α-Blocker Therapy: Current Update

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α-Blockade is the predominant form of medical therapy for the treatment of symptomatic bladder outlet obstruction due to benign prostatic hyperplasia (BPH). Recent research has shown that there is a series of α_1 receptor subtypes present in humans and that the α_{1A} subtype appears to play a primary role in mediating prostatic smooth muscle contraction. Recent interest has therefore focussed on the development of agents specific to this α_{1A} receptor subtype. The approval by the Food and Drug Administration of tamsulosin, an α_{1A}-specific antagonist, offers physicians in the United States the opportunity to prescribe a selective α_1-blocker for the treatment of BPH. Tamsulosin offers a pharmacologic means to better target α-blockade specifically to the prostatic smooth muscle and spare the vascular smooth muscle. Use of this agent has resulted in a lower incidence of clinically relevant effects on blood pressure or heart rate and minimal cardiovascular adverse effects.
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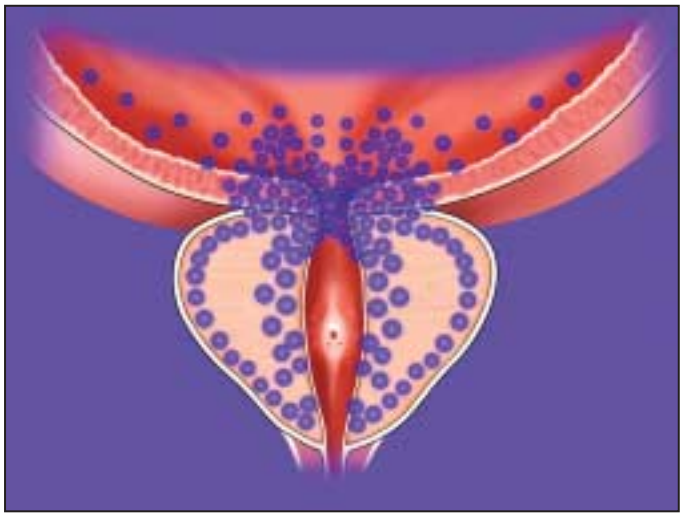
Benign prostatic hyperplasia (BPH), the nonmalignant enlargement of the prostate secondary to increased cellular growth, commonly afflicts elderly men. The incidence of BPH is increasing along with the increasing average life expectancy. Data have suggested that the prevalence of histologic BPH is 50% in men aged 60 years and as high as 88% in men up to 80 years of age.[1] Clinical BPH, defined as prostate weight greater than 20 g (as measured by transrectal

ultrasonography) in association with symptomatic urinary dysfunction and/or a urinary flow rate less than 15 mL/s, without associated malignancy, has been identified in 20% of men between the ages of 40 and 64 years and in 40% of men older than 65 years.[2] Clearly, BPH significantly impacts the aging male population.

α-Blockade continues to be the predominant form of medical therapy for symptomatic bladder outlet obstruction due to BPH, because it targets the neural elements that contribute to the dynamic component of BPH. In fact, more than 90% of new prescriptions written in the United States for the treatment of BPH are for α-blockers. A host of α-blockers are currently approved by the Food and Drug Administration (FDA) and available for general use. Others, which are in development or in the final stages of FDA approval, will become commercially available in the near future.

There are 2 subtypes of α-adrenergic receptors in the prostate capsule and bladder neck: α_1 and α_2 receptors (Figure 1). Electrophysiologic studies of prostate smooth muscle have shown that the α_1 variety predominates in the prostate capsule and is responsible for mediating smooth muscle tone.[3] Blockade of α_2 receptors outside the urinary tract is responsible for the adverse effects of adrenergic blockade in the treatment of BPH. Phenoxybenzamine, a nonspecific α-blocker, was one of the first agents to be used clinically in the treatment of BPH, and its use resulted in a high incidence of adverse effects, such as hypotension, nasal stuffiness, and dizziness.[4,5] Phenoxybenzamine has since been shown to be mutagenic in tissue culture and is no longer used.[6]

Figure 1. *Distribution of α-adrenoreceptors in the lower urinary tract: α_1 receptors predominate in the prostate capsule and are responsible for mediating smooth muscle tone.*



In the early 1970s, prazosin became the first available selective α_1-blocker for the treatment of symptomatic BPH. Prazosin's short half-life necessitated 3 daily doses, and a high incidence of first-dose syncope resulted in poor compliance. The FDA approved the use of terazosin, a once-daily specific α_1-blocker, in 1987 for the treatment of hypertension and in 1993 for use in men with symptomatic BPH. Terazosin has been shown in multicenter, placebo-controlled trials to improve both symptom scores and urinary flow rates.[7] In 1994, after an extensive review of the available literature, the Agency for Health Care Policy and Research demonstrated a benefit of α-blockers in reducing symptoms and increasing uroflow in patients with moderate to severe prostatism.[8] The median probability for symptomatic improvement with α-blocker therapy was estimated to be 74%.

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Until 1998, terazosin and doxazosin comprised approximately 75% of all prescriptions written for BPH in the United States. With the introduction of tamsulosin, another α-blocking option became available. Despite their enormous popularity, α-blockers are associated with a series of adverse effects, including dizziness, postural hypotension, asthenia, nasal stuffiness, and peripheral edema.

Recent research involving differential binding experiments and molecular cloning has revealed that a series of α_1 receptor subtypes exists in humans. These cloned α subtypes were originally designated α_{1a}, α_{1b}, and α_{1c}, with α_{1c} (pharmacologic α_{1A}) receptors predominating in the prostate stroma.[9] Investigators found that 70% of the total α_1 messenger ribonucleic acid in the human prostate is represented by the α_{1c} subtype.[10-12] So that the cloned subtypes corresponded to functional subtypes, the α_{1c} subtype was reclassified as α_{1A}; α_{1a} was reclassified as α_{1D}. Based on currently available data, the α_{1A} subtype appears to play a primary role in mediating prostatic smooth muscle contraction, although other subtypes most likely play secondary roles (Figure 2). In an effort to limit

the adverse-effect profile and improve the efficacy of α-blockers, a great deal of interest is now focused on the development of agents that are specific to the α_{1A} receptor subtype.

The α_{1D} receptor subtype is present in low levels in the smooth muscle portion of the prostate stroma. This subtype may play a role in lower urinary tract symptoms, because it is expressed in areas beyond the stroma of the prostate (ie, the bladder neck and the central nervous system).

Although the design of a "uroselective" α-blocker is the desired result of α_{1A}-specific antagonists, it must be cautioned that pharmacologic uroselectivity might differ from clinical uroselectivity. Affinity constants for the 4 most commonly prescribed α-blockers (terazosin, doxazosin, tamsulosin, and alfuzosin) vary for the different receptor subtypes (Table 1).[11] However, these differences do not translate into clinical uroselectivity. In fact, it has been argued that the combined treatment of hypertension and voiding dysfunction secondary to BPH make "nonselective" agents more attractive as a treatment choice. Ultimately, the goal is to produce and employ agents that lead to maximal improvement in symptoms and objective urodynamic parameters and have the best adverse-event profiles.

Physiologic and Molecular Basis for Use of α-Adrenoreceptor Blockade in the Treatment of BPH

As mentioned above, neural mediators impact the dynamic component of BPH via their regulation of smooth muscle tension in the prostate stroma. Innervation to the prostate is via cholinergic and adrenergic agonists, with sympathetic outflow traveling via the hypogastric nerves and the prostatic nerve plexus. In 1973, Raz and colleagues[13] demonstrated that norepinephrine, an adrenergic agonist, causes rat prostates to contract. Caine and colleagues[14] functionally localized α-adrenergic receptors to the prostatic capsule and bladder neck in men with BPH, whereas ß-adrenergic receptors were found in highest concentration in the bladder dome. Subsequently, Caine and colleagues[5] investigated the clinical efficacy of adrenergic blockade in the treatment of BPH and demonstrated that phenoxybenzamine had a therapeutic effect. Expanding on the results of previous studies, Lepor and colleagues[15] performed isometric tension studies with various adrenergic agonists. They found that α_1 agonists produced a strong contractile response in human BPH tissue, whereas α_2 and muscarinic agonists exerted little if any effect on the contractile nature of this tissue. These results suggest that selective α_1-adrenergic blockade can decrease bladder outlet obstruction in men with BPH via relaxation of contractile elements in the hyperplastic prostate stroma. Although α_1 receptors have been shown to predominate in the prostatic stroma, capsule, and bladder neck, they are not as prevalent in the majority of the bladder; therefore, α_1-blockade can selectively decrease tone in the bladder neck and prostate without affecting bladder contractility.

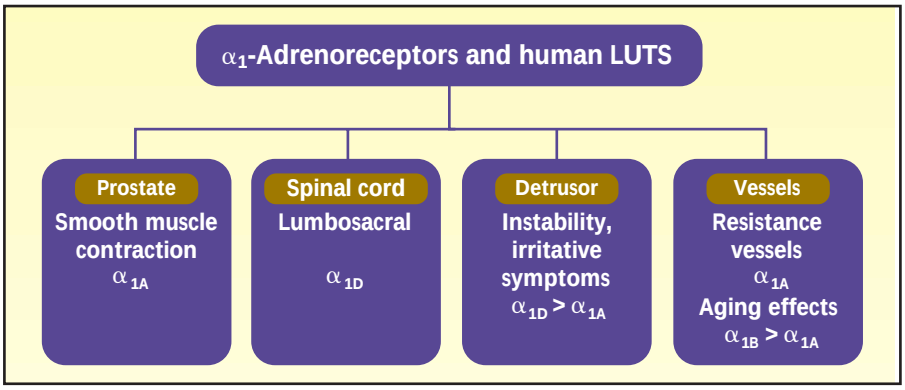

Figure 2. *The role of α_1-adrenoreceptors in lower urinary tract symptoms (LUTS). Adapted from Schwinn DA.* BJU Int. *2000;86(suppl 2):11-22.*[44]

Results of Clinical Trials

Phenoxybenzamine and Prazosin

The 2 most extensive studies examining the efficacy of phenoxybenzamine are those conducted by Abrams and colleagues and Caine and colleagues.

Table 1
Selectivity of α-Blocking Compounds for the α_1-Receptor Subtypes

	Affinities, pKi			Selectivity Ratios	
Compound	α_{1A}	α_{1B}	α_{1D}	α_{1A}/α_{1B}	α_{1A}/α_{1D}
Tamsulosin*	9.70	8.90	9.80	6.3	0.2
Prazosin†	9.70	9.60	9.50	1.23	1.3
Alfuzosin†	8.20	8.53	8.40	0.5	1.4
Doxazosin†	8.56	8.98	8.78	0.4	1.6
Terazosin†	8.16	8.71	8.48	0.3	1.8

*Data from Kenny BA et al. *Br J Pharmacol.* 1996;118:871-878.[45]
†Data from Forray C et al. *Mol Pharmacol.* 1994;45:703-708.[46]

Caine and colleagues[16] reported results of a placebo-controlled, double-blind study of 200 patients with symptomatic BPH treated at outpatient clinics. Of the 171 patients who received phenoxybenzamine, 80% reported improvement in their symptoms. Regarding specific symptoms, the following were improved significantly: obstruction (78.8%), nocturia (75.9%), and frequency (66.9%). In addition, maximum urinary flow rate was at least doubled in 46% of the 102 patients in whom it was evaluated. The limiting factor to the use of phenoxybenzamine was the occurrence of adverse effects: 30% of the study population reported adverse effects, including dizziness (n = 22), weakness or lethargy (n = 19), and palpitations (n = 13), and 10% of subjects withdrew from the study secondary to medication side effects.

In the study by Abrams and colleagues,[6] adverse effects were also reported frequently; however, no patient withdrew from the study as a result of them. This double-blind, placebo-controlled study examined 41 patients for 4 weeks. Subjects received either placebo or phenoxybenzamine, 10 mg twice daily; 1 subject in the placebo group withdrew from the study for unknown reasons. Of 21 subjects who received phenoxybenzamine, 19 reported symptomatic improvement, whereas only 8 of the 19 subjects who received placebo reported an improvement ($P < .05$). Objectively, a 40.2% improvement in maximum urinary flow rate occurred in the phenoxybenzamine group, compared with a 9.2% improvement in the placebo group. Although these studies suggest a beneficial effect with the use of this nonselective α-blocker, its adverse-effect profile and concern over potential mutagenicity have resulted in a lack of its use for the treatment of BPH.

Prazosin, a short-acting α_1-specific antagonist requiring multiple daily doses, was investigated for the treatment of BPH because of its specificity for the α_1 receptor. It was hoped that this agent would produce clinical results comparable to those of phenoxybenzamine without the high frequency of adverse effects. Kirby and colleagues[17] reported a placebo-controlled, double-blind study of 80 men with BPH. Subjects received prazosin, 2 mg, or placebo twice daily. Fifty-five subjects completed the therapy for 4 weeks. Maximum urinary flow rate increased from 8.2 mL/s to 13.0 mL/s in the prazosin group, a 59% improvement ($P < .005$), compared with a 6% improvement (+0.5 mL/s from baseline) in the placebo group. In addition, the subjects who received prazosin had a 21% improvement in postvoid residual urine volume and reported decreased urinary frequency compared with placebo subjects. No significant adverse effects were reported in the prazosin group. These results suggest a therapeutic indication for the use of prazosin for the treatment of BPH; however, the study period was brief, and the dropout rate was significant (32%).

Prazosin, a short-acting α_1-specific antagonist requiring multiple daily doses, was investigated for the treatment of BPH because of its specificity for the α_1 receptor.

In another placebo-controlled, double-blind study, conducted by Chapple and colleagues,[18] a large group of patients (N = 93) received prazosin, 2 mg, or placebo twice daily and was studied over an extended period (3 months). Seventy-five subjects completed the therapy. Maximum urinary flow rate increased in the prazosin group, with an improvement of 2.4 mL/s from baseline. However, no other significant urodynamic improvement was reported, and there was an increased incidence of adverse effects in the prazosin group versus the placebo group, including dizziness (16.7% vs 10%) and headaches (12.6% vs 5%). The results of this study were not as significant as those of the study by Kirby and colleagues,[17] suggesting that, over a longer period, a dynamic rebalancing of pressure and flow, secondary to specific α-blockade, may occur. The lack of significant symptomatic improvement may also be secondary to fluctuation of symptoms that might occur over a longer period in men with BPH.

Doxazosin and Terazosin

The use of nonspecific α-antagonists and short-acting α_1-antagonists, although associated with adverse effects, has demonstrated promising results in the symptomatic relief of BPH and has stimulated the development of other medications that may provide the same beneficial effects without the adverse-effect profiles. To increase compliance, several longer-acting α_1-antagonists that are dosed once daily, including terazosin and doxazosin, have been developed over the past 2 decades.

Doxazosin mesylate, a quinazoline compound of the methanesulfonate family, is available in 1-mg, 2-mg, 4-mg, and 8-mg tablets. Peak plasma levels are achieved within 2 to 3 hours after ingestion, with a bioavailability of 65%. Doxazosin is primarily metabolized in the liver, by O-demethylation of the quinazoline nucleus or hydroxylation of the benzodioxan

moiety, with a majority of the dose eliminated in the feces and a small portion excreted in the urine.[19]

Terazosin hydrochloride, another quinazoline long-acting α_1-antagonist, is available in 1-mg, 2-mg, 5-mg, and 10-mg tablets. Peak plasma levels are achieved within 1 hour, with a half-life of approximately 12 hours. Like doxazosin, terazosin is metabolized in the liver; however, most of the drug is eliminated as metabolites, rather than in its parent form, in the stool (60%) and urine (40%).[20]

Both terazosin and doxazosin are dosed on a once-daily basis, taken before bedtime. Administration begins with a dosage of 1 mg/d to decrease the incidence of orthostatic hypotension and first-dose syncope. The dosage can be titrated up as tolerated, to a maximum of 8 mg daily of doxazosin or 10 mg daily of terazosin for the treatment of BPH. The recommended titration interval is 1 to 2 weeks.

Lepor and colleagues[7] conducted a double-blind, parallel-group, placebo-controlled study involving 285 patients with symptomatic BPH. The subjects were randomized to receive placebo or 2 mg, 5 mg, or 10 mg of terazosin once daily for 12 weeks. All terazosin treatment groups experienced a significant decrease in symptom scores (Boyarsky scale), with the greatest improvement noted in the 10-mg group. Among the subjects who received the 10-mg terazosin dose, 69% experienced a greater than 30% improvement in symptom score, compared with 40% of subjects who received placebo. A statistically significant, dose-dependent improvement in urinary flow rate was also observed. Fifty-two percent of the subjects who received the 10-mg terazosin dose experienced an increase in maximum urinary flow rate of greater than 30%, compared with 26% of the subjects who received placebo; the 10-mg terazosin group averaged a 3.0 mL/s improvement from baseline in maximum flow rate. Only the increase in the 10-mg terazosin group was statistically significant.

Adverse effects were minor and reversible, with the most common being asthenia and dizziness. There was a statistically significant greater incidence of postural hypotension in the 5-mg terazosin group compared with the placebo group. No statistically significant difference was observed between treatment groups in terms of the reduction in blood pressure.[7] (Overall, in clinical trials of BPH, terazosin was associated with 1 or more hypotensive symptoms in 21% of patients.[20]) An attempt to identify factors that might predispose patients to a beneficial response to terazosin therapy proved unsuccessful. The beneficial effects of terazosin therapy on urinary flow rate and symptom score have been shown to be sustained over longer periods, including 24 weeks,[21] 52 weeks,[22] and 42 months.[23]

An attempt to identify factors that might predispose patients to a beneficial response to terazosin therapy proved unsuccessful.

Terazosin is also approved by the FDA for the treatment of hypertension, raising the question of how this medication affects blood pressure in hypertensive and normotensive BPH patients. Lepor[23] found that mean changes in systolic and diastolic blood pressures with terazosin therapy ranged from 1 mm Hg to 4 mm Hg in normotensive subjects, compared with 10 mm Hg to 15 mm Hg in hypertensive subjects. Conversely, studies by Wilde and colleagues[24] and Lowe[25] found blood pressure to decrease significantly in both hypertensive and normotensive subjects receiving 1 mg to 20 mg of terazosin daily.

Other potential adverse effects of terazosin therapy have been scrutinized. One study observed significantly higher incidences of dizziness, asthenia, peripheral edema, chest pain, and nausea in patients who received terazosin compared with those who received placebo; dizziness, asthenia, edema, and postural hypotension served as the major motivators for withdrawal from this study.[21] Another study reinforced the presence of bothersome adverse effects with terazosin therapy compared with placebo.[25]

Doxazosin

The other long-acting α_1-specific antagonist is doxazosin, which has gained widespread popularity. Christensen and colleagues[26] conducted a double-blind, placebo-controlled study of doxazosin therapy in 100 patients with BPH. Subjects were randomized to receive placebo or doxazosin, 4 mg once daily, over the course of 9 weeks. Median maximum urinary flow rate, average urinary flow rate, and residual urine volume all improved with doxazosin therapy compared with placebo; however, the differences were not statistically significant. Adverse events occurred with equal frequency between the 2 groups. In a 3-month, double-blind, placebo-controlled study of 135 subjects with BPH, Chapple and colleagues[27] also found no statistically significant increase in maximum urinary flow rate with doxazosin, 4 mg/d, compared with placebo. However, hesitancy, nocturia, urgency, and impaired urinary stream were all significantly improved in the subjects who received doxazosin.

Gillenwater and Mobley[28] conducted a placebo-controlled study of doxazosin therapy in 100 normotensive subjects with BPH. Subjects received placebo or 2 mg, 4 mg, 8 mg, or 12 mg of doxazosin daily, with the majority receiving the 8-mg dose. Maximum urinary flow rate increased significantly in the doxazosin group compared with the placebo group, with the maximum effect reached by 6 weeks of treatment. Symptom scores also improved significantly in the doxazosin group. Adverse events were more common in the active treatment groups than in the placebo group, with dizziness, fatigue, headache, somnolence, nausea, hypotension, and diarrhea occurring most frequently. A significant decrease in blood pressure was also observed in the doxazosin groups.

Gillenwater and colleagues[29] also reported data on 216 hypertensive BPH patients. Again, the subjects received placebo or 2 mg, 4 mg, 8 mg, or 12 mg of doxazosin daily. Mean maximum urinary flow rate increased significantly in only the 8-mg and 12-mg doxazosin groups versus the placebo group. Of interest, only subjects who received the 4-mg or 8-mg doxazosin doses had statistically significant decreases in mean total symptom score as assessed by the modified Boyarsky scale.

Tamsulosin

The FDA approval of tamsulosin, an α_{1A}-specific antagonist, provides physicians in the United States with the opportunity to prescribe a selective α_1-blocker. Extensive clinical research has led to marketing approval of tamsulosin. Tamsulosin hydrochloride is an α_{1A}-specific antagonist of the sulfonamethylamine family. It is currently available in an extended-release formulation for once-daily administration at 0.4-mg and 0.8-mg doses. Only the 0.4-mg dose is currently approved by the FDA for use in the United States. Tamsulosin is administered one half-hour after meals in the morning and achieves peak plasma levels in 8 hours. It is primarily metabolized via the cytochrome P450 hepatic enzyme system and excreted in the bile. A smaller fraction is excreted via the urine. Toxicity studies performed in animals have revealed a maximum nontoxic dose of 20 mg/kg orally, which is 4000 times higher than the approved human dose.[30]

In 1995, Lepor[31] reported the results of 2 placebo-controlled, randomized, US trials of tamsulosin, 0.4 mg or 0.8 mg daily, for the treatment of symptomatic BPH. Overall results of 1488 patients monitored for 13 weeks revealed a statistically significant improvement in symptoms in subjects who received the 0.4-mg dose of tamsulosin compared with placebo. Dose escalation to 0.8 mg daily resulted in additional improvement in efficacy. There was no increase in adverse cardiovascular events, including episodes of orthostatic hypotension, in subjects who received active treatment compared with control subjects.

Tamsulosin is administered with meals in the morning and achieves peak plasma levels in 8 hours.

In 1996, Chapple and colleagues[32] reported the results of a meta-analysis of 2 double-blind, randomized, controlled, 12-week European trials of tamsulosin administered once daily at a dose of 0.4 mg. Patients were categorized as responders on the basis of a 25% improvement in the overall Boyarsky symptom score, a 30% improvement in the maximum flow rate, or an improvement in flow rate of greater than 3 mL/s. A group of 382 patients who received tamsulosin was matched with a control group of 193 patients who received placebo. Overall response rate based on the study criteria was 32% for the subjects who received tamsulosin versus 20% for control subjects (P = .003). Boyarsky symptom scores were reduced by an average of 3.3 points in the tamsulosin arm, compared with 2.4 points in the placebo arm (P = .002). There were no significant changes in heart rate or blood pressure in the treatment arm compared with control patients.

An open-label extension by Schulman and colleagues[33] of the same 2 trials confirmed sustained efficacy of tamsulosin at 60 weeks of treatment and revealed that 21% of patients who received active treatment reported adverse events related to the medication. The most common adverse effect was dizziness (5.3%), followed by retrograde ejaculation (4.5%). Adverse effects frequently associated with nonspecific α_1-blockers, such as nasal stuffiness, asthenia, and postural hypotension, occurred in fewer than 2% of the subjects who received tamsulosin.

More recently, Schulman and the European Tamsulosin Study Group[34] presented an update on 516 patients who received tamsulosin, 0.4 mg once daily, for an average of 2 years. Of these patients, 75% had a decrease in Boyarsky symptom score and 30% had an increase in maximum flow rate of greater than 30%. No dose titration schedule was necessary. At 2-year follow-up, the most common adverse effects remained dizziness and abnormal ejaculation, with dizziness occurring at the same rate in subjects who received placebo. There were no

clinically significant changes in systolic or diastolic blood pressure in the supine or standing position in the subjects who received tamsulosin.

Long-term safety and efficacy of tamsulosin was recently evaluated in a 64-week, open-label extension study of two 13-week trials and one 40-week trial.[35] All 949 subjects began treatment with tamsulosin 0.4 mg/d; 82% of subjects had their dosage increased to 0.8 mg/d. In responding patients, improvements in symptoms and uroflow were maintained throughout the duration of treatment. Only 2% of subjects discontinued therapy because of dizziness or abnormal ejaculation, and 1% stopped treatment because of asthenia.

Alfuzosin

Alfuzosin is promoted as a uroselective α-receptor blocker. Alfuzosin has been available for years in Europe in immediate- and sustained-release formulations. A new, once-daily, extended-release formulation recently made available in Europe has received approval by the FDA. In a randomized, double-blind, placebo-controlled, 3-month study, the extended-release formulation of alfuzosin at a dosage of 10 mg/d was compared with the standard dose of 2.5 mg 3 times daily (total dosage of 7.5 mg/d) in patients with BPH. Compared with the immediate-release formulation, the extended-release formulation demonstrated similar efficacy and better safety with respect to cardiovascular adverse events.[36] In a 12-month extension of the study, the once-daily formulation produced sustained improvements in symptoms and urinary flow rate.[37]

The safety and efficacy of the immediate-release formulation of alfuzosin have been confirmed in long-term (3-year) studies.[38] Another pivotal trial demonstrated significant reductions in International Prostate Symptom Score and improvements in peak urinary flow rate in patients who received the once-daily formulation compared with those who received placebo. Moreover, cardiovascular adverse effects, including orthostatic hypotension, were no more common in the subjects who received the once-daily formulation than in those who received placebo.[39]

Table 2
α-Blockers: Putting It Together

- Efficacy
  - Similar among all α-blockers
- Adverse effects quantitatively different among the various α-blockers
- Discontinuation rates for cardiovascular events
  - Highest among terazosin, doxazosin, and alfuzosin immediate-release
  - Lower with alfuzosin extended-release
  - Lowest with tamsulosin

Are There Differences Among α-Blockers?

Heimbach and Muller[40] performed a meta-analysis of 92 phase 2 and phase 3 studies involving more than 44,000 men with BPH treated with various α-blockers. It should be cautioned that meta-analyses do not take into account differences in dose response. The results suggest that α-blockers are significantly better than placebo and that efficacy is similar among the various agents. Overall, symptoms were shown to decrease by approximately 33% and flow rate to improve by approximately 2 mL/s. It should be noted that these improvements are similar to those of finasteride responders. However, the use of more selective agents resulted in fewer adverse events. Does uroselectivity result in an altered adverse-effect profile? More important, are these differences qualitative or quantitative?

In another meta-analysis, Chapple[41] reported that when alfuzosin (sustained-release), terazosin, doxazosin, and tamsulosin were compared, the improvement in symptoms compared with placebo ranged from 8% to 20%. Flow rate improved from 1 mL/s to 2.2 mL/s.

Finally, Djavan and Marberger[42] demonstrated in a meta-analysis that the various α-blockers produced comparable improvements in lower urinary tract symptoms and urinary flow. α-Blockers improved symptoms by 30% to 45%, compared with a placebo response of 15% to 25%. Improvements in peak flow rate compared with placebo ranged from 5% to 15%. More important, differences in agents were related to adverse effects as opposed to efficacy.

Ultimately, the concept of α-blocker uroselectivity may rest more on adverse effects than on efficacy. There have been conflicting reports on the percentage of patients who experience the most typical adverse effects produced by α-blockers, which include dizziness, headache, asthenia, drowsiness, postural hypotension, and retrograde ejaculation. Overall dropout rates seem to be similar, although qualitatively different, among the 4 available agents; that is, more patients discontinue doxazosin, terazosin, and alfuzosin because of dizziness, whereas nasal congestion and retrograde ejaculation occur more commonly with tamsulosin (Table 2).

Conclusions

In light of the emerging clinical data on the use of a selective α_1-antagonist, it is apparent that tamsulosin (and perhaps alfuzosin) offers a pharmacologic means to better target α-blockade to the prostatic smooth muscle and spare the vascular smooth muscle. Use of this agent has resulted in a lower incidence of clinically relevant effects on blood pressure and heart rate and minimal cardiovascular adverse effects. Once-daily dosing without titration is an added convenience.

Patients who have discontinued nonselective α_1-antagonist agents are excellent candidates for a trial of therapy with this more specific α_{1A}-adrenergic antagonist.[43] Proof of superior efficacy for this new class of drugs will hinge upon long-term studies directly comparing nonspecific α_1-antagonists with α_{1A}-specific agents. Only then will we know whether molecular uroselectivity is clinically relevant. ■

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Main Points

- α-Blockade continues to be the predominant form of medical therapy for the treatment of symptomatic bladder outlet obstruction due to benign prostatic hyperplasia (BPH), because it targets the neural elements that contribute to the dynamic component of BPH.
- Based on currently available data, the α_{1A} subtype appears to play a primary role in mediating prostatic smooth muscle contraction. In an effort to limit the adverse-effect profile and improve the efficacy of α-blockers, a great deal of interest is focused on the development of agents that are specific to the α_{1A} receptor subtype.
- Meta-analyses have shown that α-blockers are significantly more effective than placebo and that efficacy is similar among the various agents.
- Differences among α-blockers are related to adverse effects as opposed to efficacy; the use of more selective agents results in fewer adverse events.
- Tamsulosin hydrochloride, an α_{1A}-specific antagonist, is currently approved by the Food and Drug Administration in an extended-release form (0.4 mg) for once-daily administration. Use of this agent has resulted in a lower incidence of clinically relevant effects on blood pressure or heart rate and minimal cardiovascular adverse effects.

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