of life with dutasteride, the novel dual 5-reductase inhibitor. *BJU Int*, 92:262–6.
- Ok JH, Cambio A, Lara PN, et al. 2005. Is the use of anything but MVAC justified in the evidence-based medicine era? *Curr Opin Urol*, 15:312–14.
- Palacio A, Hernandez C, Marques A, et al. 2004. Long-term study to assess the efficacy of tamsulosin in the control of symptoms and complications developed in patients with symptomatic benign prostatic hyperplasia (OMNICONROL study): first-year follow-up report. *Arch Esp Urol*, 57:451–60.
- Peters CA, Walsh PC. 1987. The effect of nafarelin acetate, a luteinizing-hormone-releasing hormone agonist, on benign prostatic hyperplasia. *N Engl J Med*, 317:599–604.
- Rhodes PR, Krogh RH, Bruskwitz RC. 1999. Impact of drug therapy on benign prostatic hyperplasia-specific quality of life. *Urology*, 53:1090–8.
- Rhodes T, Girman CJ, Jacobsen SJ, et al. 1999. Longitudinal prostate growth rates during 5 years in randomly selected community men 40 to 79 years old. *J Urol*, 161:1174–9.
- Richardson CD, Donatucci CF, Page SO, et al. 1997. Pharmacology of tamsulosin: saturation-binding isotherms and competition analysis using cloned alpha 1-adrenergic receptor subtypes. *Prostate*, 33:55–9.
- Roberts RO, Bergstralh EJ, Farmer SA, et al. 2006. Polymorphisms in genes involved in sex hormone metabolism may increase risk of benign prostatic hyperplasia. *The Prostate*, 66:392–404.
- Roberts RO, Jacobsen SJ, Jacobson DJ, et al. 2000. Longitudinal changes in peak urinary flow rates in a community based cohort. *J Urol*, 163:107–13.
- Roberts RO, Lieber MM, Jacobson DJ, et al. 2005. Limitations of using outcomes in the placebo arm of a clinical trial of benign prostatic hyperplasia to quantify those in the community. *Mayo Clin Proc*, 80:759–64.
- Roehrborn CG, Boyle P, Nickel JC, et al. 2002. Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. *Urology*, 60:434–41.
- Roehrborn CG, Lukkariinen O, Mark S, et al. 2005. Long-term sustained improvement in symptoms of benign prostatic hyperplasia with the dual 5 alpha-reductase inhibitor dutasteride: results of 4-year studies. *BJU Int*, 96:572–7.
- Roehrborn CG, Malice MP, Cook TJ, et al. 2001. Clinical predictors of spontaneous acute urinary retention in men with LUTS and clinical BPH: a comprehensive analysis of the pooled placebo groups of several large clinical trials. *Urology*, 58:210–16.
- Roehrborn CG, Oesterling JE, Auerbach S, et al. 1996. The hytrin community assessment trial study: A one-year study of terazosin versus placebo in the treatment of men with symptomatic benign prostatic hyperplasia. *Urology*, 47:159–68.
- Roehrborn CG, and Schwinn DA. 2004. Alpha1-adrenergic receptors and their inhibitors in lower urinary tract symptoms and benign prostatic hyperplasia. *J Urol*, 171:1029–35.
- Roehrborn CG, Van Kerrebroeck P, Nordling J. 2003. Safety and efficacy of alfuzosin 10 mg once-daily in the treatment of lower urinary tract symptoms and clinical benign prostatic hyperplasia: a pooled analysis of three double-blind, placebo-controlled studies. *BJU Int*, 92:257–61.
- Rule AD, Jacobson DJ, McGree ME, et al. 2005. Longitudinal changes in post-void residual and voided volume among community dwelling men. *J Urol*, 174:1317–21, discussion 1321–2, author reply 1322.
- Sarma AV, Jacobsen SJ, Girman CJ, et al. 2002. Concomitant longitudinal changes in frequency of and bother from lower urinary tract symptoms in community dwelling men. *J Urol*, 168:1446–52.
- Schulman CC, Lock TM, Buzelin JM, et al. 2001. Long-term use of tamsulosin to treat lower urinary tract symptoms/benign prostatic hyperplasia. *J Urol*, 166:1358–63.
- Smith TJ, Somerfield MR. 1997. The ASCO experience with evidence-based clinical practice guidelines. *Oncology (Williston Park)*, 11: 223–7.
- Stachon A, Schluter T, Junker K, et al. 2004. The secretion of endothelin-1 by microvascular endothelial cells from human benign prostatic hyperplasia is inhibited by vascular endothelial growth factor. *Growth Factors*, 22:281–9.
- Thigpen AE, Silver RI, Guileyardo JM, et al. 1993. Tissue distribution and ontogeny of steroid 5 alpha-reductase isozyme expression. *J Clin Invest*, 92:903–10.
- Vallancien G, Emberton M, Harving N, et al. 2003. Sexual dysfunction in 1,274 European men suffering from lower urinary tract symptoms. *J Urol*, 169:2257–61.
- van Moorselaar RJ, Hartung R, Emberton M, et al. 2005. Alfuzosin 10 mg once daily improves sexual function in men with lower urinary tract symptoms and concomitant sexual dysfunction. *BJU Int*, 95:603–8.
- Verhamme KMC, Dieleman JP, Bleumink GS, et al. 2003. Treatment strategies, patterns of drug use and treatment discontinuation in men with LUTS suggestive of benign prostatic hyperplasia: the Triumph Project. *Eur Urol*, 44:539–45.
- Vermeulen A, Giagulli VA, De Schepper P, et al. 1989. Hormonal effects of an orally active 4-azasteroid inhibitor of 5 alpha-reductase in humans. *Prostate*, 14:45–53.
- Walsh PC, Retik AB, Vaughan ED, et al. 2002. *Campbell's Urology*, 8th ed, Philadelphia: WB Saunders.
- Wei JT, Calhoun E, Jacobsen SJ. 2005. Urologic diseases in America project: benign prostatic hyperplasia. *J Urol*, 173:1256–61.
- Wright EJ, Fang J, Metter EJ, et al. 2002. Prostate specific antigen predicts the long-term risk of prostate enlargement: results from the Baltimore Longitudinal Study of Aging. *J Urol*, 167:2484–7, discussion 2487–8.
- Wyllie MG. 2005. Evergreening: there's life in the old drug yet. *BJU Int*, 95:1359–60.