Ciprofloxacin or Tamsulosin in Men with Chronic Prostatitis/Chronic Pelvic Pain Syndrome

A Randomized, Double-Blind Trial

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Background: Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) in men is principally defined by pain in the pelvic region lasting more than 3 months. No cause of the disease has been established, and therapies are empirical and mostly untested. Antimicrobial agents and α-adrenergic receptor blockers are frequently used.

Objective: To determine whether 6-week therapy with ciprofloxacin or tamsulosin is more effective than placebo at improving symptoms in men with refractory, long-standing CP/CPPS.

Design: Randomized, double-blind trial with a 2×2 factorial design comparing 6 weeks of therapy with ciprofloxacin, tamsulosin, both drugs, or placebo.

Setting: Urology outpatient clinics at 10 tertiary care medical centers in North America.

Patients: Patients were identified from referral-based practices of urologists. One hundred ninety-six men with a National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) score of at least 15 and a mean of 6.2 years of symptoms were enrolled. Patients had received substantial previous treatment.

Measurements: The authors evaluated NIH-CPSI total score and subscores, patient-reported global response assessment, a generic measure of quality of life, and adverse events.

Interventions: Ciprofloxacin, 500 mg twice daily; tamsulosin, 0.4 mg once daily; a combination of the 2 drugs; or placebo.

Results: The NIH-CPSI total score decreased modestly in all treatment groups. No statistically significant difference in the primary outcome was seen for ciprofloxacin versus no ciprofloxacin ($P = 0.15$) or tamsulosin versus no tamsulosin ($P > 0.2$). Treatments also did not differ significantly for any of the secondary outcomes.

Limitations: Treatment lasting longer than 6 weeks was not tested. Patients who had received less pretreatment may have responded differently.

Conclusion: Ciprofloxacin and tamsulosin did not substantially reduce symptoms in men with long-standing CP/CPPS who had at least moderate symptoms.

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common disorder and accounts for approximately 2 million visits to physicians annually in the United States (1). The substantial impact of CP/CPPS includes bothersome lower urinary tract symptoms, sexual dysfunction, reduced quality of life (2–5), and increased health care expenditures (6). The syndrome is diagnosed only on the basis of symptoms, principally pain or discomfort in the pelvic region. No objective measures can help define the disease.

Although bacteria can infect the prostate, most men with prostatitis have a negative midstream urine culture, indicating that bacteria may not be the cause of their symptoms (2). Such men are classified as having National Institutes of Health (NIH) category III prostatitis, the most common of the clinically defined prostatitis syndromes (7). It is by no means clear that the disease is characterized by inflammation of the prostate or that the prostate is responsible for symptoms in a substantial proportion of patients. Because of this uncertainty, the term *CP/CPPS* is used.

Chronic prostatitis/chronic pelvic pain syndrome is commonly seen by primary care practitioners, internists, and urologists. In the Olmsted County Study of Urinary Symptoms and Health Status Among Men (8), a population-based study in Olmstead County, Minnesota, the overall prevalence rate of a physician-assigned diagnosis of prostatitis was 9%. Population-based surveys of symptoms have estimated that the prevalence of the syndrome ranges from 9% to 12% among men (9, 10).

It is difficult to estimate the proportion of patients with symptoms lasting longer than 3 months whose disorder remains refractory to empirical therapy. These patients are commonly seen by urologists, but whether they represent a minor subpopulation of the overall symptomatic group or make up the majority of patients is unknown. We chose to study these patients because they present with a troubling, long-standing problem and are usually treated with agents of unclear benefit. Even if a relatively large number of men whose symptoms last 3 months or more are cured by standard empirical therapy and the clinical scenario we describe is uncommon, men with refractory symptoms still present a substantial problem to internists and urologists who have little information to guide therapy.

Because the cause of CP/CPPS is unknown, affected men receive many empirical therapies. The 2 most common treatments prescribed by physicians are antimicrobial

Context

Although the cause of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is unknown, physicians sometimes try to treat it with antibiotics or α-receptor blockers.

Contribution

In this multicenter, double-blind factorial trial, 196 men with moderately severe CP/CPPS were randomly assigned to 6 weeks of treatment with ciprofloxacin, tamsulosin, both drugs, or placebo. Neither ciprofloxacin nor tamsulosin substantively reduced symptoms.

Implications

Ciprofloxacin and tamsulosin were not effective treatments for CP/CPPS.

Cautions

Patients had long-standing, refractory CP/CPPS and received trial treatments for only 6 weeks. Patients with new diagnoses who are given longer courses of the trial treatments might respond differently.

–The Editors

agents and α-adrenergic receptor antagonists (2), although there is little objective evidence to support their use (11). Quinolones, such as ciprofloxacin, are commonly used to treat CP/CPPS because of their excellent penetration into the prostate and broad spectrum of coverage for uropathogens and other organisms traditionally believed to be associated with the syndrome (12). Tamsulosin, an α-blocker, is an effective treatment for lower urinary tract symptoms in men with benign prostatic hyperplasia, and it has been hypothesized that tamsulosin may improve these symptoms in men with CP/CPPS.

This randomized clinical trial was designed to evaluate whether ciprofloxacin or tamsulosin reduces symptoms of long-standing CP/CPPS of at least moderate severity, typical of the 488 men in our Chronic Prostatitis Cohort Study (2). The primary purpose of the trial was to test the most common prescription treatments given to men with CP/CPPS, who are commonly seen in our referral-based urologic practices.

METHODS

Organization

The Chronic Prostatitis Collaborative Research Network, a consortium sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), conducted the trial. Urologists and their clinical associates recruited patients at 10 sites in the United States and 1 site in Canada. The NIDDK established an independent data and safety monitoring board to review the progress, safety, and final analysis of the trial. The individual institutional review boards at each of the 10 participating clinical centers approved the study, and all men gave written informed consent.

Participants

The design of this trial has been described in detail previously (13). Participating urologists recruited both newly referred patients and patients with established CP/CPPS from their referral-based clinical practices at 10 tertiary medical centers in North America. Trial referrals came from primary care providers, internists, and other urologists. The primary diagnostic criterion was pain or discomfort in the pelvic region for at least 3 months in the previous 6 months. Severity of symptoms was assessed by using the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) (14, 15). This instrument is a validated questionnaire, completed by the patient, consisting of 4 questions about pain, 3 about voiding symptoms, and 2 about quality of life. The scores in these 3 individual domains (pain, voiding, and quality of life) are combined without weighting to yield the NIH-CPSI total score. Eligible men were required to have at least "moderate" symptoms, defined as an NIH-CPSI score of at least 15 of 43 possible points, at the time of randomization.

We excluded men who had a documented urinary tract infection (midstream urine culture > 100 000 colonies/mL) within the past 3 months, a history of active genital herpes within the previous year, a history of genitourinary cancer, inflammatory bowel disease, active urethral stricture, pros-

Table 1. **Study Design**

Variable	Tamsulosin		Comparison for Ciprofloxacin Main Effect
	Placebo	**Drug**	
Ciprofloxacin			
Placebo	Ciprofloxacin placebo, 1 tablet twice daily, *plus* tamsulosin placebo, 1 tablet daily	Tamsulosin alone: ciprofloxacin placebo, 1 tablet twice daily, *plus* tamsulosin, one 0.4-mg tablet daily	No ciprofloxacin
Drug	Ciprofloxacin alone: ciprofloxacin, one 500-mg tablet twice daily, *plus* tamsulosin placebo, 1 tablet daily	Combination: ciprofloxacin, one 500-mg tablet twice daily, *plus* tamsulosin, one 0.4-mg tablet daily	Ciprofloxacin
Comparison for tamsulosin main effect	No tamsulosin	Tamsulosin	

Table 2. Baseline Characteristics by Individual Treatment Groups*

Characteristic	Placebo Group	Ciprofloxacin Group	Tamsulosin Group	Combination Group
Patients, *n*	49	49	49	49
Ethnicity, *n (%)*				
White	26 (53)	35 (71)	34 (69)	32 (65)
Black or African American	6 (12)	10 (20)	6 (12)	9 (18)
Hispanic	11 (22)	4 (8)	4 (8)	7 (14)
Other†	6 (12)	0 (0)	5 (10)	1 (2)
Age, *y*	42.6 ± 12.0	45.9 ± 11.7	45.3 ± 9.7	44.5 ± 11.4
Time since diagnosis, *y*	6.7 ± 7.3	6.7 ± 7.2	6.3 ± 7.7	5.0 ± 6.0
NIH-CPSI‡				
Total score	25.0 ± 5.1	24.2 ± 6.2	24.6 ± 6.2	25.3 ± 6.1
Pain score	12.2 ± 3.0	11.7 ± 3.1	11.3 ± 3.6	12.0 ± 3.4
Urinary score	4.5 ± 2.5	4.8 ± 2.8	5.1 ± 2.9	5.0 ± 2.4
Quality-of-life score	8.3 ± 1.9	7.7 ± 2.2	8.2 ± 2.2	8.2 ± 2.3
Medical Outcomes Study 12-Item Short-Form Survey				
Mental summary score	41.6 ± 12.7	46.3 ± 11.6	45.7 ± 9.1	47.5 ± 12.3
Physical summary score	45.4 ± 9.2	45.3 ± 8.2	43.9 ± 9.8	44.9 ± 9.2

* Values presented with a plus/minus sign are means ± SD. NIH-CPSI = National Institutes of Health Chronic Prostatitis Symptom Index.
† Includes Asian, Pacific Islander, Native American, and multiracial.
‡ Scores on the NIH-CPSI represent the average of 2 baseline scores. The ranges of possible scores on the 3 NIH-CPSI domains are as follows: pain, 0–21 points; urinary, 0–10 points; quality of life, 0–12 points. The total score ranges from 0 to 43 points. The 3 domain scores may not sum to the total score because of rounding.

tate or bladder surgery, or neurologic disease affecting the bladder. We used ligase chain reaction to screen for *Chlamydia* in urethral urine samples and excluded men whose tests yielded positive results. Previous treatment with antimicrobial agents or α-adrenergic receptor blockers, including the study drugs, had to be completed at least 4 weeks before eligibility screening. Additional details of the eligibility criteria are available elsewhere (13).

Study Design and Interventions

Men were randomly assigned in equal proportions within a 2 × 2 factorial design to receive placebo; ciprofloxacin alone, 500 mg twice daily; tamsulosin alone, 0.4 mg once daily; or a combination of both drugs (**Table 1**). Patients were treated for 6 weeks, at which time the primary end point was assessed. Symptoms at 9 and 12 weeks after randomization (6 weeks after completion of treatment) were also assessed to evaluate longer-term treatment response. The 2 baseline screening contacts and the primary end point contact at 6 weeks were clinic visits; interim contacts at 3, 9, and 12 weeks were conducted by telephone.

Each patient was randomly assigned by computer. A permuted block randomization schedule with varying block sizes was used, stratified by clinical site. The research pharmacist at each site provided the blinded study drugs in 2 tamper-evident bottles. All clinical investigators, research nurses, and patients were blinded to treatment assignments until all patients had completed follow-up.

Outcomes

The primary outcome was the change in the NIH-CPSI total score from baseline to 6 weeks. The NIH-CPSI was administered at each of the 2 baseline screening visits, 1 to 3 weeks apart, and every 3 weeks thereafter until 12 weeks. The average of the 2 scores before randomization was used as the baseline score. Evaluation of the responsiveness of the NIH-CPSI indicates that a 4-point change on a scale of 0 to 43 points represents a difference detectable by the patient.

Secondary outcomes included changes in the pain, voiding, and quality-of-life subscales of the NIH-CPSI; physical and mental summary scores on the Medical Outcomes Study 12-Item Short-Form Health Survey (16); and a 7-point patient-reported global response assessment. Responders for the global response assessment were defined as men reporting that they were "markedly improved" or "moderately improved" at 6 weeks compared with baseline. Men for whom the global response assessment was missing were considered nonresponders and were included in the denominator for the assessment of response rates.

Adverse events were monitored throughout the study and graded according to the National Cancer Institute Common Toxicity Criteria (http://ctep.cancer.gov/reporting/ctc .html). Patients were asked at each contact to report any adverse events that had occurred since the previous contact. The questions were open-ended, and researchers did not ask about any specific categories of adverse events. All events, regardless of whether they were expected reactions to the study drugs, were recorded. Attribution to treatment was also assessed. However, because it was difficult to determine whether certain adverse events, such as pain, were related to treatment or to CP/CPPS, all events were analyzed.

Statistical Analysis

For each of the 2 primary treatment comparisons, the recruitment goal of 184 patients provided 80% power, at a 2-sided significance level of 5%, to detect a 4-point treatment difference in the NIH-CPSI total score between baseline and 6 weeks. We recognized that although patients could detect this difference, most might not perceive it as a major improvement. However, we did not want to miss

Figure 1. **Flow of patients through the study, according to individual treatment group.**
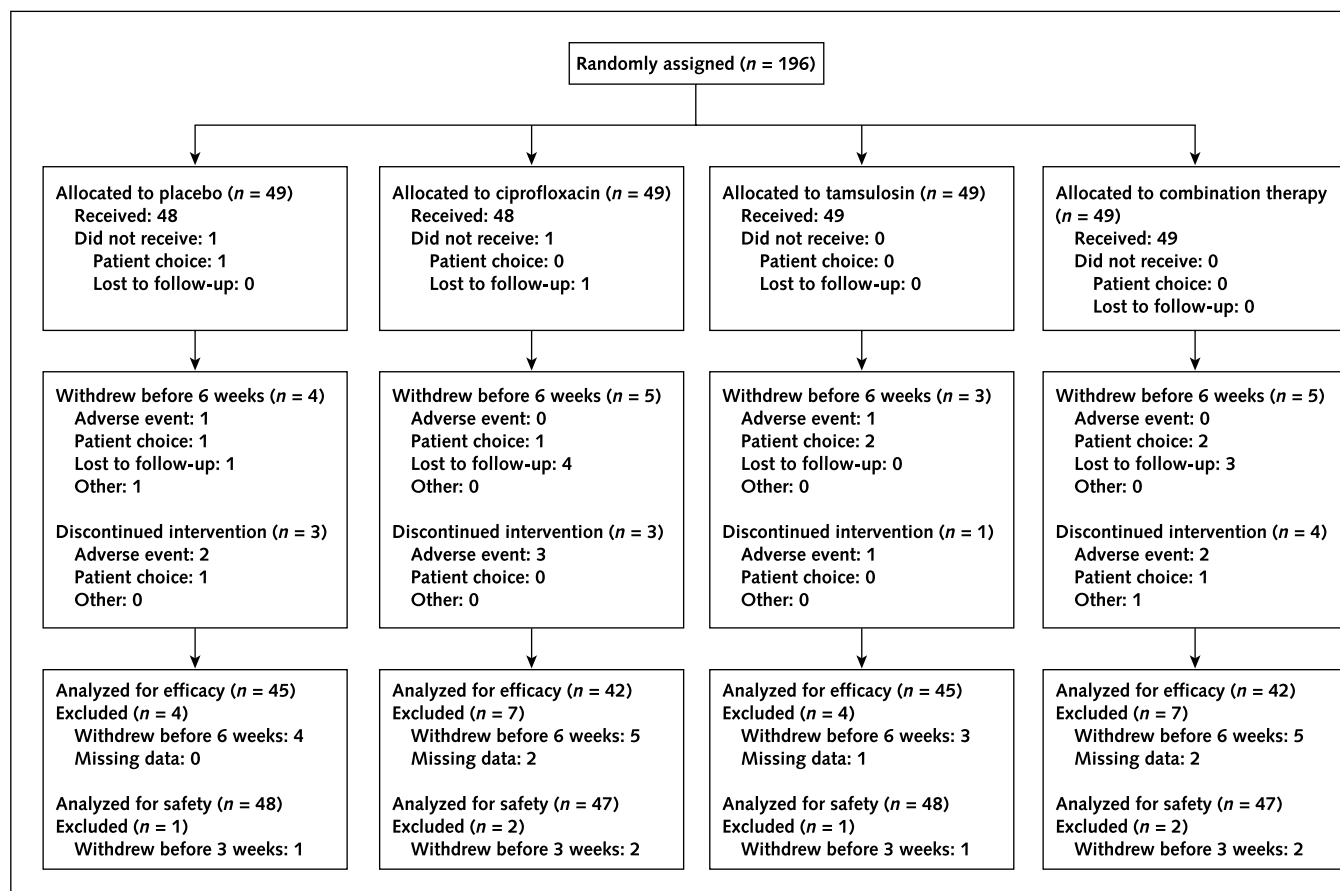
The number of patients to whom the study was presented and discussed was not captured.

even a minor change in the NIH-CPSI that could be attributed to a study drug.

We used an intention-to-treat analysis whenever possible for all comparisons, incorporating all available data on all randomly assigned patients. All statistical tests were 2-sided. Fisher exact and Kruskal–Wallis tests were performed on baseline demographic and symptom measures to assess the balance of randomization (17). We compared patient study status (completed or withdrawn) and response rates based on the global response assessment among groups by using the exact conditional test version of the Mantel–Haenszel test to control for clustering on clinical center (17). Overall adverse event rates, classifying each patient according to the worst grade reported across all body systems, were compared by using exact Jonckheere–Terpstra tests.

We compared changes over time in the NIH-CPSI total score and subscores among treatment groups by using random-effects regression models with a random slope and intercept for each patient (18). All available data on all randomly assigned patients were included in these models. The statistical analysis was based on a comparison of the slopes over time, represented by treatment-by-time interaction terms. The analysis was conducted in 2 parts within

the context of the factorial design. First, the potential presence of a treatment-by-treatment (by time) interaction term was tested at the 5% level of significance. We had statistical power to detect only large interaction effects. If there was evidence of a statistically significant interaction effect, the second part of the analysis considered the 4 treatment groups separately. If not, the second part of the analysis used a set of analyses to compare ciprofloxacin with no ciprofloxacin and a separate set of analyses to compare tamsulosin with no tamsulosin.

Two sets of descriptive statistics are presented for the changes in NIH-CPSI total score over time. First, the mean change from baseline to 6 weeks is presented for all patients who had complete data at both time points. Second, the estimated change over 6 weeks, based on the slope from the longitudinal regression models described earlier, is presented, along with a 95% CI for the slope. For the secondary longitudinal end points, only the mean change from baseline is shown for simplicity of presentation. All *P* values were derived from the longitudinal regression models.

Study conduct and safety were monitored throughout the trial. Because of the rapid accrual and the brief follow-up, we did not perform an interim analysis to compare

efficacy among treatment groups. The primary study results were presented to the data safety and monitoring board before unblinding of the treatment assignments.

Role of the Funding Sources

Project officers from the NIDDK were involved in the design and conduct of the study, the interpretation of the data, and the decision to submit the manuscript for publication.

RESULTS

One hundred ninety-six men were randomly assigned between July 2001 and June 2002. Most (65%) were white, with a mean age of approximately 45 years, a mean of 6.2 years since diagnosis of CP/CPPS, and a mean (±SD) NIH-CPSI total score of 24.7 ± 5.9 points (maximum potential score, 43 points) (**Table 2**). Treatment groups did not differ significantly in baseline demographic and clinical characteristics. We did not collect detailed information about previous treatments. However, 28% of the patients in the trial had also participated in the Chronic Prostatitis Cohort Study (2), which evaluated detailed information about previous therapy.

The flow of patients through the treatment portion of the study is shown in **Figure 1**. Of the 196 patients randomly assigned to a treatment group, 17 (9%) withdrew from the study before 6 weeks. Another 5 patients continued the study but missed the clinic visit at 6 weeks. Thus, 174 men (89%) were available for evaluation at 6 weeks. Eleven patients who discontinued treatment early but agreed to continue follow-up were included in all analyses. There was no statistically significant difference in the completion rate at 6 weeks for the ciprofloxacin or tamsulosin comparison ($P > 0.2$ for both). Another 3 participants withdrew from study follow-up between 6 and 12 weeks.

The changes in the primary end point from baseline to 6 weeks are shown in **Table 3**, both for the 2 main comparisons and for the individual treatment groups. The NIH-CPSI total score demonstrated a significant mean improvement of approximately 3 to 6 points in all 4 treatment groups. The test results for the treatment-by-treatment interaction for the primary end point were nonsignificant ($P = 0.075$). Therefore, the primary analysis considered the 2 main treatment comparisons separately.

For ciprofloxacin compared with no ciprofloxacin, no significant difference was seen in the decrease in NIH-CPSI total score from baseline to 6 weeks (slope estimate in the longitudinal regression model, -5.4 [95% CI, -6.8 to -3.9] vs. -3.9 [CI, -5.3 to -2.4]; $P = 0.15$). The difference in the slope estimate between these 2 groups was -1.5 (CI, -3.5 to 0.5). Of note, a decrease of 3.5 points is less than the 4 points considered to be detectable to patients. There was also no significant difference in NIH-CPSI total score for tamsulosin compared with no tamsulosin (slope estimate in the longitudinal regression model, -4.4 [CI, -5.8 to -2.9] vs. -4.8 [CI, -6.2 to -3.3]; $P > 0.2$). Similar overlap among the confidence intervals was seen for the individual treatment groups (**Table 3**). The end points of secondary symptoms and quality of life are shown in **Table 4** and **Table 5**. No significant effects of drug treatment were observed at 6 weeks for ciprofloxacin compared with no ciprofloxacin or tamsulosin compared with no tamsulosin.

Analyses of outcomes at 12 weeks demonstrated that additional changes after the end of treatment at 6 weeks were minimal. Changes over the entire 12-week study period for the individual treatment groups are illustrated in **Figure 2**. No statistically significant differences in the changes from 6 to 12 weeks were seen in any of the symptom-

Table 3. **Primary End Point: Change from Baseline to 6 Weeks in Total Score on the National Institutes of Health Chronic Prostatitis Symptom Index***

Treatment	Change from Baseline to 6 Weeks in Patients with Complete Data		Slope Estimate in the Longitudinal Regression Model (95% CI)	Difference in the Slope Estimate between Treatments (95% CI)
	Patients, *n (%)*	Mean NIH-CPSI Score ± SD†		
Ciprofloxacin‡				
No	90 (93)	−3.9 ± 5.7	−3.9 (−5.3 to −2.4)	−1.5 (−3.5 to 0.5)
Yes	84 (86)	−5.2 ± 6.8	−5.4 (−6.8 to −3.9)	
Tamsulosin§				
No	87 (89)	−4.7 ± 6.4	−4.8 (−6.2 to −3.3)	0.4 (−1.6 to 2.5)
Yes	87 (89)	−4.3 ± 6.1	−4.4 (−5.8 to −2.9)	
Individual groups				
Placebo	45 (92)	−3.4 ± 5.0	−3.2 (−5.2 to −1.2)	
Ciprofloxacin	42 (86)	−6.2 ± 7.3	−6.5 (−8.6 to −4.5)	
Tamsulosin	45 (92)	−4.4 ± 6.3	−4.5 (−6.5 to −2.6)	
Combination	42 (86)	−4.1 ± 6.1	−4.2 (−6.3 to −2.2)	

* NIH-CPSI= National Institutes of Health Chronic Prostatitis Symptom Index.
† The NIH-CPSI total score ranges from 0 to 43 points. A negative change indicates improvement.
‡ $P = 0.15$ for the test of the difference in change of NIH-CPSI score over 6 weeks between ciprofloxacin vs. no ciprofloxacin.
§ $P > 0.2$ for the test of the difference in change of NIH-CPSI score over 6 weeks between tamsulosin vs. no tamsulosin.

Table 4. **Secondary End Points: Changes from Baseline to 6 Weeks, Main Effects***

Symptom Score	Ciprofloxacin			Tamsulosin		
	No	Yes	P Value	No	Yes	P Value
Patients, *n*	98	98		98	98	
Responders, *n (%)*†	23 (24)	16 (16)	>0.2	22 (23)	17 (17)	>0.2
Patients with complete data at 6 weeks, *n (%)*‡	90 (92)	84 (86)		87 (89)	87 (89)	
NIH-CPSI§						
Total score	−3.9 ± 5.7	−5.2 ± 6.8	0.15	−4.7 ± 6.4	−4.3 ± 6.1	>0.2
Pain score	−1.9 ± 3.3	−2.4 ± 4.2	>0.2	−2.3 ± 3.8	−2.0 ± 3.7	>0.2
Urinary score	−0.7 ± 2.0	−1.2 ± 2.0	0.10	−0.9 ± 2.1	−1.0 ± 1.9	>0.2
Quality-of-life score	−1.2 ± 1.8	−1.6 ± 2.2	0.20	−1.5 ± 2.0	−1.3 ± 2.0	>0.2
Medical Outcomes Study 12-Item Short-Form Survey						
Mental composite score	1.2 ± 10.1	−0.9 ± 8.9	0.19	0.8 ± 9.7	−0.5 ± 9.5	>0.2
Physical composite score	2.7 ± 7.2	2.6 ± 7.6	>0.2	2.0 ± 7.3	3.3 ± 7.4	0.17

* Values presented with a plus/minus sign are means ± SD. NIH-CPSI= National Institutes of Health Chronic Prostatitis Symptom Index.
† Patients who withdrew before 6 weeks were considered nonresponders and were included in the denominator for the calculation of response rates in an intention-to-treat analysis.
‡ Means ± SDs for symptom and quality-of-life end points include only the 174 patients who had complete data at both baseline and 6 weeks. Thus, this analysis excludes the 17 patients who withdrew from study before 6 weeks as well as 5 patients who continued in the study but missed the clinic visit at 6 weeks for various reasons. *P* values are derived from the longitudinal regression models that included all available data on all patients. These results do not represent an intention-to-treat analysis and should be interpreted cautiously because of the potential bias related to patient withdrawal from the study.
§ The ranges of possible scores on the 3 NIH-CPSI domains are as follows: pain, 0–21; urinary, 0–10; quality of life, 0–12. Total possible score ranges from 0 to 43 points. A negative change indicates improvement. The 3 domain scores may not sum to the total score because of rounding.

related outcomes for either of the treatment comparisons (data not shown).

Adverse events in each individual treatment group are shown in the **Appendix Table** (available at www.annals .org). All events that occurred during the 6-week treatment period are shown, regardless of attribution to study drugs. Among the 190 men followed for at least 3 weeks, 41 (22%) reported grade 1 ("mild"), 33 (17%) reported grade 2 ("moderate"), and 2 (1%) reported grade 3 ("severe") adverse events. Most adverse events involved nonpelvic pain and gastrointestinal disturbances. The grade 3 events were progression of chronic pelvic pain in 1 patient receiving placebo and 1 patient receiving ciprofloxacin alone. No statistically significant difference was seen in overall adverse event rates for ciprofloxacin compared with no ciprofloxacin (*P* > 0.2) or tamsulosin compared with no tamsulosin

(*P* > 0.2). We also saw no difference when all 4 treatment groups were compared (*P* > 0.2).

DISCUSSION

We tested 2 of the drugs most commonly prescribed for treatment of CP/CPPS in men with moderate to severe long-standing symptoms. The data show that neither ciprofloxacin nor tamsulosin significantly reduced the NIH-CPSI total score over 6 weeks compared with placebo. Moreover, neither treatment showed a significant benefit among a wide range of secondary outcomes related to symptoms and quality of life.

The cause of CP/CPPS remains unknown. Because bacterial infections of the prostate do occur (19), it has long been assumed that CP/CPPS is due to bacterial infec-

Table 5. **Secondary End Points: Changes from Baseline to 6 Weeks in Individual Groups***

| Variable	Placebo Group	Ciprofloxacin Group	Tamsulosin Group	Combination Group
Patients, *n*	49	49	49	49
Responders, *n (%)*†	11 (22)	11 (22)	12 (24)	5 (10)
Patients with complete data at 6 weeks, *n (%)*‡	45 (92)	42 (86)	45 (92)	42 (86)
NIH-CPSI§				
Total score	−3.4 ± 5.0	−6.2 ± 7.3	−4.4 ± 6.3	−4.1 ± 6.1
Pain score	−1.6 ± 2.9	−3.0 ± 4.6	−2.3 ± 3.7	−1.8 ± 3.7
Urinary score	−0.5 ± 2.0	−1.3 ± 2.1	−0.9 ± 2.0	−1.1 ± 1.8
Quality-of-life score	−1.2 ± 1.5	−1.9 ± 2.4	−1.3 ± 2.0	−1.3 ± 1.9
Medical Outcomes Study 12-Item Short-Form Survey				
Mental composite score	2.7 ± 9.5	−1.2 ± 9.7	−0.3 ± 10.6	−0.7 ± 8.3
Physical composite score	1.5 ± 6.6	2.5 ± 7.9	3.9 ± 7.5	2.7 ± 7.3

* Values presented with a plus/minus sign are means ± SD. NIH-CPSI= National Institutes of Health Chronic Prostatitis Symptom Index.
† Patients who withdrew before 6 weeks were considered nonresponders and were included in the denominator for the calculation of response rates in an intention-to-treat analysis.
‡ Means ± SDs for the symptom and quality-of-life end points include only the 174 patients who had complete data at both baseline and 6 weeks. Thus, this analysis excludes the 17 patients who withdrew from the study before 6 weeks as well as 5 patients who continued the study but missed the clinic visit at 6 weeks for various reasons. These results do not represent an intention-to-treat analysis and should be interpreted cautiously because of the potential bias related to patient withdrawal from the study.
§ The ranges of possible scores on the 3 NIH-CPSI domains are as follows: pain, 0–21; urinary, 0–10; quality of life, 0–12. Total possible score ranges from 0 to 43 points. A negative change indicates improvement. The 3 domain scores may not sum to the total score because of rounding.
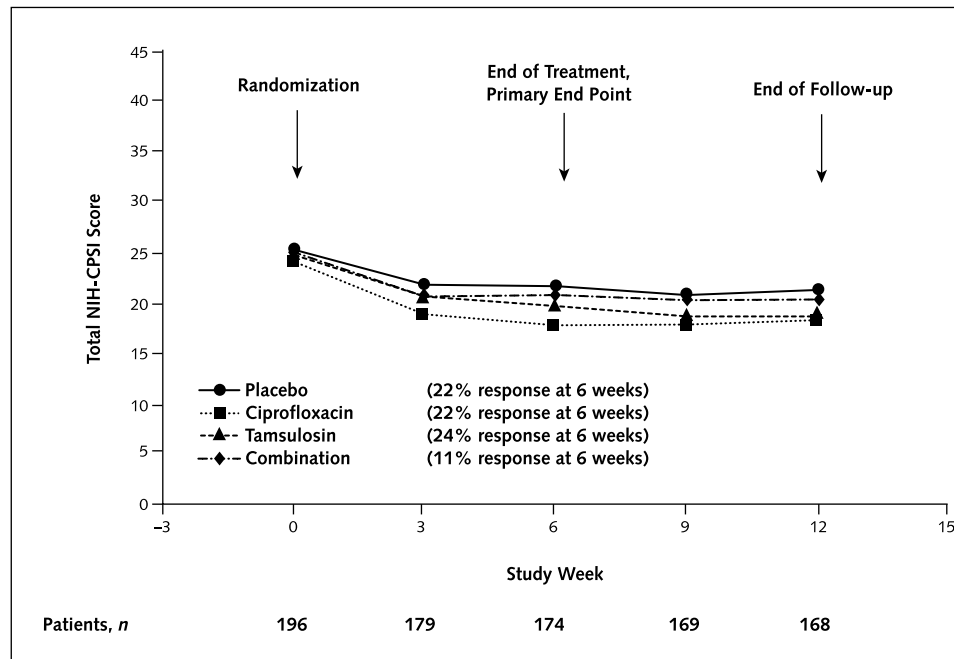
All available data on all patients are included in the means; the sample sizes at each time point are as shown.

tion. However, recent studies have shown that the presence of bacteria localized to the prostate does not correlate with symptoms (20) and that the localization of bacteria in prostatic secretions is indistinguishable in men with CP/CPPS and age-matched asymptomatic men (21). These data suggest that the presence of bacteria in the prostatic fluid cannot itself explain CP/CPPS symptoms. Since antibiotics can improve symptoms but response to antimicrobial agents does not correlate with bacteriologic status (22), a placebo-controlled trial of antimicrobial agents was essential. In a recently reported clinical trial whose design was similar to ours, Nickel and colleagues (23) found no significant difference in the NIH-CPSI total score in men treated with 6 weeks of levofloxacin compared with placebo.

α-Adrenergic receptor blockers such as tamsulosin have proven to be effective in treating voiding symptoms attributed to benign prostatic hypertrophy (24). Presumably, these drugs are used empirically in patients with CP/CPPS because such patients have similar voiding symptoms (3). However, until recently (25, 26), no placebo-controlled studies of these drugs supported their use in men with CP/CPPS.

It is possible that the patients we chose to study, men with refractory long-standing symptoms, represent a small subpopulation of the overall group of men with CP/CPPS. Nonetheless, further study of such men is urgently needed because they have a persistent problem of unknown cause for which there is minimal evidence to guide therapy. The agents we selected for testing might be more effective in men who have received less previous treatment, as suggested by Cheah and associates, who performed a similar study using terazosin (25). As shown in the Chronic Prostatitis Cohort Study (2), men with persistent symptoms who are seen by a physician most commonly receive antimicrobial agents or α-adrenergic receptor blockers, and it is this practice that we specifically wished to test. Thus, the purpose of the study was not to identify a population more likely to respond to standard empirical therapy but to determine whether this therapy for men with long-standing symptoms was more effective than placebo.

We did not test the use of these drugs for longer than 6 weeks. A longer treatment interval may have resulted in improved symptom scores. Six weeks was chosen because it was representative of the usual interval of treatment with antimicrobial agents; it is generally believed that bacterial organisms responsible for symptoms should be eradicated within this time. Testing of α-adrenergic receptor blockers for longer periods may be justifiable. In their study in men with CP/CPPS, which was reported after we completed recruitment, Cheah and associates (25) compared terazosin with placebo and found that terazosin provided a statistically significant improvement in outcomes based on the NIH-CPSI total score. Patients were treated with terazosin for 12 weeks, including upward dose titration, and had never been treated with α-adrenergic receptor blockers. However, Cheah and associates' study sample was drawn from diverse Asian nations and the median age was younger than that in our study. Another study of alfuzosin (26) showed that this agent modestly but statistically significantly improved symptoms compared with placebo after 6

months of treatment. These studies suggest that longer treatment with α-adrenergic receptor blockers may be warranted in patients with CP/CPPS.

Our study is also limited because patients' previous therapy may have included the study drugs we tested. Although men who have previously experienced treatment failure with a fluoroquinolone antimicrobial agent, for example, would probably be unlikely to respond to another course of ciprofloxacin, this is precisely how the disease is managed at present. Men often receive initial treatment with antimicrobial agents and report improvement in symptoms. After they finish treatment, however, their symptoms recur and they present requesting further therapy. We specifically sought to determine whether improvement after ciprofloxacin therapy exceeded that achieved with placebo in a blinded study and found that it did not.

The ideal study would involve men with CP/CPPS who are naive to antimicrobial therapy. However, CP/CPPS cannot be defined as chronic until symptoms have been present for 3 months, and in that interval most men are treated with antimicrobial agents. Therefore, recruiting antimicrobial-naive patients might be problematic. Also, researchers cannot tell in advance whether men presenting with initial symptoms consistent with CP/CPPS will remain chronically symptomatic or will be cured. Until practice patterns for CP/CPPS change, it will be difficult to test antimicrobial agents in affected men. A trial testing α-blockers in less heavily pretreated patients who are naive to the study drug is planned.

In conclusion, 6 weeks of treatment with ciprofloxacin or tamsulosin did not significantly reduce symptoms as assessed by the NIH-CPSI total score in men with CP/CPPS. Our data do not support the use of these agents as empirical therapy for men with long-standing CP/CPPS and at least moderate symptoms.

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