

Treatment and Pharmacologic Management of BPH in the Context of Common Comorbidities

Michael P. O'Leary, MD, MPH

Abstract

Benign prostatic hyperplasia (BPH) is extremely common in the aging man and may cause significant lower urinary tract symptoms (LUTS) necessitating treatment. Drug treatment is the mainstay of treatment for symptomatic BPH and is directed at relaxing prostatic smooth muscle, reducing prostate volume, or a combination of these effects. The most commonly used drugs for this indication are alpha₁-adrenergic receptor antagonists, which relax prostatic smooth muscle, and 5-alpha-reductase inhibitors, which reduce prostatic androgen levels and consequently prostate size. Invasive interventions include the gold standard, transurethral resection of the prostate (TURP), and several minimally invasive surgical options. Although effective in alleviating symptoms, TURP carries a higher risk of morbidity and complications, including sexual side effects (mainly ejaculatory dysfunction), than medical therapy or minimally invasive techniques. Treatment for BPH, whether medical or surgical, must take patients' comorbid conditions into consideration so that LUTS may be effectively relieved, with the smallest risk of exacerbating any concomitant conditions.

(*Am J Manag Care.* 2006;12:S129-S140)

The progressive development of benign prostatic hyperplasia (BPH)-associated lower urinary tract symptoms (LUTS) is the principal reason patients seek treatment.¹ Bothersome LUTS associated with BPH include urinary hesitancy and intermittency, weak urine stream, nocturia, frequency, urgency, and the sensation of incomplete bladder emptying.^{2,3} Pharmacologic treatments are aimed at modifying 1 or both components of BPH, ie, the increased tone of prostatic smooth muscle, and the enlarged prostate gland.^{3,4}

Despite the high prevalence of BPH, not all men develop LUTS, and the risk for developing major complications, such as acute urinary retention (AUR), over time is unclear.³ Accordingly, the decision to imple-

ment treatment for BPH-associated LUTS depends largely on the degree of symptom bother and its impact on the patient's quality of life (QOL).^{1,3}

Pharmacologic treatment is often considered the first line of therapy for patients with moderate-to-severe symptoms. Transurethral resection of the prostate (TURP) remains the gold standard for invasive treatment; however, a number of minimally invasive surgical therapies are also now available.³

As was described in the previous article, BPH in the aging male population frequently exists concomitant with other disorders such as hypertension, diabetes, and erectile dysfunction (ED).^{1,5-7} Concomitant conditions should be noted when evaluating patients for BPH therapy, because their presence may affect the choice of treatment, its efficacy, and long-term tolerability. In this article, we examine the current treatment options for BPH-associated LUTS, with an emphasis on pharmacologic therapy in those patients having 1 or more age-related comorbidities.

BPH: Watchful Waiting

Given that not all men with pathologic evidence of BPH may go on to develop bothersome LUTS, some individuals can be managed by watchful waiting, with therapy implemented only if and when symptoms become troublesome enough. The American Urological Association (AUA) defines such patients as having mild symptoms (AUA Symptom Index [SI] score of ≤ 7 points), or

Corresponding author: Michael O'Leary, MD, Brigham and Women's Hospital, ASB II-3, 45 Francis Street, Boston, MA 02115. Tel: 617-732-6425; Fax: 617-566-3475; E-mail: moleary1@partners.org.

Editorial assistance in the preparation of this manuscript was provided by Insight Medical Communications.

as those with moderate-to-severe symptoms (AUA SI score ≥ 8 points) who are not bothered by their symptoms.³ Because the degree of symptom distress that patients are willing to tolerate can vary greatly, watchful waiting may be a useful approach even for those with high symptom scores. Bother-some symptoms can sometimes be sufficiently reduced with minor lifestyle modifications (eg, decreasing fluid intake at bedtime, reducing caffeine and alcohol intake).³

BPH: Pharmacologic Treatments

Rationale and Overview. The primary pharmacologic therapies for LUTS associated with BPH are the α_1 -selective adrenergic receptor (α_1 -AR) antagonists and the 5- α -reductase inhibitors (5- α RI), with the former most commonly used. α_1 -ARs have been shown to play an important role in the sympathetic control of prostatic muscle contraction.⁴ There are 3 known subtypes of α_1 -ARs (α_{1A} , α_{1B} , α_{1D}); the expression of the α_{1A} receptor predominates in the prostate (70%) and mediates its contractile response.⁴ All α_1 -AR antagonist drugs bind to the α_{1A} subtype, effectively reducing prostatic smooth muscle tone, and therefore relieving bladder outlet tension and increasing urinary flow.⁴ Terazosin, doxazosin, and alfuzosin are α_1 -AR antagonists that show equal affinity for all α_1 -AR subtypes; thus, they are categorized as nonsubtype selective.⁸⁻¹⁰ Tamsulosin was designed to have a higher affinity for the α_{1A} - and α_{1D} -ARs, while showing less affinity for the α_{1B} subtype, which is found in vascular tissue; the α_{1D} subtype is believed to be associated with bladder muscle contraction.⁸⁻¹² Hence, it is known as subtype selective.

Growth of the prostate depends on androgens; modulation of androgenic activity may effectively reduce prostate volume in men with BPH.^{4,13} The inhibition of prostate 5- α -reductase with the 5- α RI dutasteride and finasteride blocks the conversion of testosterone by the enzyme 5- α -reductase to its metabolite, 5- α -dihydrotestosterone (DHT). Finasteride is a competitive inhibitor of the type 2 isoform of 5- α -reductase, whereas dutasteride blocks both type 1 and type 2 isoforms, creating a stable enzyme complex from which dissociation is slow.^{14,15} The

type 2 isozyme is active mostly in reproductive tissues, whereas the type 1 isozyme also catalyzes the formation of DHT in the skin and liver; the blockade of both subtypes by dutasteride results in more suppression of DHT synthesis.¹⁴⁻¹⁶ Both finasteride and dutasteride act to reduce androgen-dependent increases in prostatic volume^{3,4,13}; however, adequate symptomatic relief may require several months of therapy.³

Combination therapy with an α_1 -AR and a 5- α RI, used for rapid symptomatic relief and gradual, concomitant reduction in prostate size, is another treatment option that has been investigated in several trials.¹⁷⁻¹⁹

Nonsubtype-selective α -Blockers. Nonsubtype-selective α_1 -AR antagonists include alfuzosin, doxazosin, and terazosin. All have comparable efficacy for the management of LUTS caused by BPH when titrated to the appropriate dose,²⁰ and their long-term efficacy and safety have been reported in various studies. However, all 3 drugs were developed as antihypertensive agents and as such have effects on vasodilation and blood pressure,²⁰⁻²⁴ although studies suggest that the effects are greater in hypertensive than normotensive patients.

Terazosin has been evaluated in 2 long-term studies. The first, a 42-month, open-label extension study (N = 494), reported that terazosin-treated subjects showed a significant improvement in total Boyarsky scores, a measure of LUTS severity, in the first 3 months ($P < .05$ for each time point).²⁵ These effects were sustained through the end of the trial. Three of the 4 most commonly reported adverse events (dizziness [7.0%], asthenia [4%], somnolence [2%], and headache [1.0%]) were vasodilatory in nature. Clinically significant reductions in systolic (12-15 mm Hg) and diastolic (11-12 mm Hg) blood pressure were also observed in hypertensive patients treated with terazosin; these effects were observed regardless of concomitant antihypertensive therapy. Decreases in blood pressure were not observed in normotensive patients, suggesting that the vasodilatory properties of terazosin may be exaggerated in patients with abnormal regulation of blood pressure.²⁵

Similar observations were reported in another, 12-month placebo-controlled study (N = 2084).²⁶ Terazosin-treated subjects had significant, progressive improvements in symptomatic and QOL assessments during weeks 4 through 17; these effects were sustained from 17 weeks through the end of the trial. As was the case in the previous study,²⁵ the most commonly occurring adverse events were mostly vasodilatory or cardiovascular (CV) in nature and included dizziness (11.7% for terazosin-treated subjects vs 5.8% for placebo subjects; $P \leq .001$), asthenia (7.5% vs 2.9%; $P \leq .001$), peripheral edema (4.0% vs 0.9%; $P < .001$), and chest pain (3.9% vs 1.7%; $P = .01$). Postural dizziness and hypotension were more frequent in the terazosin arm of the study. In a third study, normotensive and hypertensive patients treated with terazosin for BPH had statistically significant reductions in blood pressure during single-blind treatment.²³ Dizziness was the most common adverse event and cause of discontinuation.

Similarly, studies have been done with doxazosin, including a long-term, open-label extension study of doxazosin (N = 450) that showed a sustained improvement in BPH symptoms and urodynamic parameters in patients who were maintained on therapy for up to 48 months.²¹ Frequently reported adverse events were mostly vasodilatory in nature; their incidence increased with dose and included dizziness (18.7% vs 6.7%), fatigue (10.3% vs 2.7%), hypotension (3.9% vs 0%), and edema (3.4% vs 1.3%) (values are for doxazosin-treated subjects vs placebo subjects, respectively). Decreases in blood pressure were also observed and occurred more frequently among hypertensive than normotensive patients.²¹ These findings were corroborated by results from a pooled analysis of 7 placebo-controlled studies using doxazosin for the treatment of BPH.²⁷ The most common adverse events related to doxazosin were fatigue, headache, and dizziness; reductions in blood pressure were observed in both older (>65 years) and younger (<65 years) normotensive patients.²⁷

Thus, adverse events associated with terazosin and doxazosin relate in part to their vasodilatory properties and nonspecific effects on other α_1 -ARs, and these may com-

promise long-term tolerability for some patients. Another disadvantage of these drugs is that, owing to their vasodilatory effects, they require titration to their optimal dose, which can delay symptom alleviation in patients with BPH.^{20,28}

Alfuzosin is another nonsubtype-selective α_1 -AR antagonist. The efficacy of alfuzosin is similar to that of other α_1 -AR antagonists, with significant improvement in the International Prostate Symptom Score (IPSS) and significant increases in mean peak flow rate (Q_{max}) (observed in double-blind, placebo-controlled studies).^{24,29,30} Although alfuzosin (10 mg once daily) is better tolerated than doxazosin or terazosin, its use is nevertheless also associated with vasodilatory adverse events. Dizziness was the most or second most frequently occurring adverse event in the above studies, with an incidence ranging from 2.5% to 6.1%.^{29,30} The percentage of patients with asymptomatic orthostatic hypotension (defined as a decrease of 20 mm Hg or greater upon standing) ranged between 2.1% and 2.8%.

Additionally, several long-term studies on the efficacy and safety of alfuzosin have been reported. Two successive 12-month open-label extensions of a French 6-month placebo-controlled study of alfuzosin 2.5 mg 3 times daily (N = 518; N = 131 in first extension study, N = 50 in second) showed that mean Boyarsky scores, mean flow rate, and postvoid residual urine volume were significantly improved from baseline at 12 months ($P < .01$), with patients remaining urodynamically stable for up to 30 months.^{31,32} Vasodilatory side effects (vertigo [3%], malaise [0.74%], postural hypotension [0.74%], and headache [0.74%]) were reported by 5.3% of patients during the first 12-month extension period; dizziness was reported by 4% of subjects in the second extension period.^{31,32}

Sustained efficacy was also reported in other open-label studies of alfuzosin 2.5 mg 3 times daily, with sustained reductions in symptomatic scores up to 12 and 36 months.^{33,34} Both of these studies reported that many of the main adverse events were vasodilatory in nature, with the earlier study listing vertigo (1.3%), dizziness (0.8%), malaise (0.7%), headache (0.6%), hypotension (0.4%), and palpitations (0.3%).³³ The Italian Alfuzosin

Co-Operative Group reported a 3.9% incidence of vasodilatory adverse events in the study population, with hypotension, the most common adverse event, occurring in 2.6% of trial subjects.³⁴

Similar observations were noted for the long-term efficacy and safety of alfuzosin 10 mg given once daily, the currently available formulation.³⁵ In a 9-month open-label extension of the 3-month double-blind study described earlier (N = 311), significant reductions in IPSS scores were sustained at 12 months (-7.5 points from baseline, $P < .001$). Vasodilatory adverse events occurred in 4.4% of subjects; orthostatic hypotension was reported in 2.8% of subjects, dizziness in 2.5%, and headache in 1.4% of study subjects.²⁹ As was the case with terazosin, vasodilatory adverse events were more common among hypertensive (5.7%) than normotensive subjects (3.9%).²⁹ Thus, although alfuzosin is better tolerated than doxazosin or terazosin, it is nevertheless associated with several vasodilatory or CV adverse events.

The efficacy and safety of nonsubtype-selective α_1 -AR antagonists have been compared in recent clinical studies. The efficacy of doxazosin was compared with that of terazosin in a 3-month randomized study with crossover nonresponders.³⁶ Significant improvements in IPSS ($P < .01$ for each), as well as in Q_{\max} ($P < .001$ for each), were noted for both doxazosin and terazosin. Patients who did not show any improvements switched their drug. Fifteen of 19 patients who switched did not show any improvement in either IPSS or Q_{\max} .

In a comparative study of doxazosin and alfuzosin, doxazosin was found to have significantly greater effects on IPSS ($P < .001$), although both agents had comparable efficacy for maximum and mean flow rates.³⁷ In addition, both agents were comparable in terms of safety and tolerability.³⁷

Selective α -Blockers. Tamsulosin is unique among the α -AR antagonists available for the treatment of BPH, in that it was designed to selectively antagonize the α_{1A} -AR, which as noted above is predominant in the prostate and is the primary mediator of its contractile response.⁴ Subtype selectivity of tamsulosin allows for efficacy in alleviating BPH symp-

toms without the vasodilatory side effects that may be attributable to nonsubtype-selective receptor binding. In addition, unlike some nonselective agents (eg, terazosin, doxazosin), tamsulosin does not require titration to an effective dose, owing to its comparatively lower action on blood vessel adrenoceptors.^{38,39}

A recent analysis of 14 randomized studies using tamsulosin for BPH (4122 subjects) showed that tamsulosin was as effective as other α -blocker therapies in improving symptom scores and peak flow rates relative to placebo. However, in most cases, the incidence of dizziness in tamsulosin-treated subjects was comparable to that of placebo.⁴⁰ In a meta-analysis comparing tamsulosin with terazosin or alfuzosin, the incidence of dizziness in subjects treated with tamsulosin was approximately 25% of that observed in patients treated with terazosin and comparable to that observed in patients treated with alfuzosin.⁴⁰ Another analysis of two phase 3 randomized trials showed tamsulosin 0.4 or 0.8 mg/day to be effective in alleviating BPH symptoms, with a rapid onset of action, no orthostatic changes, no clinically or statistically significant changes in blood pressure, and no alterations in laboratory or electrocardiographic findings compared with placebo.⁴¹

The therapeutic benefit of tamsulosin over nonselective α -blocker therapy (terazosin) has been demonstrated in a recent open-label, randomized, 11-week study. Patients (N = 1993) with symptomatic BPH and LUTS were treated with tamsulosin (0.4 mg/day) or terazosin (5 mg/day after titration).²⁸ A significant difference in the AUA SI score reduction between tamsulosin and terazosin was observed after 4 days of treatment in the total population as well as in those with moderate or severe LUTS (**Table 1**).²⁸ Of note, α_1 -AR-associated adverse events were significantly less frequent in the tamsulosin-treated patients (**Table 1**). This resulted in fewer treatment discontinuations with tamsulosin (4.3% vs 6.6% for terazosin).²⁸

The long-term efficacy and safety of tamsulosin 0.4 mg and 0.8 mg once daily has been investigated in several studies. In a 10-month extension (N = 418) of a 13-week double-blind trial, symptomatic relief was

Table 1. Efficacy and Safety of Tamsulosin and Terazosin in Patients With BPH and LUTS

Efficacy/Safety End Point	Tamsulosin	Terazosin	P value
	n = 1002	n = 981	
Δ AUA SI score (day 4—all patients)	-4.8	-3.4	<.001
Δ AUA SI score (day 4—patients with moderate BPH)	-3.5	-2.9	.026
Δ AUA SI score (day 4—patients with severe BPH)	-6.6	-4.8	<.001
Dizziness (% patients)	5.5	12.1	<.001
Somnolence (% patients)	0.9	3.0	.001

BPH indicates benign prostatic hyperplasia; LUTS, lower urinary tract symptoms; Δ, change in; AUA SI, American Urological Association Symptom Index.

Source: Reference 28.

comparable between dosing arms, with significant reductions in AUA SI scores (-9.4 points and -9.7 points, respectively) maintained over the combined 53-week course of therapy.⁴² The incidence of CV adverse events was comparable between both tamsulosin groups and placebo; no clinically significant differences were found among patient subgroups in blood pressure or pulse rate.

These results were corroborated in a 48-month open-label study (N = 609) that extended up to 6 years (N = 109).⁴³ Sustained, significant improvement from baseline was reported for QOL ($P < .001$), AUA SI subset scores ($P < .05$), and Boyarsky symptom scores ($P < .05$) throughout the 6-year study period. Orthostatic hypotension was observed in 1.3% of study subjects. Dizziness, postural hypotension, and syncope each led 0.2% of patients to withdraw from the study.⁴³ Thus, the efficacy, safety, and tolerability of tamsulosin in patients with BPH are well established, with a minimal incidence of vasodilatory adverse events.

5- α RIIs. The 5- α RIIs used in the treatment of BPH include finasteride and dutasteride. As previously discussed, dutasteride is a dual inhibitor of type 1 and type 2 5- α -reductase,⁴⁴ whereas finasteride inhibits type 2 alone.¹⁵ These drugs are indicated for men with enlarged prostates (with no evidence of prostate cancer) in addition to BPH symptoms.^{14,15} Indeed, baseline prostate size appears to be an important determinant of therapeutic response to 5- α RIIs, in that the larger the prostate, the greater the improve-

ment in symptom score and flow rate.^{13,15,45} As noted above, these drugs effectively reduce prostate gland sizes by 15% to 25% versus baseline.^{14,15,45}

Since the release of finasteride in the United States more than 10 years ago, long-term use of this agent has been shown to significantly reduce the risk of both AUR and BPH-related surgery in patients with LUTS caused by BPH.¹⁹ Interestingly, benefits from treatment with finasteride were also noted in men with smaller glands; finasteride has also been shown to significantly improve symptom score parameters and urinary flow rates, albeit to a more modest degree.^{13,46,47}

Dutasteride has also demonstrated efficacy in reducing the risk of AUR and BPH-related surgery. Investigators for a 24-month, double-blind, placebo-controlled trial of dutasteride in BPH reported a 57% risk reduction for AUR and a 48% risk reduction for surgical intervention.⁴⁸ Significant reductions in prostate volume size, as well as improvement in AUA SI scores, were also observed in the 24-month study.⁴⁸

Because of their mode of action, however, 5- α RIIs may take longer than α_1 -AR antagonists to relieve LUTS.³ In 1 study, the efficacy of finasteride (5 mg/day; n = 204) was compared with that of tamsulosin (0.4 mg/day; n = 199) after 26 weeks of treatment.⁴⁹ Both treatments were well tolerated, with an equivalent incidence of adverse events; however, tamsulosin was more effective in reducing the total Symptom Problem Index (SPI) (Table 2).⁴⁹ These differences were evident for both SPI and Q_{max} as early

Table 2. Improvement in Symptom Problem Index (SPI) in Patients Treated With Finasteride or Tamsulosin at Week 26

	Tamsulosin (n = 199)	Finasteride (n = 204)
Reduction in SPI (points)*	-5.2	-4.5
Improvement (%)*	-37	-31

*P = .055 for intent-to-treat population; P = .032 for per-protocol population. Source: Reference 49.

as the first week and were maintained until the end of the study.

Long-term therapy with finasteride has been well tolerated, with 56% of patients (n = 43) in 1 multicenter North American extension study judged as successfully treated, and with no new adverse events or apparent cumulative effects of the drug after 10 years of follow-up.⁵⁰ Similarly, a 2-year, open-label extension study of dutasteride has shown significant improvements in AUA SI score and Q_{max} at 24 months and 48 months of treatment in patients treated who continued on dutasteride compared with patients who crossed over to dutasteride from placebo, with no new safety issues identified over the treatment period.⁴⁴ The most comprehensive assessment of 5-αRIs in the treatment of BPH, however, comes from the Medical Therapy of Prostatic

Table 3. Reduction in Rate of Overall Clinical Progression in the Medical Therapy of Prostatic Symptoms Trial

Clinical Progression*	Placebo (n = 737)	Doxazosin (n = 756)	Finasteride (n = 768)	Combination (n = 786)
Rate/100 person-years	4.5	2.7	2.9	1.5
Reduction vs placebo (%)	—	39 [†]	34 [‡]	66 ^{†§}

*Defined as first occurrence of increase in AUA SI of ≥4 points, AUR, renal insufficiency, recurrent urinary tract infection, or urinary incontinence.

[†]P < .001 vs placebo.

[‡]P = .002 vs placebo.

[§]P < .001 vs either treatment alone.

AUA SI indicates American Urological Association Symptom Index; AUR, acute urinary retention.

Source: Reference 19.

Symptoms (MTOPS) trial, which evaluated the efficacy of doxazosin, finasteride, or combination therapy versus placebo on BPH and LUTS in more than 3000 men over a 4.5-year mean follow-up.¹⁹

Combination Therapy

MTOPS Trial. An important goal of the MTOPS trial was to compare the efficacy and safety of combination therapy (an α-blocker and a 5-αRI) with that of either agent alone. Efficacy results did not show a significant difference between doxazosin and finasteride, but efficacy was significantly improved with combination therapy compared with doxazosin or finasteride alone (Table 3).¹⁹ The cumulative 4-year incidence of overall clinical progression in MTOPS was 17%, 10%, and 10% in the placebo, doxazosin, and finasteride groups, respectively, compared with 5% in the combination therapy arm (P < .001 vs placebo or either agent alone).¹⁹ Improvement in AUA SI was also significantly greater in the combination therapy group compared with the finasteride (P < .001) or doxazosin (P = .006) groups. Adverse events, however, were significantly increased in nearly all patients with combination therapy (Table 4).¹⁹ Despite the increase in adverse events, however, the percentage of patients discontinuing both drugs by study end was not greater in the combination arm (Table 4). It has been suggested that patients who will benefit the most from combination therapy are those at high risk of progression (ie, those with large prostates and high prostate-specific antigen values).⁵¹ The role of combination therapy in men with minimal prostatic enlargement is less clear and will require an individualized assessment of risks and benefits with the patient.

Prospective European Doxazosin and Combination Therapy (PREDICT) Trial.

The PREDICT trial was a randomized, placebo-controlled study that evaluated the utility of combination therapy compared with treatment with either doxazosin or finasteride alone.¹⁸ This trial did not address the question of disease progression, but rather assessed the effects of combination therapy on symptomatic relief. Although significant

Table 4. Ten Most Frequently Reported Adverse Events in the Medical Therapy of Prostatic Symptoms Trial Treatment Arms

Adverse Events	Rate Per 100 Person-years of Follow-up			
	Placebo	Doxazosin	Finasteride	Combination
Erectile dysfunction	3.32	3.56	4.53*	5.11*
Dizziness	2.29	4.41*	2.33	5.35*
Postural hypotension	2.29	4.03*	2.56	4.33*
Asthenia	2.06	4.08*	1.56	4.20*
Decreased libido	1.40	1.56	2.36*	2.51*
Abnormal ejaculation	0.83	1.10	1.78*	3.05*
Peripheral edema	0.66	0.88	0.72	1.25*
Dyspnea	0.57	0.93	0.56	1.20*
Allergic reaction	0.46	0.85*	0.58	0.73
Somnolence	0.37	0.82*	0.39	0.78*
Patients discontinuing therapy by study end (%)	—	27	24	18

* $P < .05$ vs placebo.

Source: Adapted with permission from Reference 19.

improvement was reported in symptom scores and urinary flow rates in both the doxazosin and combination therapy arms compared with placebo or finasteride alone ($P < .05$), the addition of finasteride to doxazosin did not offer any advantage in symptomatic relief over a 1-year period. Patients treated with combination therapy did not experience AUR or require TURP; however, this trial was not designed or statistically powered to detect differences among treatment groups in this regard.

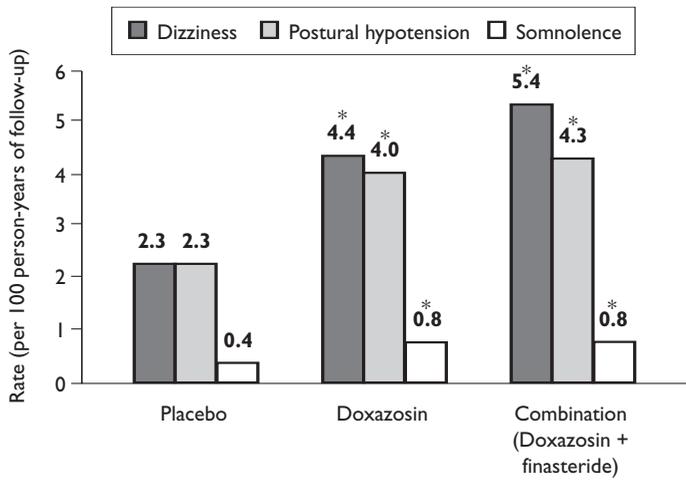
The most frequently reported adverse events for doxazosin-treated subjects (>5%) were dizziness (15.6%), asthenia (10.5%), postural hypotension (5.8%), impotence (5.8%), and hypotension (5.1%). The incidence of several adverse events in the doxazosin arm (dizziness, asthenia, postural hypotension, hypotension) was significantly greater compared with the placebo and finasteride arms ($P < .05$ for each). Frequent adverse events reported for subjects in the finasteride arm (>3%) included dizziness (8%), impotence (4.9%), asthenia (4.2%), and hypertension (4.2%). Subjects in the combination arm reported dizziness (13.6%), impotence (10.5%), and asthenia (9.1%) as the most frequently occurring adverse events (>5%).¹⁸

Symptom Management After Reducing Therapy (SMART) Study. Combination therapy may be useful in managing patients with severe symptoms. The SMART study compared the effects of a combination of dutasteride and tamsulosin over a 36-week period with subjects randomized to continue combination therapy or switch to dutasteride monotherapy at week 24.¹⁷ Among subjects with severe symptoms (IPSS ≥ 20), 42.5% of those who were switched to dutasteride monotherapy experienced a worsening of symptoms, compared with 14% in the continuation group.¹⁷

When prescribing medical therapy for BPH, several factors should be considered: the patient's degree of prostate enlargement, the medication's onset of action, symptomatic relief, and tolerability.

BPH Treatment: Comorbidities and Concomitant Medications. Because treatment for BPH and LUTS is generally initiated in older men who are more likely to have concomitant medical conditions, the choice of therapy should always factor in these comorbidities. Nonselective α_1 -AR antagonists (eg, terazosin) have been found to reduce both systolic and diastolic blood pressure and

Figure 1. Fall-related Side Effects in the Medical Therapy of Prostatic Symptoms Trial Treatment Arms



**P* < .05 vs placebo.
Source: Reference 19.

heart rate to a greater degree than subtype-selective agents (eg, tamsulosin), and most of these effects are observed on titration of the nonselective agent to its full dose.²⁸ Of importance, these treatment effects are observed irrespective of the patient's baseline hypertensive status.²⁸ In addition, when considering drug treatment for BPH in the elderly, it is important to consider the potential for side effects that can precipitate a fall. Dizziness, orthostatic hypotension, and syncope are common in the elderly, and falls can be a significant cause of morbidity, disability, and mortality.⁵²⁻⁵⁴ In fact, a significantly higher occurrence of fall-related adverse events has been reported among patients receiving doxazosin therapy (as either monotherapy or in combination) in comparison with those patients receiving placebo (Figure 1).¹⁹ Because tamsulosin virtually does not affect blood pressure,^{55,56} it can be used safely in elderly men requiring BPH therapy who may be taking antihypertensive medications (eg, calcium channel blockers for CV disease). Thus, the patient's CV health should be considered when therapy for BPH is prescribed.

ED, which can have a dramatic impact on overall QOL, is also a significant problem for men as they age.^{57,58} Because a large percentage of men with BPH symptoms may also have ED,¹ the use of BPH therapies with the least effect on sexual function is highly

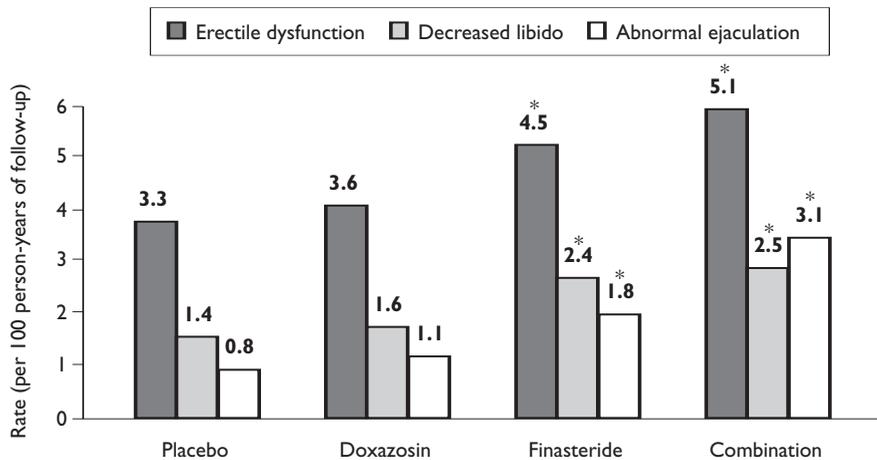
desirable. In addition, LUTS are regarded as a risk factor for the development of ED.⁵⁹ The MTOPS trial demonstrated that the safety profile of α_1 -AR antagonists is distinct from that of 5- α RI with respect to sexual side effects (Table 4).¹⁹ Sexual side-effect profiles also differ among drugs within the α_1 -AR antagonist class. The rate of ejaculation failure is higher with tamsulosin than with terazosin (2.1% vs 0% for tamsulosin and terazosin, *P* < .001). Tamsulosin-treated patients also had a greater rate of ejaculation disorder than patients treated with terazosin (3.7% vs 0.3%, respectively). However, the overall rates of these adverse events are low and not a major cause of treatment discontinuation.²⁸

Pooled data from 3 European studies (N = 830) further indicate that tamsulosin may significantly improve sexual function compared with no treatment (placebo), a result likely attributable to the effective treatment of LUTS by tamsulosin (*P* = .042).⁶⁰ Although abnormal ejaculation occurred at a higher frequency than in the placebo group, this was once again not a significant source of treatment discontinuation (3 patients; 0.8% of those in the tamsulosin group). Other more troublesome sexual side effects (impotence, decreased libido) occurred at low frequency; their incidence was not different from that seen with placebo or alfuzosin treatment.⁶⁰ These findings suggest that subtype-selective α_1 -adrenergic antagonist therapy for BPH can improve BPH symptoms and improve sexual function without compromising erectile function or libido.

The MTOPS trial confirmed that treatment with 5- α RI is associated with a higher rate of decreased libido and impotence than is the case with α_1 -AR antagonists (Figure 2).¹⁹ Although this treatment option is particularly beneficial in patients with demonstrated enlargement of the prostate, the sexual dysfunction associated with this treatment and need for long-term therapy should be presented to the patient to ensure an informed decision.³

Surgical and Minimally Invasive Therapies for BPH

Despite the efficacy and safety of pharmacotherapy, the surgical management of BPH

Figure 2. Sexual Side Effects in the Medical Therapy of Prostatic Symptoms Trial Treatment Arms

* $P < .05$ vs placebo.

Source: Reference 19.

is still recommended in certain situations, including the presence of refractory urinary retention, bladder stones, persistent gross hematuria, recurrent urinary tract infections, or renal insufficiency secondary to BPH.³ The selection of surgical treatment may be patient-driven, because it is usually more effective than pharmacotherapy⁶¹ and only 1 procedure is generally required in comparison with a lifetime of medication, although re-treatment may occasionally be necessary.³

Watchful waiting is often the prelude to surgical or pharmacologic treatment.⁶² If a patient decides on surgical treatment, several newer, minimally invasive outpatient procedures are gaining in popularity as alternatives to TURP; these include transurethral vaporization of the prostate (TUVAP), transurethral microwave thermotherapy of the prostate (TUMT), transurethral needle ablation (TUNA), and transrectal high-intensity focused ultrasound.⁶²

Although TURP is an effective intervention for BPH (nearly 90% chance of symptom improvement and 125% increase in Q_{max}), complications of the procedure may include a decline in sexual function, incontinence, retrograde ejaculation, and urethral stricture.⁶² In addition, the procedure is not recommended for those men wishing to

stay fertile.⁶² The newer alternatives to TURP generally have a lower risk of these side effects at the expense of somewhat lower efficacy.

A recent 5-year safety and efficacy study comparing TUNA and TURP ($N = 121$) revealed equivalent efficacy for the 2 procedures in terms of IPSS, QOL, and Q_{max} .⁶³ Retrograde ejaculation was not reported in the TUNA arm; this adverse event was noted in 41% of the TURP patients. Similarly, ED, incontinence, and stricture formation also occurred at a higher frequency with TURP compared with TUNA.⁶³ Another comparative study of TURP and TUNA ($N = 59$) showed no difference between the treatments in IPSS and QOL measures, although the increase in Q_{max} was higher with TURP.⁶⁴ In addition, although no complications occurred with TUNA, retrograde ejaculation, ED, incontinence, and urethral stricture occurred with TURP.⁶⁴ Other minimally invasive techniques have also been compared with TURP. In a 3-year follow-up study, TUVAP was compared with TURP in 104 patients with BPH.⁶⁵ Symptom improvement was comparable in both groups and was maintained up to 3 years; however, rates of impotence (TUVAP vs TURP, 17% vs 11%; P not significant) and retrograde ejaculation (72% vs 89%; P not

significant) were not different.⁶⁵ TUMT has been examined in a prospective, open-label, single-center study in 41 patients.⁶⁶ Response rate (IPSS <7; Q_{max} >15 mL/sec; or 50% improvement from baseline in either parameter) was 88% (29/33) at 12 months, with a significant improvement in IPSS, bother score, Q_{max} , and prostate volume (all $P < .001$). Bladder spasm and urinary tract infections were the most common adverse events, and coital ability was unchanged (from 71% at baseline to 74.3%); however, there was a slight decrease in patients' ejaculation ability (from 78% to 51.4%).⁶⁶

Overall, the newer, less invasive options to TURP may provide an adequate level of symptomatic relief with fewer of the more objectionable side effects of TURP—incontinence and impotence.

Conclusions

Medical intervention is the mainstay of treatment for patients with troublesome LUTS associated with BPH. Although the popularity of less invasive surgical options such as TUNA, TUVF, and TUMT is increasing, pharmacotherapy is likely to remain popular as a means of alleviating bothersome LUTS and preventing associated complications such as AUR. α_1 -AR antagonists provide effective and safe relief of BPH symptoms. However, there are clear benefits to drugs that are subtype-selective, including a rapid onset of symptomatic relief and a lower incidence of CV side effects such as orthostatic hypotension. Therapy with 5- α RI is also effective in reducing BPH symptoms, although a longer period may be required for full effect, and the benefit appears to be greatest in men with large prostates. Results from MTOPS show that combination therapy with α_1 -AR antagonists and 5- α RI is effective and safe for BPH, but some side effects, such as ED, reduced libido, dizziness, and postural hypotension, may prove troublesome in a small subset of patients. The selection of therapy for BPH should also be guided by the presence of other comorbid conditions such as CV disease, hypertension, diabetes, and ED, all of which are commonly seen in the same patient population.

REFERENCES

1. O'Leary MP. LUTS, ED, QOL: alphabet soup or real concerns to aging men? *Urology*. 2000;56(5 suppl 1):7-11.
2. Wei JT, Calhoun E, Jacobsen SJ. Urologic Diseases in America project: benign prostatic hyperplasia. *J Urol*. 2005;173:1256-1261.
3. AUA Practice Guidelines Committee. AUA guideline on management of benign prostatic hyperplasia (2003). Chapter 1: Diagnosis and treatment recommendations. *J Urol*. 2003;170(2 Pt 1):530-547.
4. Chapple CR. Selective α_1 -adrenoreceptor antagonists in benign prostatic hyperplasia: rationale and clinical experience. *Eur Urol*. 1996;29:129-144.
5. Boyle P, Napalkov P. The epidemiology of benign prostatic hyperplasia and observations on concomitant hypertension. *Scand J Urol Nephrol*. 1995;29:7-12.
6. Vasan RS, Beiser A, Seshadri S, et al. Residual lifetime risk for developing hypertension in middle-aged women and men: the Framingham Heart Study. *JAMA*. 2002;287:1003-1010.
7. National Diabetes Information Clearinghouse (NDIC). National Diabetes Statistics. NIH Publication No. 06-3892. November 2005. Available at: <http://diabetes.niddk.nih.gov/dm/pubs/statistics>. Accessed November 4, 2005.
8. Beduschi MC, Beduschi R, Oesterling JE. Alpha-blockade therapy for benign prostatic hyperplasia: from a nonselective to a more selective α_{1A} -adrenergic antagonist. *Urology*. 1998;51:861-872.
9. Foglar R, Shibata K, Horie K, Hirasawa A, Tsujimoto G. Use of recombinant α_1 -adrenoreceptors to characterize subtype selectivity of drugs for the treatment of prostatic hypertrophy. *Eur J Pharmacol*. 1995;288:201-207.
10. Richardson CD, Donatucci CF, Page SO, Wilson KH, Schwinn DA. Pharmacology of tamsulosin: saturation-binding isotherms and competition analysis using cloned alpha 1-adrenergic receptor subtypes. *Prostate*. 1997;33:55-59.
11. Hatano A, Takahashi H, Tamaki M, Komeyama T, Koizumi T, Takeda M. Pharmacological evidence of distinct alpha 1-adrenoreceptor subtypes mediating the contraction of human prostatic urethra and peripheral artery. *Br J Pharmacol*. 1994;113:723-728.
12. Schwinn DA, Michelotti GA. α_1 -adrenergic receptors in the lower urinary tract and vascular bed: potential role for the α_{1d} -subtype in filling symptoms and effects of ageing on vascular expression. *BJU Int*. 2000;85(suppl 2):6-11.
13. Boyle P, Lawrence G, Gould AL, Roehrborn CG. Prostate volume predicts outcome of benign prostatic hyperplasia with finasteride: meta-analysis of randomized clinical trials. *Urology*. 1996;48:398-405.
14. Avodart [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2005.
15. Proscar [package insert]. Whitehouse Station, NJ: Merck & Co, Inc; 2004.
16. Clark RV, Hermann DJ, Cunningham GR, Wilson TH, Morrill BB, Hobbs S. Marked suppression of dihydrotestosterone in men with benign prostatic hyperplasia by dutasteride, a dual 5 α -reductase inhibitor. *J Clin Endocrinol Metab*. 2004;89:2179-2184.
17. Barkin J, Guimaraes M, Jacobi G, Pushkar D, Taylor S, van Vierssen Trip OB. Alpha-blocker therapy can be withdrawn in the majority of men following initial com-

bination therapy with the dual 5 α -reductase inhibitor dutasteride. *Eur Urol.* 2003;44:461-466.

18. Kirby RS, Roehrborn C, Boule P, et al; Prospective European Doxazosin and Combination Therapy Study Investigators. Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. *Urology.* 2003;61:119-126.

19. McConnell JD, Roehrborn CG, Bautista OM, et al; Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med.* 2003;349:2387-2398.

20. Milani S, Djavan B. Lower urinary tract symptoms suggestive of benign prostatic hyperplasia: latest update on alpha-adrenoceptor antagonists. *BJU Int.* 2005;95(suppl 4): 29-36.

21. Lepor H, Kaplan SA, Klimberg I, et al. Doxazosin for benign prostatic hyperplasia: long-term efficacy and safety in hypertensive and normotensive patients. The Multicenter Study Group. *J Urol.* 1997;157:525-530.

22. de Mey C. Cardiovascular effects of alpha-blockers used for the treatment of symptomatic BPH. *Eur Urol.* 1998;34(suppl 2):18-28.

23. Kirby RS. Terazosin in benign prostatic hyperplasia: effects on blood pressure in normotensive and hypertensive men. *Br J Urol.* 1998;82:373-379.

24. Höfner K, Jonas U. Alfuzosin: a clinically uroselective α_1 -blocker. *World J Urol.* 2002;19:405-412.

25. Lepor H. Long-term efficacy and safety of terazosin in patients with benign prostatic hyperplasia. Terazosin Research Group. *Urology.* 1995;45:406-413.

26. Roehrborn CG, Oesterling JE, Auerbach S, et al. The Hytrin Community Assessment Trial study: a one-year study of terazosin versus placebo in the treatment of men with symptomatic benign prostatic hyperplasia. HYCAT Investigator Group. *Urology.* 1996;47:159-168.

27. Kaplan SA, D'Alisera PM. Tolerability of α -blockade with doxazosin as a therapeutic option for symptomatic benign prostatic hyperplasia in the elderly patient: a pooled analysis of seven double-blind, placebo-controlled studies. *J Gerontol A Biol Sci Med Sci.* 1998;53: M201-M206.

28. Narayan P, O'Leary MP, Davidai G. Early efficacy of tamsulosin versus terazosin in the treatment of men with benign prostatic hyperplasia: a randomized, open-label trial. *J Appl Res.* 2005;5:237-245.

29. van Kerrebroeck P, Jardin A, van Cangh P, Laval KU; ALFORTI Study Group. Long-term safety and efficacy of a once-daily formulation of alfuzosin 10 mg in patients with symptomatic benign prostatic hyperplasia: open-label extension study. *Eur Urol.* 2002;41:54-60.

30. Roehrborn CG, Van Kerrebroeck P, Nordling J. 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.* 2003;92:257-261.

31. Jardin A, Bensadoun H, Delauche-Cavallier MC, Attali P. Long-term treatment of benign prostatic hyperplasia with alfuzosin: a 12-18 month assessment. BPHALF Group. *Br J Urol.* 1993;72(5 Pt 1):615-620.

32. Jardin A, Bensadoun H, Delauche-Cavallier MC, Stalla-Bourdillon A, Attali P. Long-term treatment of benign prostatic hyperplasia with alfuzosin: a 24-30

month survey. BPHALF group. *Br J Urol.* 1994;74: 579-584.

33. Lukacs B, Grange JC, McCarthy C, Comet D. Clinical uroselectivity: a 3-year follow-up in general practice. BPA Group in General Practice. *Eur Urol.* 1998;33(suppl 2):28-33.

34. Safety, efficacy and impact on patients' quality of life of a long-term treatment with the α_1 -blocker alfuzosin in symptomatic patients with BPH. Italian Alfuzosin Co-Operative Group. *Eur Urol.* 2000;37:680-686.

35. Uroxatral [package insert]. New York, NY: Sanofi-Synthelabo, Inc; 2003.

36. Samli MM, Dincel C. Terazosin and doxazosin in the treatment of BPH: results of a randomized study with crossover in non-responders. *Urol Int.* 2004;73:125-129.

37. deReijke TM, Klarskov P. Comparative efficacy of two alpha-adrenoreceptor antagonists, doxazosin and alfuzosin, in patients with lower urinary tract symptoms from benign prostatic enlargement. *BJU Int.* 2004;93: 757-762.

38. Harada K, Ohmori M, Fujimura A. Comparison of the antagonistic activity of tamsulosin and doxazosin at vascular α_1 -adrenoceptors in humans. *Naunyn-Schmiedeberg's Arch Pharmacol.* 1996;354:557-561.

39. Harada K, Ohmori M, Kitoh Y, Sugimoto K, Fujimura A. A comparison of the antagonistic activities of tamsulosin and terazosin against human vascular α_1 -adrenoceptors. *Jpn J Pharmacol.* 1999;80: 209-215.

40. Wilt TJ, Mac Donald R, Rutks I. Tamsulosin for benign prostatic hyperplasia. *Cochrane Database Syst Rev.* 2003;(1):CD002081.

41. Narayan P, Bruskevitz R. A comparison of two phase III multicenter, placebo-controlled studies of tamsulosin in BPH. *Adv Ther.* 2000;17:287-300.

42. Lepor H. Long-term evaluation of tamsulosin in benign prostatic hyperplasia: placebo-controlled, double-blind extension of phase III trial. Tamsulosin Investigator Group. *Urology.* 1998;51:901-906.

43. Narayan P, Evans CP, Moon T. Long-term safety and efficacy of tamsulosin for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia. *J Urol.* 2003;170(2 Pt 1):498-502.

44. Debruyne F, Barkin J, van Erps P, Reis M, Tammela TL, Roehrborn C; ARIA3001, ARIA3002 and ARIA3003 Study Investigators. Efficacy and safety of long-term treatment with the dual 5 alpha-reductase inhibitor dutasteride in men with symptomatic benign prostatic hyperplasia. *Eur Urol.* 2004;46:488-494.

45. Kaplan SA. 5 α -reductase inhibitors: what role should they play? *Urology.* 2001;58(6 suppl 1):65-70.

46. Gormley GJ, Stoner E, Bruskevitz RC, et al. The effect of finasteride in men with benign prostatic hyperplasia. The Finasteride Study Group. *N Engl J Med.* 1992;327:1185-1191.

47. Finasteride (MK-906) in the treatment of benign prostatic hyperplasia. The Finasteride Study Group. *Prostate.* 1993;22:291-299.

48. Roehrborn CG, Boyle P, Nickel JC, Hoefnerk, Andriole G; ARIA3001, ARIA3002 and ARIA3003. Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. *Urology.* 2002;60:434-441.

49. Rigatti P, Brausi M, Scarpa RM, Porru D, Schumacher H, Rizzi CA; MICTIS Study Group. A comparison of the efficacy and tolerability of tamsulosin and finasteride in patients with lower urinary tract symptoms

- suggestive of benign prostatic hyperplasia. *Prostate Cancer Prostatic Dis.* 2003;6:315-323.
- 50. Lam JS, Romas NA, Lowe FC.** Long-term treatment with finasteride in men with symptomatic benign prostatic hyperplasia: 10-year follow-up. *Urology.* 2003;61:354-358.
- 51. Desgrandchamps F.** Who will benefit from combination therapy? The role of 5 alpha reductase inhibitors and alpha blockade: a reflection from MTOPS. *Curr Opin Urol.* 2004;14:17-20.
- 52. Campbell AJ.** Drug treatment as a cause of falls in old age. A review of the offending agents. *Drugs Aging.* 1991;1:289-302.
- 53. Mets TF.** Drug-induced orthostatic hypotension in older patients. *Drugs Aging.* 1995;6:219-228.
- 54. Man In't Veld AJ, van der Camme TJ, van Loon K.** Drug treatment of hypertension in the elderly: the role of α -adrenoceptor blockade. *Br J Urol.* 1998;81(suppl 1):21-25.
- 55. Lowe FC.** Coadministration of tamsulosin and three antihypertensive agents in patients with benign prostatic hyperplasia: pharmacodynamic effect. *Clin Ther.* 1997;19:730-742.
- 56. Lopor H.** Phase III multicenter placebo-controlled study of tamsulosin in benign prostatic hyperplasia. Tamsulosin Investigator Group. *Urology.* 1998;51:892-900.
- 57. Schulman C.** Impact of treatment of BPH on sexuality. *Prostate Cancer Prostatic Dis.* 2001;4(suppl 1):S12-S16.
- 58. Calais Da Silva F, Marquis P, Deschaseaux P, Gineste JL, Cauquil J, Patrick DL.** Relative importance of sexuality and quality of life in patients with prostatic symptoms. Results of an international study. *Eur Urol.* 1997;31:272-280.
- 59. Nicolosi A, Glasser DB, Moreira ED, Villa M; Erectile Dysfunction Epidemiology Cross National Study Group.** Prevalence of erectile dysfunction and associated factors among men without concomitant diseases: a population study. *Int J Impot Res.* 2003;15:253-257.
- 60. Höfner K, Claes H, De Reijke TM, Folkestad B, Speakman MJ; the European Tamsulosin Study Group.** Tamsulosin 0.4 mg once daily: effect on sexual function in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. *Eur Urol.* 1999;36:335-341.
- 61. Djavan B.** Is transurethral microwave thermotherapy an alternative to medical therapy for patients with benign prostatic hyperplasia? *Tech Urol.* 2000;6:300-306.
- 62. Jepsen JV, Bruskewitz RC.** Surgical and nonsurgical invasive treatment of benign prostatic hyperplasia. *Drugs Today (Barc).* 1998;34:353-360.
- 63. Hill B, Belville W, Bruskewitz R, et al.** Transurethral needle ablation versus transurethral resection of the prostate for the treatment of symptomatic benign prostatic hyperplasia: 5-year results of a prospective, randomized, multicenter clinical trial. *J Urol.* 2004;171(6 Pt 1):2336-2340.
- 64. Cimentepe E, Unsal A, Saglam R.** Randomized clinical trial comparing transurethral needle ablation with transurethral resection of the prostate for the treatment of benign prostatic hyperplasia: results at 18 months. *J Endourol.* 2003;17:103-107.
- 65. Hammadeh MY, Madaan S, Singh M, Philp T.** A 3-year follow-up of a prospective randomized trial comparing transurethral electrovaporization of the prostate with standard transurethral prostatectomy. *BJU Int.* 2000;86:648-651.
- 66. Gravas S, Laguna MP, de la Rosette JJ.** Efficacy and safety of intraprostatic temperature-controlled microwave thermotherapy in patients with benign prostatic hyperplasia: results of a prospective, open-label, single-center study with 1-year follow-up. *J Endourol.* 2003;17:425-430.