Terazosin in the Treatment of Benign Prostatic Hyperplasia

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Objective: To evaluate the efficacy and tolerability of terazosin, a long-acting selective α_1-receptor antagonist, in patients with benign prostatic hyperplasia.

Design and Setting: Randomized, double-blind, multicenter (eight government and private facilities), placebo-controlled study.

Patients: Men aged 45 years or older, with qualifying signs and symptoms of benign prostatic hyperplasia (n=160).

Interventions: Terazosin or placebo once daily, with terazosin dosage titrated to the patient's response. After a 4-week placebo lead-in, 1 to 10 mg of terazosin or placebo was administered for 24 weeks.

Outcome Measures: Decreases in mean Boyarsky scores for obstructive and irritative symptoms and total scores and increases in peak urine flow rate.

Results: Terazosin-treated patients had decreases in Boyarsky obstructive, irritative, and total scores of 3.3 (52%), 1.3 (29%), and 4.6 (42%), respectively, compared with decreases of 0.7 (12%), 0.4 (9%), and 1.1 (11%), respectively, in the placebo group ($P<.05$). Peak urine flow increased by a mean of 2.6 mL/s (30%) in terazosin-treated patients and 1.2 mL/s (14%) in placebo-treated patients ($P\leq.05$). Adverse events that differed significantly in the two groups were dizziness (19% in the terazosin group vs 5% in the placebo group) and urinary tract infection (1% in the terazosin group vs 10% in the placebo group).

Conclusions: These results suggest that terazosin given once daily in doses up to 10 mg alleviates symptoms and improves peak urine flow rate in men with benign prostatic hyperplasia and has an acceptable adverse event profile.

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SURGERY IS the treatment most commonly offered to men with benign prostatic hyperplasia (BPH). Absolute indications for prostatectomy include urinary retention, azotemia, gross hematuria, and recurrent urinary tract infection. In the majority of cases, however, indications for surgery are relative, and most patients undergo this procedure because of bothersome symptoms.

In 1976, Caine and coworkers[1] reported the successful treatment of BPH with α-blockers. Subsequently, Caine[2] and Lepor[3] demonstrated that terazosin (Hytrin, Abbott Laboratories, North Chicago, Ill), a new long-acting α_1-blocker approved for the treatment of hypertension, produced smooth-muscle relaxation in the bladder and relieved bladder neck obstruction. Since then, several groups of investigators have shown that drug therapy with terazosin has significant therapeutic benefit in men with BPH.[4-8] In the first large, randomized, placebo-controlled, multicenter trial, Lepor et al[8] found that patients treated with terazosin for 12 weeks had significantly greater improvement in Boyarsky symptom scores and urinary flow rates than patients given placebo.

The present randomized, placebo-controlled, multicenter study was performed to evaluate the efficacy and safety of terazosin in men with BPH treated for a 24-week period.

See Patients and Methods on next page

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PATIENTS AND METHODS

STUDY DESIGN

This was a multicenter, randomized, placebo-controlled, parallel study involving once-daily administration of terazosin or placebo. The study was divided into two parts: (1) a 4-week, single-blind, placebo lead-in period, during which patients were evaluated to determine whether they met study criteria, and (2) a 24-week, double-blind, dose titration and maintenance period.

Entry criteria were assessed at three visits during the placebo lead-in period. Criteria included age at least 45 years, BPH of sufficient severity for the patient to score 1 point or more on at least two items in the Boyarsky obstructive symptom scale[9] (described below), and unadjusted peak urine flow rate between 5 and 12 mL/s. Patients with absolute indications for prostatectomy, detrusor instability, carcinoma of the prostate, or significant cardiopulmonary disease were excluded from the study. In all, 215 patients entered the study during the placebo lead-in period; 55 were disqualified prior to randomization because of failure to meet the criteria, leaving 160 qualified patients in the double-blind protocol.

During the last visit of the placebo lead-in period, these patients were randomized in equal numbers to receive placebo or terazosin. Those randomized to terazosin treatment were given 1 mg daily for the first 4 weeks of the double-blind period; those randomized to placebo treatment received identical-appearing capsules of placebo at the lowest of four "doses." Every 4 weeks, the dose of terazosin or placebo was increased until either the titration criteria were met or the maximum dose of either 10 mg of terazosin or the fourth and highest "dose" of placebo was reached. The patient's dose was to be raised unless he had an increase of at least 6 mL/s in peak urine flow and improvement in the total score for obstructive symptoms.

Approval for the study protocol was obtained from the institutional review board of each participating institution. All patients signed an approved informed consent form after the purpose and procedures of the study had been explained and before they underwent any study-related procedure.

EVALUATION

Initial evaluation during the placebo lead-in period included a complete medical history, physical examination, and urologic evaluation. The latter included digital rectal examination, urinalysis with culture and sensitivity, and renal imaging studies.

Patients were evaluated every 2 weeks for the first 20 weeks and every 4 weeks for the final 8 weeks of the study. At each visit, drug efficacy was assessed by urine flow rates, Boyarsky symptom scores,[9] and the investigator's global assessment. In addition, vital signs and body weight were measured, and the patient was questioned about adverse events. At the last visit of the treatment phase, urinalysis was performed, including culture and sensitivity testing. Complete blood cell count, serum chemistry studies, physical examination, and cystometrography also were performed at the last study visit.

Urine flow rates were measured with a Dantec Urodyne 1000 Uroflowmeter (Dantec Electronics Inc, Santa Clara, Calif). A minimum voided volume of 150 mL was required for a valid urine flow determination. Peak and mean urine flow rate and voided volume were recorded electronically. A central reader, blinded to the treatment assignments, evaluated all flow strips to eliminate electronic "noise" that could affect the reading of peak urine flow rates.

Investigators evaluated bladder obstruction and irritation on the basis of interviews using the Boyarsky symptom scale.[9] Obstructive symptoms included hesitancy, intermittency, terminal dribbling, impairment of volume and force of urinary stream, and sensation of incomplete bladder emptying. Irritative symptoms included increased daytime frequency, nocturia, urgency, and dysuria. The severity of each symptom was ranked from 0 to 3, with 0 representing absence of the symptom or minimal severity and 3 representing frequent presence or severe manifestations of that symptom. The total symptom score equaled the sum of the obstructive and irritative scores; the maximum possible score was 27.

Investigators also assigned subjective global assessment scores describing the overall condition of each patient's BPH as within normal limits (1 point), mild (2 points), moderate (3 points), or severe (4 points). Global assessment scores were based on interviews with the patients, Boyarsky symptom scores, and urine flow results.

STATISTICAL ANALYSES

Treatment groups were evaluated for comparability of baseline and demographic variables by two-way analysis of variance with factors for center, treatment group, and interaction of treatment groups. The primary objective variables of efficacy included changes in peak and mean urinary flow rates. Subjective efficacy variables included changes in obstructive, irritative, and total Boyarsky scores and global assessments by the investigator. Changes were calculated as the difference between the final assessable visit of the placebo lead-in period and the final assessable visit of the double-blind period. Treatment groups were compared using contrasts obtained from the two-way analysis of variance model. Repeated-measures analyses were also performed, yielding similar conclusions. Confirmatory analyses were performed to adjust urine flow variables for voided and total bladder volume[10-12] and to adjust all efficacy variables for baseline values. Differences in proportions of patients experiencing adverse events were tested using Fisher's Exact Test. All P values were two-tailed. Analyses were performed using the Statistical Analysis System computer software (version 5.18, SAS Institute, Cary, NC).

RESULTS

Of the 160 patients entering the double-blind treatment period, 79 were in the placebo group and 81 in the terazosin group. Mean age was 64 years. No significant baseline differences were observed between treatment groups in age, height, weight, or baseline urodynamics and symptoms.

The final doses of terazosin were as follows: nine patients received 1 mg; five patients, 2 mg; 18 patients, 5 mg; and 49 patients, 10 mg. Sixty-two patients were titrated to the highest of the four "doses" of placebo.

Baseline uroflowmetric measurements and at least one uroflowmetric measurement during treatment or within 4 days after the end of treatment were available for 150 patients, who were thus included in efficacy analysis. Safety data were analyzed for all 160 patients. During the treatment phase, 26 patients who were included in the efficacy analysis were disqualified from the study (10 placebo- and 16 terazosin-treated patients).

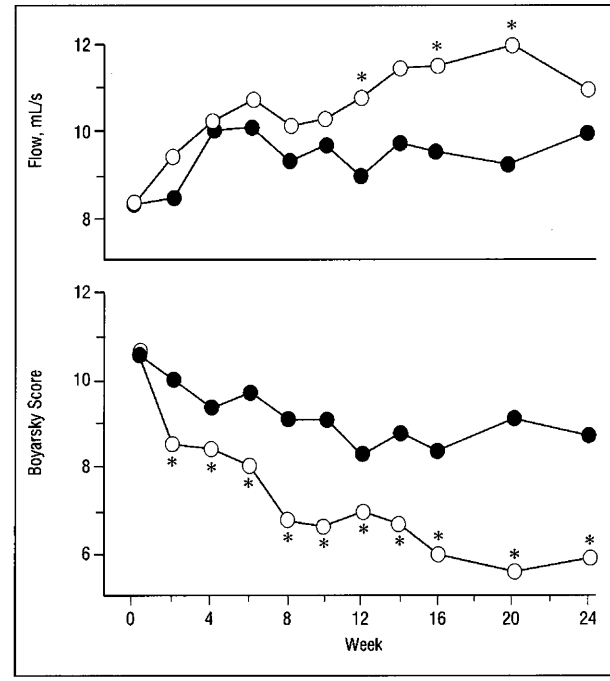

Figure 1. *Top, Unadjusted peak flow rate. Bottom, Total Boyarsky symptom score. Line with open circles indicates terazosin-treated patients; closed circles, placebo-treated patients; and asterisk, P≤.05.*

BOYARSKY SCORES

Overall, decreases in Boyarsky scores were significantly greater in the terazosin group than those in the placebo group (**Table 1**). The differences were significant at all times beginning at the first visit in week 2 (**Figure 1**). The greatest improvement was observed in obstructive symptoms in terazosin-treated patients. The beneficial effect on obstructive and total symptom scores was sustained for the entire treatment period of 24 weeks. Irritative symptom scores were also higher with terazosin, but a statistically significant difference did not emerge until the sixth week of treatment; thereafter, the difference remained significant. Statistically significant differences were observed between the terazosin and placebo groups at the end of treatment for the following symptoms: hesitancy, intermittency, force of stream, nocturia, and daytime frequency (**Figures 2** and **3**).

The total symptom score deteriorated or showed little change in 15% of the terazosin group and 46% of the placebo group. Twenty-seven (37%) of 73 patients treated with terazosin had an improvement of more than 50% in

Table 1. Changes in Efficacy Variables From Baseline to Final Visit

	Placebo (n=74)		Terazosin (n=73)		
Variable	Baseline Value	Mean (±SEM) Change	Baseline Value	Mean (±SEM) Change	Treatment Difference (95% CI)*
Boyarsky symptom scores					
Obstructive	5.8	−0.7±0.3†	6.4	−3.3±0.3†	−2.5 (−3.5 to −1.5)‡
Irritative	4.6	−0.4±0.2†	4.5	−1.3±0.2†	−0.9 (−1.5 to −0.3)‡
Total	**10.4**	−1.1±0.4†	**10.9**	−4.6±0.4†	**−3.4** (−4.6 to −2.2)‡
Urine flow, mL/s					
Unadjusted peak flow rate	8.8	1.2±0.4†	8.6	2.6±0.4†	1.4 (0.2 to 2.6)‡
Adjusted peak flow rate§	8.8	1.2±0.4†	8.6	2.6±0.4†	1.3 (0.1 to 2.5)‡
Unadjusted mean flow rate	4.4	0.4±0.2	4.2	1.8±0.2†	1.4 (0.6 to 2.2)‡
Adjusted mean flow rate§	4.4	0.4±0.2	4.2	1.7±0.3†	1.3 (0.5 to 2.1)‡
Voided volume, mL	254.2	−0.3±12.7	248.7	23.6±12.7	23.9 (−11.4 to 59.2)
Investigator global assessment	2.9	0.0±0.1	2.9	−0.4±0.1†	−0.5 (−0.7 to 0.3)‡

**CI indicates confidence interval.*
†P≤.05 compared with baseline mean.
‡P≤.05 for comparison between treatments.
§Adjusted for voided volume.

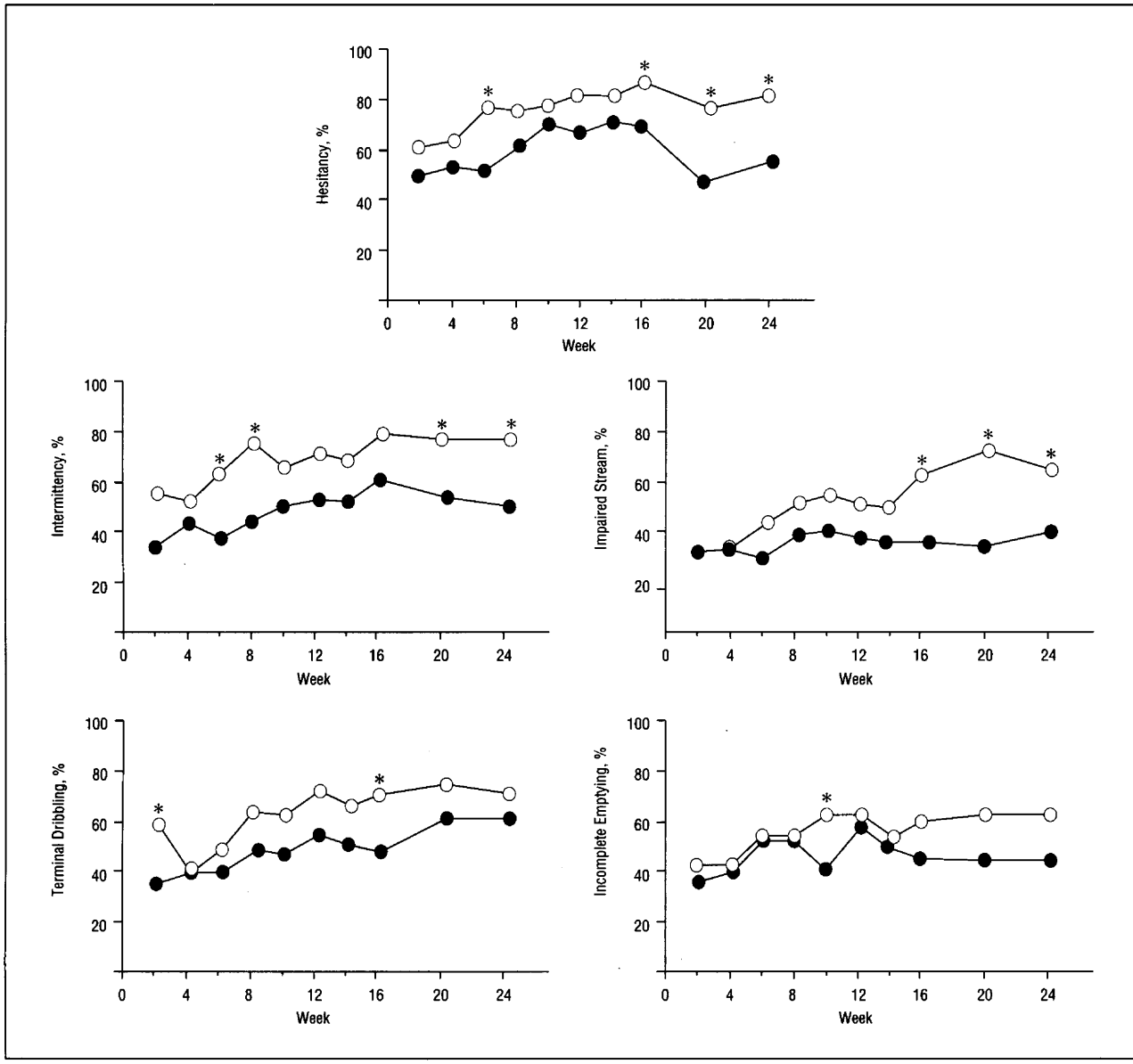

Figure 2. *Symptomatic patients demonstrating improvement compared with baseline in Boyarsky score for obstructive symptoms of benign prostatic hyperplasia. Line with open circles indicates terazosin-treated patients; closed circles, placebo-treated patients; and asterisk, P≤.05.*

the total symptom score compared with eight (11%) of 74 patients given placebo.

PEAK URINE FLOW RATES

Unadjusted peak urine flow increased by a mean of 1.2 mL/s (14%) in placebo-treated patients and 2.6 mL/s (30%) in terazosin-treated patients, a statistically significant difference (Table 1). In the placebo group, near-maximum improvement occurred between weeks 4 and 8 of treatment; in the terazosin group, the increase was gradual from baseline until week 14 of treatment, after which it stabilized. The change from baseline was significant between groups at weeks 12, 16, and 20 (Figure 1). Peak urine flow improved 50% in 15 placebo-treated men and 24 terazosin-treated subjects. Unadjusted mean urine flow rate increased by 0.4 mL/s (9%) in the placebo group and 1.8 mL/s (43%) in the terazosin group ($P<.001$).

Similar between-group differences were apparent for peak and mean flow rates adjusted for voided urine volume, which increased slightly in the terazosin group but not significantly more than in the placebo group.

GLOBAL ASSESSMENT

Mean global assessment scores by the investigator increased in the terazosin group, but no change was seen in the placebo group. The increase over baseline values in the terazosin group was statistically significant ($P<.05$), as was the comparison between terazosin-treated patients and patients receiving placebo ($P<.05$).

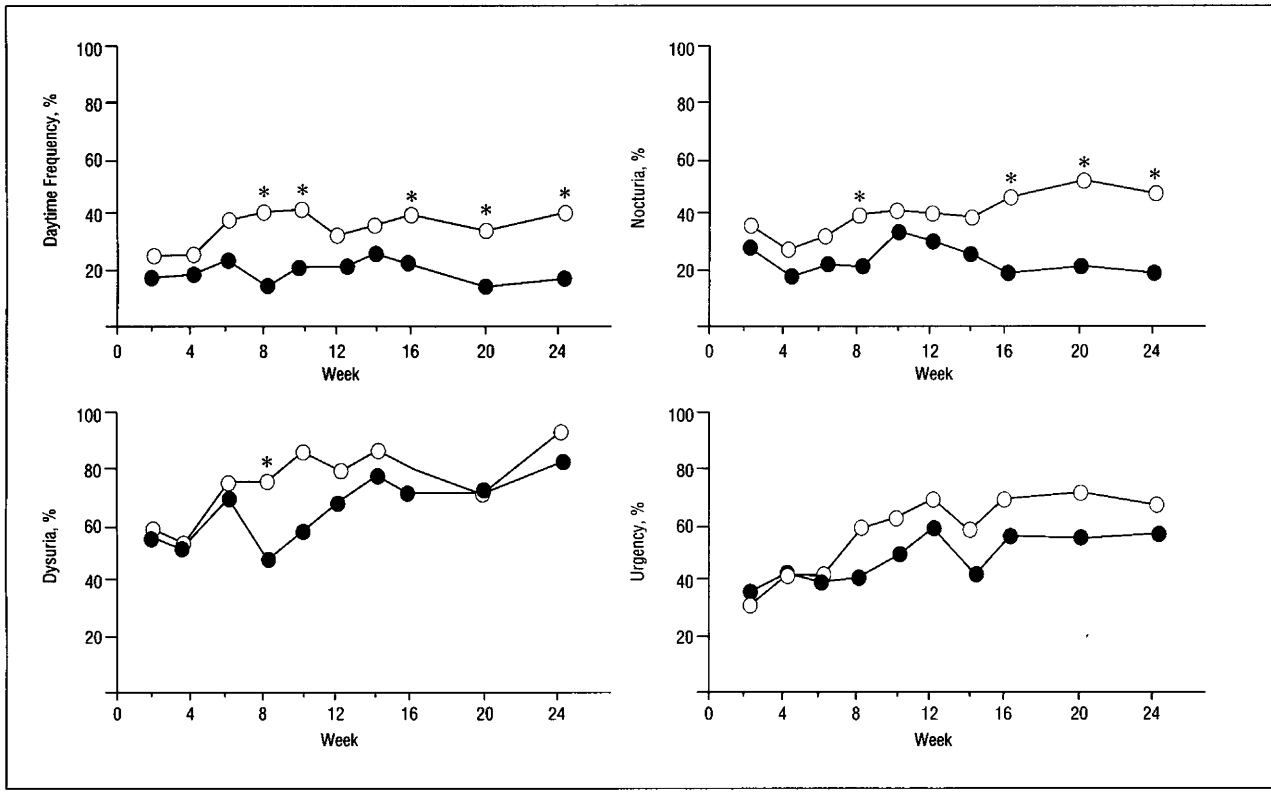

Figure 3. *Symptomatic patients demonstrating improvement in Boyarsky score compared with baseline for symptoms of irritation due to benign prostatic hyperplasia. Line with open circles indicates terazosin-treated patients; closed circles, placebo-treated patients; and asterisk, P≤.05.*

ADVERSE EVENTS

The most common adverse events are listed in **Table 2**. Urinary tract infection was reported significantly more often in placebo-treated patients and dizziness significantly more often in terazosin-treated patients. Six terazosin-treated and two placebo-treated patients were removed from the study due to symptoms of dizziness. Seven patients in the placebo group and 12 in the terazosin group discontinued participation due to adverse events. Dropout rates in the terazosin group did not increase with increasing dose (1, 2, 5, and 10 mg); there were eight dropouts in the 1-mg group, one each in the 2-mg and 5-mg groups, and two in the 10-mg group. The other patients who were terminated from the study prematurely were either unavailable for follow-up or dropped for administrative reasons.

One patient in the terazosin group experienced syncope and gastrointestinal hemorrhage while receiving 2 mg of the drug. On the day of the event, his antihypertensive medication had been changed from hydrochlorothiazide to enalapril. The investigator deemed this event unrelated to the study medication. There were no subsequent sequelae, and the patient continued in the study.

Urinary tract infection was reported . . . more often in placebo-treated patients

The blood pressure changes from baseline values can be seen in **Table 3**. Hypertension was defined as diastolic pressure higher than 90 mm Hg. The only significant between-group difference was for patients with uncontrolled hypertension; terazosin-treated patients had a 16.1–mm Hg decrease in diastolic pressure, placebo-treated patients an 8.1–mm Hg decrease ($P<.05$). Differences in pulse rate were minimal.

COMMENT

In our 24-week study, terazosin produced significantly more improvement than did placebo in both Boyarsky scores and urine flow rates. The difference in obstructive symptom scores began to be apparent at the first return visit, after 2 weeks of treatment with the lowest dose of terazosin (1 mg). Increases in unadjusted peak urine flow rates were also significantly better in terazosin-treated patients, although significant differences were not observed until the 12th week of treatment. At this point, some patients were still receiving 1 mg of terazosin, but others were receiving higher doses. From these observations, it is apparent that 1 or 2 mg of the drug may offer symptomatic improvement, but maximum therapeutic benefit may not be achieved until higher doses (5 or 10 mg) have been administered for a period. The variability of find-

ings among patients in our study indicates that the terazosin dose will have to be adjusted according to the individual's response to the drug.

Using 30% improvement as a criterion for a clinically significant response, 66% of our terazosin-treated patients achieved a significant clinical response as judged by total symptom score compared with 32% of placebo-treated patients. Similarly, 47% of patients in the terazosin group had clinically significant increases in peak urine flow rate compared with 34% of those in the placebo group.

Other selective α_1-blockers that have been studied for the treatment of BPH include prazosin, alfuzosin, YM617 (a compound as yet unnamed), and phenoxybenzamine. The various clinical trials have used nonstandardized outcome measures, making valid comparisons difficult[13-17]; but the efficacy of terazosin appears to be better than that of alfuzosin and YM617.[13] Phenoxybenzamine, a nonselective α-antagonist, has shown good results in relieving symptoms of BPH, but unlike the other drugs, it has a poor safety profile.[18-22]

Recently, Gormley and colleagues[23] reported results of a 12-month placebo-controlled trial of finasteride, a competitive inhibitor of 5-α-reductase, in men with BPH. Daily treatment with 5 mg of finasteride resulted in significant decreases in obstructive symptoms and significantly increased urinary flow at a slightly increased risk of sexual dysfunction. In general, however, the patients in this study required longer to achieve sustained symptomatic improvement than those in our study, suggesting that selective α-blockers such as terazosin may be more promising as pharmacologic alternatives to surgery.[24]

Side effects were of limited clinical relevance in this investigation. As expected with an α-blocker, asthenia and dizziness were among the most common treatment-emergent adverse events; asthenia occurred in 7% of the terazosin group and dizziness in 19%. Erectile dysfunction occurred in 7% of terazosin-treated patients, a somewhat higher rate than reported in previous terazosin trials.[4-7] A lower incidence of urinary tract infection was observed in terazosin-treated (1%) than in placebo-treated patients (10%). This finding is consistent with a terazosin-related improvement in bladder outlet obstruction secondary to BPH. Overall, the adverse events observed in our study were similar to those reported in studies of hypertensive patients who received terazosin.[25,26]

Table 2. Most Common Adverse Events in Placebo- and Terazosin-Treated Patients*

Adverse Event	No. (%) of Patients		
	Placebo (n=79)	Terazosin (n=81)	P
Asthenia	2 (3)	6 (7)	.277
Back pain	5 (6)	3 (4)	.492
Chest pain	4 (5)	3 (4)	.718
Dizziness	4 (5)	15 (19)	.013†
Dyspepsia	4 (5)	1 (1)	.207
Erectile dysfunction	1 (1)	6 (7)	.117
Flu syndrome	1 (1)	5 (6)	.210
Headache	7 (9)	5 (6)	.562
Pharyngitis	5 (6)	4 (5)	.744
Urinary tract infection	8 (10)	1 (1)	.017†

*To be listed, adverse events had to occur in at least 5% of either treatment group.
†Statistically significant at P≤.05.

Table 3. Effects of Terazosin on Blood Pressure in Normotensive Patients, Patients With Hypertension Controlled by Diuretics or Angiotensin Converting Enzyme Inhibitors, and Patients With Untreated Hypertension

Patient Group	Mean Baseline Blood Pressure, Systolic/Diastolic, mm Hg	Mean Change, mm Hg	
		Systolic	Diastolic
Normotensive			
Placebo (n=58)	134/80	0.0	−0.8
Terazosin (n=59)	135/80	−5.2*	−2.8*
Hypertension controlled			
Placebo (n=10)	142/87	−8.2	−6.5*
Terazosin (n=9)	143/86	−9.1	−6.6
Hypertension uncontrolled			
Placebo (n=11)	157/99	−12.0*	−8.1*
Terazosin (n=8)	148/96	−10.0	−16.1*†

*P<.05 for within-group comparison, ie, significant decrease from baseline values.
†P<.05 for between-group comparison, ie, the terazosin group had significantly greater decrease than the placebo group.

When prescribed for BPH, terazosin will be used mainly by an older population. The lack of effect on blood pressure in normotensive patients and in those with moderate hypertension controlled by diuretics or angiotensin-converting enzyme inhibitors was reassuring. The greatest decline in blood pressure was seen in terazosin-treated patients with uncontrolled, untreated hypertension. Thus, terazosin had a dual benefit for these patients.

We recommend that a trial of terazosin be offered to patients with BPH who have bladder outlet obstruction but no absolute indications for prostatectomy. Symptomatic improvement may be expected as early as 2 weeks after beginning treatment with doses as low as 1 mg daily. Increasing the dose to 10 mg, as was done for some patients in our study, is likely to yield additional, sustained improvement in micturition symptoms. Further studies are needed to determine whether terazosin in doses above 10 mg offers greater therapeutic benefit and has an acceptable safety profile.

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