LONG-TERM EFFICACY AND SAFETY OF TERAZOSIN IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT—Objectives. To evaluate long-term efficacy and safety of terazosin, a selective alpha blocker, in the treatment of benign prostatic hyperplasia (BPH).

Methods. This was a long-term (42 months), open-label, multicenter study with patients evaluated at 1- to 6-month intervals. Twenty-three outpatient clinics throughout the United States and Canada participated in the study. A total of 494 men with symptomatic BPH, lacking absolute indications for surgery, were enrolled in this study; 298 were transferred into the study from randomized, placebo-controlled studies of terazosin and 196 had no prior terazosin therapy. Terazosin was given starting at 1 mg/d and titrated upward until symptoms were relieved or a maximum dose of 20 mg/d was achieved, whichever came first.

Results. Peak urinary flow rates at all visits were significantly higher than baseline values, with mean improvements ranging from 1.0 to 4.0 mL/s. At 3 months, 40% of patients exhibited a 30% or greater improvement in peak flow rate; this improvement was maintained through 42 months. Boyarsky symptom scores improved significantly at all visits: mean total score improved by at least 4.0 points (40%) at all visits beyond 3 months. The most common adverse events resulting in premature termination from the study were dizziness (6.7%), asthenia (3.8%), and somnolence (2.0%).

Conclusions. This study suggests that terazosin is well tolerated and effective in long-term treatment of patients with BPH.

Benign prostatic hyperplasia (BPH) is primarily a stromal process,1,2 with smooth muscle constituting about 40% of the area density of the prostate. The tension of prostate smooth muscle is mediated primarily by the alpha, adrenoceptor.3,4 Because alpha, adrenoceptor density is higher in the bladder outlet than the bladder body,5 selective alpha blockers presumably decrease resistance along the bladder outlet without interfering with detrusor function. In a study of 26 men treated for BPH with terazosin, a direct relationship was observed between the area density of prostate smooth muscle prior to treatment and subsequent increases in peak urinary flow rate.6 This observation further supports the hypothesis that the therapeutic benefit of alpha blockers is mediated in part by relaxation of prostate smooth muscle.

A number of open-label and placebo-controlled studies of alpha blockers in the treatment of BPH have been reported,7-21 and most studies of selective alpha blockers have shown these drugs to be both effective and safe. However, the duration of treatment in the various studies has been limited to 1 to 12 months. Because BPH is a chronic and potentially progressive disease, studies of the long-term effects of pharmacotherapy are needed. We designed a long-term open-label multicenter study of the selective alpha blocker terazosin. This report represents an interim analysis of patients treated for periods up to 42 months.
MATERIAL AND METHODS

PATIENTS

Between December 1989 and December 1991, 494 men with BPH were enrolled at 23 institutions. Patients diagnosed with symptomatic BPH but lacking absolute indications for surgical intervention were eligible. Patients were either entered in this study without previous participation in any terazosin study (n = 196), or they were transferred into the study from multicenter, randomized, placebo-controlled studies of terazosin in the treatment of BPH (n = 298).

New patients were entered into an open-label dose titration period if they met all selection criteria, including a Boyarsky symptom score of 1 or higher on at least two of the five symptoms classified as obstructive, a peak urinary flow rate of 15 mL/s or less at each visit of the lead-in period, a voided volume of 150 mL or more at each visit, and a residual volume of 200 mL or less as determined by catheterization. Having already met similar entry criteria, transfer patients were entered directly from previous double-blind studies. Neither the transfer patients nor the investigators knew whether patients received placebo or terazosin during the treatment period of the previous study.

All patients signed informed consent documents after the study was described to them and before taking the first dose of study medication. Approval of the study protocol was obtained from the institutional review board of each participating center.

STUDY DESIGN

Initially, the study protocol was designed to follow patients undergoing terazosin administration for a maximum of 2 years, but the duration of follow-up was subsequently extended to 4 years. Screening procedures included a complete medical history, physical examination, urinalysis, urine culture, and routine hematology and serum chemistry determinations. Also, a baseline cystometrogram, renal ultrasonogram, transrectal ultrasonogram, electrocardiogram, and chest roentgenogram were performed.

After the lead-in period, terazosin was started at 1 mg/d and titrated upward at monthly intervals at the investigators' discretion to a maximum dose of 20 mg/d. Dose levels were 1, 2, 5, 10, and 20 mg of terazosin per day. If the patient had an adverse event, the dose was reduced until the event resolved.

Uroflowmetry was performed using the Dantec Urodyn 1000 Flowmeter (Dantec Medical, Santa Clara, Calif). Postvoid residual was determined by sterile catheterization or ultrasound imaging using the Bladder Volume Instrument 2000 (Diagnostics Ultrasound, Redmond, Wash). Peak urinary flow rates were interpreted by a central reader. Prostate volume was determined by transrectal ultrasonography.

Urinary symptoms were assessed using the interviewer-administered Boyarsky Symptom Index, which includes five questions regarding the patient's obstructive symptoms and four regarding irritative symptoms. Each symptom is scored from 0 to 3, with 0 indicating that the symptom is minimal or absent and 3 indicating that it is severe and frequent. Obstructive symptoms have a total possible score of 0 to 15 and include urinary hesitancy, intermittency, terminal dribbling, impairment in size or force of urinary stream, and the sensation of incomplete emptying. Irritative symptoms have a total possible score of 0 to 12 and include daytime frequency, nocturia, urgency, and dysuria. The total Boyarsky score (range, 0 to 27) is the sum of the obstructive and irritative scores.

Primary efficacy variables were peak urinary flow rate and total Boyarsky symptom score. Study procedures were performed approximately 24 hours after the last dose of terazosin. Study visits were conducted at 1-month intervals up to 3 months, at 3-month intervals up to 24 months, and at 6-month intervals thereafter. Uroflowmetry, Boyarsky symptom scores, and vital signs were recorded at each visit, and the patient was questioned about adverse events. Drug compliance was assessed by pill counts. Hematology, serum chemistries, and urinalysis were performed at 12-month intervals. Transrectal ultrasonography was performed on completion of the study or at the last study visit if the patient withdrew prematurely.

STATISTICAL ANALYSIS

Changes from baseline for peak flow rate, Boyarsky symptom scores, and vital signs were analyzed with paired t tests. Associations between variables were evaluated with simple correlation coefficients.

RESULTS

A total of 494 patients entered the study. Results are reported based on interim analysis of all study visits on or before December 31, 1993. Durations of follow-up ranged from 3 to 42 months: 457 patients at 3 months, 429 at 6 months, 352 at 12 months, 274 at 18 months, 234 at 24 months, 135 at 30 months, 103 at 36 months, and 47 at 42 months. The percentage of patients on final terazosin doses of 1, 2, 5, 10, and 20 mg were 7, 12, 26, 34, and 21, respectively. Of the 494 patients,
FIGURE 1. Kaplan-Meier plot of premature terminations in patients treated with terazosin. Overall, 55 patients (11%) were withdrawn due to treatment failure, most within 1 year after the initiation of therapy.

FIGURE 2. Mean change in peak flow rate between baseline and 42 months in terazosin-treated patients. The numbers across the top of the graph indicate the number of patients available at each time interval. All data points were significantly different from baseline at the P < 0.05 level.

213 (43.1%) withdrew prematurely: 55 (11%) due to therapeutic failure, 96 (19%) due to adverse events, and 62 (13%) due to administrative reasons (Fig. 1). This long-term, open-label study was originally designed to be a 2-year clinical trial. The duration was extended to 4 years after some patients had completed 2 years of treatment. Specifically, 102 patients (21%) of the 494 patients had completed the study according to the original 2-year protocol and were, therefore, not included among premature withdrawals.

Urinary Flow Rates
At all follow-up visits, the mean peak urinary flow rates were significantly higher than baseline values (Fig. 2). At baseline, peak flow rate was 10.0 mL/s. During early dose titration at months 1 and 2, it improved by 1.0 and 1.4 mL/s, respectively. From 3 to 42 months, improvement ranged from 2.3 to 4.0 mL/s above baseline. Between months 3 and 42, at least a 30% improvement in peak flow rate from baseline was observed in 40% to 59% of the patients (Fig. 3).

Boyarsky Symptom Scores
At all follow-up intervals, the mean Boyarsky symptom scores were significantly lower than at baseline; this was true of obstructive, irritative, and total scores (Fig. 4). At baseline, the mean total score for the overall population was 10.5, with a mean obstructive score of 6.2 and a mean irritative score of 4.3. Total Boyarsky scores during early dose titration at months 1 and 2 improved by 2.1 and 3.2 points, respectively. From 3 months onward, improvement ranged from 4.0 to 5.4 points. Between months 3 and 42, at least a 30% improvement in total symptom score from baseline was observed in 62.4% to 77.1% of the patients (Fig. 5).

Predictive Factors
Baseline characteristics for age, prostate size, symptom score, and peak urinary flow rate were examined with respect to absolute changes in peak flow rate and total Boyarsky symptom score (Table I). The only significant associations noted were between baseline peak flow rate and change in peak flow rate and between baseline symptom score and change in symptom score. Patients with
lower peak flow rates at baseline experienced greater improvements in peak flow rate. Those with higher baseline scores on the Boyarsky Symptom Index (i.e., more symptoms or more severe symptoms) had greater improvements in their scores. No other significant associations were found.

ADVERSE EVENTS

The most common adverse events resulting in discontinuation from the study were dizziness (6.7%), asthenia (3.8%), and somnolence (2.0%) (Table II). To draw conclusions about the occurrence of adverse events in this long-term study, the prevalence and incidence rates of selected adverse events were evaluated (Table III). Prevalence in any interval was defined as the proportion of patients experiencing the event in that interval divided by the number of patients who entered the interval; these patients may or may not have had the event in a previous interval. Incidence was defined as the number of newly reported events in any interval divided by the number of patients in the interval who had not experienced the event previously. Any patients who experienced the event previously were subtracted from the denominator. During each of the last three intervals, the prevalence of dizziness

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>55</td>
<td>6.7</td>
</tr>
<tr>
<td>Asthenia</td>
<td>19</td>
<td>3.8</td>
</tr>
<tr>
<td>Somnolence</td>
<td>10</td>
<td>2.0</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
<td>1.6</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6</td>
<td>1.2</td>
</tr>
<tr>
<td>Prostate carcinoma</td>
<td>5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

FIGURE 5. Percent of patients with more than 30% improvement in Boyarsky total symptom scores at each study visit. The numbers across the top of the graph indicate the number of patients available at each time interval.

<table>
<thead>
<tr>
<th>Treatment Interval</th>
<th>1-180 days</th>
<th>181-360 days</th>
<th>361-540 days</th>
<th>541-720 days</th>
<th>&gt; 720 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>14</td>
<td>14</td>
<td>11</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Asthenia</td>
<td>11</td>
<td>11</td>
<td>9</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Postural symptoms</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Impotence</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Key: Prev. = prevalence, percent of cases of the adverse events occurring in the interval; Inc. = incidence, percent of new cases reported during the interval.

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TABLE IV. Effect of terazosin on blood pressure in normotensive and hypertensive patients at 6 months

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean Blood Pressure (mm Hg)</th>
<th>Mean Pulse Rate (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>Change</td>
</tr>
<tr>
<td>No concurrent antihypertensives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive</td>
<td>291</td>
<td>129</td>
<td>78</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>84</td>
<td>146</td>
<td>92</td>
</tr>
<tr>
<td>Concurrent antihypertensives†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive</td>
<td>22</td>
<td>134</td>
<td>70</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>20</td>
<td>153</td>
<td>94</td>
</tr>
</tbody>
</table>

*P ≤ 0.05.
†Concurrent antihypertensives consisted of diuretics or angiotensin-converting enzyme inhibitors. Hypertensive was defined as a baseline diastolic blood pressure of 90 mm Hg or higher.

Mean changes in blood pressure and pulse from baseline to 6 months are summarized in Table IV; the BPH patients were divided into four groups according to whether they were normotensive or hypertensive and whether they were taking concurrent antihypertensive medication. In normotensive patients, small, clinically insignificant decreases in blood pressure were noted. Hypertensive patients had larger, clinically significant decreases irrespective of treatment for hypertension. No clinically significant changes in pulse rates were noted. Mean changes in blood pressure over time are portrayed in Figure 6 for normotensive and hypertensive patients without concurrent antihypertensive medication. The results at all time intervals, including those beyond 6 months, were similar to the results just discussed. The larger variability in blood pressure in the hypertensive group was due to the smaller number of patients in this group.

**COMMENT**

The objective of medical therapy in BPH is to relieve bladder outlet obstruction and bothersome urinary symptoms. Therefore, treatment efficacy is evaluated by increases in urinary flow rates and decreases in BPH symptom scores.18,23 Outcome measures are expressed either as mean changes from baseline or as the percentage of patients exhibiting a threshold level of improvement.

Terazosin administration resulted in peak urinary flow rates consistently greater than those recorded at baseline. At 1-month intervals during the first 5 months, the dose of terazosin was titrated to clinical response up to a maximum dose of 20 mg. Usually, clinical response was
achieved within the first 3 months of treatment and was maintained through 42 months. Thereafter, the peak flow rate and percentage of patients with a 30% or greater increase in peak flow rate were maintained through 42 months. At 3 months, the mean increase in peak flow rate was 23%; an improvement of at least 30% in peak flow rate was seen in 40% of the patients. This is consistent with the results of other studies, both open-label and double-blind, evaluating the efficacy of terazosin in men with BPH.13–21

The Boyarsky Symptom Index has been used extensively to assess symptom improvement during treatment for BPH.22 In this study, significant decreases in total, obstructive, and irritative Boyarsky scores were observed at all follow-up visits, starting at month 1, with the greatest decreases first recorded at 6 months and maintained throughout the 42 months of treatment. Other investigators have reported significant improvement in Boyarsky symptom scores within 2 weeks of reaching the final dose level.18 The relatively long time to maximum therapeutic effect observed in our study was due to the protracted titration schedule of 1-month intervals. At 6 months, the mean decrease in total, obstructive, and irritative Boyarsky scores was 4.5, 3.3, and 1.2, respectively. The percentage of patients exhibiting a 30% or greater decrease in the total Boyarsky scores was 67%. These findings are similar to those reported in other open-label and double-blind studies in which terazosin dose was titrated to clinical response. The changes we observed in total, obstructive, and irritative scores at 6 months were maintained throughout the 42 months of follow-up.

Recently, a multicenter, randomized, placebo-controlled study of the efficacy and safety of terazosin in patients with BPH has been reported in which the drug was titrated to a fixed dose.18 There were 285 patients randomized either to placebo or to terazosin in one of three doses: 2, 5, or 10 mg. The percent of patients who achieved at least a 30% improvement in total Boyarsky scores was 40% in the placebo group, 51% in the 2-mg terazosin group, 51% in the 5-mg group, and 69% in the 10-mg group. The percent of patients with 30% improvement in peak flow rate in the placebo, 2-mg, 5-mg, and 10-mg groups were 26%, 40%, 35%, and 52%, respectively. Because the clinical response to terazosin was dose-dependent and the 10-mg dose was associated with relatively few adverse events, the authors recommended that all patients with clinical BPH be treated with gradually increasing doses of the drug until reaching a daily dosage of 10 mg, providing that no significant adverse events occur.

In the present study, a titration-to-response protocol was utilized, with dose titration left to the discretion of individual investigators. Although the final dosages ranged from 1 to 20 mg daily, approximately half of the patients in the trial were receiving a regimen of 5 mg or less of terazosin per day at the time of this report. Because the clinical response to terazosin is dose-dependent, and other studies have shown that the maximum therapeutic dose of terazosin exceeds 5 mg, it is likely that the level of improvement seen in our study is conservative.

The incidence of adverse events in this study was moderate. The most common adverse events resulting in premature termination from the study were dizziness (6.7%), asthenia (3.8%), and somnolence (2.0%). The proportion of adverse events that were treatment-emergent is unknown, as the study design did not include a parallel placebo group. Over the 42-month course of the study, 19% of the patients were withdrawn due to the occurrence of an adverse event. In a recent 3-month, randomized, placebo-controlled study, only 7% of terazosin-treated patients and 4% of placebo-treated patients had their drug treatment terminated due to an adverse event.18 Other randomized, double-blind, placebo-controlled studies have demonstrated comparably low incidences of adverse events that resulted in withdrawal of terazosin-and placebo-treated patients.17,19 The evaluation of adverse events in an open long-term study is problematic. The overall, cumulative incidence of adverse events (ie, the number of events for the entire study duration), whether presumed terazosin-related (eg, dizziness, asthenia) or time-related (eg, headaches, colds, influenza), tends simply to increase with time and is, therefore, difficult to interpret. For this reason, we performed an additional analysis of prevalence and incidence rates of selected adverse events over discrete time intervals.

In this study, the prevalence of both dizziness and asthenia remained constant in each of the last three intervals at 7% to 8%, indicating that a subpopulation of patients continued to experience these events over the course of the study. In the case of dizziness, however, new events continued to arise over the entire study, with an incidence of 3% to 4% observed in each of the last three intervals. Thus, the prevalence of dizziness represented a mixture of patients, those with persistent dizziness and those experiencing symptoms for the first time.
Cases of asthenia followed a somewhat different pattern. The incidence declined over time, so that the relatively steady prevalence was largely due to patients with persistent asthenia rather than those reporting it for the first time in later intervals. The prevalence and incidence of other adverse events tended to decrease after the first interval, that is, there were no persistent events and few new events. The exception was impotence; all of these cases were identified early and persisted throughout the study, for there were no new events reported in later intervals.

Terazosin, an approved antihypertensive agent, elicited a predictable response in patients' blood pressures. The mean changes from baseline in systolic and diastolic blood pressures for normotensive patients ranged between 1 and 4 mm Hg; for patients hypertensive at baseline, the range was 10 to 15 mm Hg. Thus, terazosin lowered blood pressure in patients with BPH primarily when it was a desirable clinical outcome, but the drug had no clinically significant effect on the blood pressure of normotensive patients. Because 50% of men with BPH who are candidates for prostatectomy are also hypertensive, the dual therapeutic effect of terazosin is a desirable feature of the drug.

When our data were evaluated for dependence of clinical response to terazosin on baseline characteristics of patients, age was found to have no association with the response to terazosin therapy. Only two significant associations were found between baseline symptoms and treatment response: (1) patients with lower peak flow rates at baseline were observed to have greater improvements in peak flow rate, and (2) those with higher Boyarsky scores on obstructive and irritative symptoms had greater declines (ie, improvements) in their scores during treatment.

Our study design may be criticized for lack of a placebo control group and potential selection bias. However, the mean changes in peak flow rates and Boyarsky symptom scores observed in this open-label study were comparable to data from randomized, placebo-controlled studies. When we examined the data for potential differences between the cohort of patients transferred into the study from randomized, placebo-controlled studies and the cohort treated with terazosin for the first time, they were found to be comparable in baseline characteristics, outcome measurements, and incidence of adverse events.

The present study has the longest duration of treatment reported to date for evaluating the safety and efficacy of alpha blockers in the treatment of BPH. Our data and those of any long-term open-label study should be interpreted with caution, however, as nonresponders are unlikely to remain on long-term drug therapy when an agent has failed to produce the desired effect. Overall, 30% of the patients were withdrawn from therapy owing to adverse events (19%) or lack of efficacy (11%). Although our data are encouraging, the durability of terazosin efficacy needs to be studied for even longer periods of time. The findings in this 42-month study confirm previously reported data for the efficacy, safety, and tolerability of terazosin in the treatment of BPH.

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References
The management of benign prostatic hyperplasia (BPH) has changed dramatically in the last 5 years. Urologists recognize that BPH is not universally progressive and that surgical therapy done in the spirit of "do it now because the patient will need it eventually" is inappropriate. Selective alpha, antagonists (terazosin and doxazosin) and 5-alpha-reductase inhibitor therapy (finasteride) are now recognized as appropriate options that must be presented to the patient, along with the traditional approaches of watchful waiting and prostatectomy. Although medical therapy is clearly less effective than transurethral resection or incision of the prostate (TURP or TUIP), many patients will be satisfied with less than optimal symptom improvement in exchange for less risk, especially if their symptoms are not severely affecting their quality of life. However, despite the widespread acceptance of medical therapy for BPH, significant questions about long-term effectiveness, cost-effectiveness, and the etiology of treatment failure remain.

The study by Lepor and colleagues is an extremely important contribution to the field. Although the study lacks a control arm, it provides information on the long-term efficacy of terazosin that was previously lacking in the literature. The author discusses the limitations of the study design and correctly points out that a long-term, randomized trial would be necessary to establish unequivocally the benefits and risks of therapy. Only 47 patients had 42-month data available for analysis, significantly limiting our confidence that the estimates of treatment effect at 42 months accurately reflect the true effect. Nevertheless, several important conclusions can be drawn.

Based on these data and similar data from the long-term extension of the finasteride trials, it appears that only 50% to 60% of patients will stay on a drug for 4 years. This is somewhat disappointing and perhaps a point of concern from a cost-effective point of view. If a majority of patients who stop medical therapy go on to surgery, the true cost of medical management may be substantial. However, this scenario is unlikely to evolve for two reasons. First, in my experience, many (if not most) patients who stop one form of medical therapy try another medication or go back to watchful waiting. Second, the side effects of terazosin do not increase over time. However, 43% of the patients withdrew from the study prematurely: 19% due to adverse events, 11% due to treatment failure, and 13% due to administrative reasons.

Based on this information and other studies, medical therapy is clearly less effective than transurethral resection or incision of the prostate (TURP or TUIP), many patients will be satisfied with less than optimal symptom improvement in exchange for less risk, especially if their symptoms are not severely affecting their quality of life. However, despite the widespread acceptance of medical therapy for BPH, significant questions about long-term effectiveness, cost-effectiveness, and the etiology of treatment failure remain.

Long-term studies will be necessary to determine whether medical therapy actually prevents the progression of BPH over time. The National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health is beginning a trial to determine whether medical therapy delays or prevents the progression of the disease. Moreover, this trial should provide significant new insight into the etiology of treatment failure. If we understood why currently available forms of medical therapy produce only limited symptom improvement, it is likely that more effective pharmaceuticals could be designed. Until that day, "new" BPH medical therapies are likely to parallel the cephalosporin story: much fanfare about minor differences in efficacy.

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