α-Blockers for Treatment of the Prostatitis Syndromes

J. Curtis Nickel, MD

Department of Urology, Queen's University, Kingston, Ontario, Canada

The prostatitis syndromes are among the most common and frustrating clinical challenges for urologists in outpatient practice. Available treatment, especially for the chronic prostatitis syndromes, is poor, with no standard therapy producing significant cure rates. α-Blocker therapy has been advocated (with various levels of evidence) as a treatment modality for all categories of the prostatitis syndromes. This article reviews the evidence supporting the use of α-blocker therapy in patients with prostatitis. Further trials of longer duration, perhaps employing combination therapies, are indicated to better evaluate the role of α-blockers in the management of the prostatitis syndromes.
[Rev Urol. *2005;7(suppl 8):S18–S25*]

Key words: α-Blockers • Benign prostatic hyperplasia • Lower urinary tract symptoms • Prostatitis syndromes

Clinical benign prostatic hyperplasia (BPH) is the most common cause of lower urinary tract symptoms (LUTS) in older men. However, LUTS may occur in men of all ages and are not necessarily related to BPH. The prostatitis syndromes, acute and chronic as well as bacterial and nonbacterial, can also result in variable LUTS and pain/discomfort. The pain and discomfort associated with prostatitis is localized to the perineum, suprapubic/pelvic area, testes, and

penis. Storage (irritative) symptoms, such as increased frequency, urgency, and nocturia, which are recognized as being the most bothersome urinary symptoms of BPH, are commonly seen in patients with prostatitis syndrome. Voiding (obstructive) symptoms, such as hesitancy, slow stream, intermittency, and terminal dribble, occur not only in patients with BPH but also in patients with prostatitis.

Prostatitis: A Clinical Challenge

The prostatitis syndromes are among the most frustrating clinical challenges for urologists in outpatient practice. The prevalence of men experiencing prostatitis-like symptoms may range up to 6%.[1-3] The prevalence of men with a concurrent or previous diagnosis of prostatitis ranges from 11% to 14%.[4-6] Prostatitis comprises approximately 8% and 12% of outpatient visits made by men to urologists in North America and Europe, respectively.[7,8] The quality of life of men with chronic prostatitis is dismal and significantly below that of patients with BPH, as well as most patients with prostate cancer.[9] Available treatment, especially for the chronic prostatitis syndromes, is poor, with no standard therapy producing significant cure rates.[10]

Table 1
National Institutes of Health Classification of Prostatitis Syndromes

Category	Characteristics
I: Acute bacterial prostatitis	Acute infection of the prostate gland
II: Chronic bacterial prostatitis	Chronic infection of the prostate characterized by recurrent urinary tract infections
III: Chronic prostatitis/ chronic pelvic pain syndrome	Symptoms of discomfort or pain in the pelvic region for at least 3 months in the absence of uropathogenic bacteria cultured by standard techniques
IIIA: Inflammatory chronic pelvic pain syndrome	Significant number of leukocytes in EPS, VB3, or semen (ejaculate)
IIIB: Noninflammatory chronic pelvic pain syndrome	No evidence of significant leukocytes in EPS, VB3, or semen
IV: Asymptomatic inflammatory prostatitis	Leukocytes in EPS, VB3, semen, or prostate tissue during evaluation for other disorders in men without symptoms of prostatitis
Iatrogenic treatment-induced prostatitis*	Clinical evidence (symptoms and/or inflammatory cells) of iatrogenically induced prostatic inflammation by prostate-specific treatments (eg, heat or radiation therapy)

*This category is not recognized in the National Institutes of Health classification system.
EPS, expressed prostatic secretion; VB3, post–prostatic massage urine.
Data from Krieger JN et al. *JAMA*. 1999;282:236-237.[11]

Classification and Diagnosis of Prostatitis

The prostatitis syndromes have recently been reclassified by the National Institutes of Health (NIH) Advisory Committees (Table 1)[11,12]: category I (acute bacterial prostatitis) is associated with acute bacterial infection of the prostate gland; category II (chronic bacterial prostatitis) is associated with chronic infection of the prostate gland, characterized by recurrent lower urinary tract infections; category III (chronic prostatitis/chronic pelvic pain syndrome [CP/CPPS]) is characterized by chronic pain/discomfort (of longer than 3-months duration) in the pelvic/perineal area with negative bacterial cultures employing standard microbiologic techniques; and category IV (asymptomatic inflammatory prostatitis) is diagnosed in patients with prostatic inflammation but no symptoms. Other prostatitis-like syndromes exist that are difficult to classify under the NIH classification system. These include iatrogenic prostatic inflammation resulting from heat treatment of BPH (eg, transurethral microwave thermal therapy [TUMT]) and radiation therapy for prostate cancer (external beam radiotherapy and brachytherapy). These treatment-induced syndromes are characterized by obstructive and irritative voiding symptoms and significant risk of acute urinary retention (AUR).

Acute bacterial prostatitis is diagnosed clinically and confirmed by a positive urine culture. Chronic bacterial prostatitis is suspected in men with recurrent lower urinary tract infection and a confirmed culture of uropathogenic bacteria in prostate-specific specimens (expressed prostatic secretion [EPS] or post–prostatic massage urine). Category III prostatitis, CP/CPPS, is a diagnosis of exclusion made in men presenting with chronic pelvic/perineal pain and variable voiding symptoms.

North American and international consensus groups have established criteria for the diagnosis and evaluation of men presenting with suspected CP/CPPS.[13] A North American consensus group considered medical history taking, physical examination, and urinalysis/urine culture mandatory for the evaluation of all patients with suspected CP/CPPS. Recommended evaluations included a lower urinary tract localization test, symptom inventory or index (NIH Chronic Prostatitis Symptom Index [NIH-CPSI]),[14] flow rate measurement, residual urine determination, and urine cytology. Optional evaluations included semen analysis and cultures, urethral swab for culture, pressure flow studies, videourodynamics (including flow electromyography), cystoscopy, transrectal ultrasound, pelvic imaging (pelvic ultrasound), computed tomography scan, magnetic resonance imaging, and prostate-specific antigen measurement in selected patients.

Category IV prostatitis is diagnosed by the observation of excessive leukocytosis in specimens of EPS, post–prostatic massage urine sediment, or semen. The diagnosis of iatrogenic prostatic inflammation is made in patients presenting with acute exacerbation of irritative and obstructive voiding symptoms (including AUR) following the treatment of BPH or prostate cancer with thermotherapy or radiation. Urine culture should be sterile, and the prostate, if examined (not mandatory), may feel swollen and tender.

Therapy for the Prostatitis Syndromes

Category I: Acute Bacterial Prostatitis

Treatment of acute bacterial prostatitis should consist of immediate wide-spectrum antibiotic therapy (usually starting with parenteral antibiotics), supportive therapy and, if necessary, bladder drainage (with either a urethral or suprapubic catheter). Obstructive voiding symptoms and AUR are common in men presenting with acute bacterial prostatitis. α-Blocker therapy has been suggested to ameliorate obstructive voiding symptoms in men with category I prostatitis who do not have obvious AUR.[15]

Category II: Chronic Bacterial Prostatitis

Category II prostatitis is characterized by relapsing infection (usually with the same organism) and recurrent symptoms. The mainstay of treatment is long-term antibiotic therapy; the fluoroquinolone class of antibiotics appears to be the most effective. Men presenting with chronic bacterial prostatitis also experience irritative and obstructive voiding symptoms, which persist to some extent in many men after successful resolution of the bacterial infection. It is believed that dysfunctional obstructive voiding may be associated with the pathogenesis of this condition by allowing bacteria to reflux into the prostate via the prostatic ducts.

Combining α-blocker therapy with antibiotics appears to reduce the risk of prostatitis recurrence compared with the use of antibiotics alone. Barbalias and colleagues[16] conducted a retrospective, uncontrolled study of combined α-blocker and antibiotic therapy in patients with prostatitis. Of the 270 subjects evaluated in the study, 64 were classified as having category II prostatitis. All 64 subjects with chronic bacterial prostatitis received antibiotic therapy, and half received α-blocker therapy as well. Patients were followed for a mean of 22 months. The authors noted a symptomatic recurrence rate of 84% in the subjects who received both α-blockers and antibiotics, compared with an 88% symptomatic recurrence rate in those who received antibiotics alone. The culture-positive recurrence rate was 16% with combination α-blocker and antibiotic therapy, compared with 75% with the use of antibiotics alone.

Category III: CP/CPPS

Treatment. CP/CPPS is characterized by pain and discomfort in the perineum, pelvis, testes, and penis and is associated with obstructive and irritative voiding symptoms. Dysfunctional high-pressure voiding (and possibly related intraprostatic ductal reflux) is thought to be implicated in the pathogenesis of CP/CPPS. Treatment of CP/CPPS includes an empiric trial of antibiotics, as well as the use of anti-inflammatory agents, 5-α-reductase inhibitors, pentosan polysulfate, phytotherapies, muscle relaxants, antidepressants, and analgesics. None of these treatments results in significant cure rates, although most of them result in modest symptom amelioration compared with placebo. α-Blockers have become an important therapeutic tool in the physician's armamentarium for the treatment of CP/CPPS.

Mechanisms. There are a number of reasons why α-blockers may benefit patients with CP/CPPS. Dysfunctional voiding is implicated in the pathogenesis of this disorder. α-Blockers have been demonstrated to improve bladder outlet obstruction and subsequent voiding dysfunction. Men with CP/CPPS experience significant LUTS

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(overlapping with BPH-like symptoms). α-Blockers have proven efficacy in ameliorating similar LUTS in older men with BPH. α-Receptors are present in the prostate, bladder neck, and central nervous system. α-Blockade in the bladder neck and prostate results in the improvement in LUTS noted above. Over time, improvement in voiding function may lead to less inflammation (and/or pressure), eventually resulting in less pain. There is a possibility that α-receptors in the central nervous system may be implicated in long-term pain syndromes. The favorable pain response seen in these patients may be secondary to central α-blockade mechanisms.

Early trials. There have been numerous anecdotal reports of α-blockers ameliorating symptoms of chronic prostatitis (chronic nonbacterial prostatitis and prostatodynia). An early, uncontrolled, open-label trial of terazosin in 25 patients with chronic prostatitis/prostatodynia demonstrated significant improvement in a new prostatitis-specific symptom score of 76%.[17] In the retrospective review of prostatitis patients performed by Barbalias and colleagues,[16] 163 patients with nonbacterial prostatitis/prostatodynia received either terazosin or alfuzosin. Of these patients, 105 (64%) had a satisfactory symptom response.

A number of randomized, placebo-controlled trials of α-blockers in patients with nonbacterial prostatitis and prostatodynia were conducted in the 1980s and early 1990s (Table 2). At that time, however, there were no validated outcome parameters for this particular disease. In a randomized, placebo-controlled trial of 37 patients with nonbacterial prostatitis, Osborn and colleagues[18] noted that 50% of men who received phenoxybenzamine had a satisfactory symptom response, compared with 8% of those who received placebo. Dunzendorfer and colleagues[19] confirmed these findings in a randomized, controlled trial of 39 men. The investigators noted a subjective decrease in pain in subjects who received phenoxybenzamine compared with placebo ($P < .05$). de la Rosette and colleagues[20] randomized 20 patients with chronic nonbacterial prostatitis to either alfuzosin or placebo for 6 weeks and noted mild symptom improvement in the subjects who received alfuzosin ($P = .01$).

In a study by Lacquaniti and colleagues,[21] 18 patients who had received a diagnosis of nonbacterial prostatitis were randomized to receive terazosin, tamsulosin, or placebo. Both terazosin and tamsulosin significantly

Table 2
Clinical Trials Evaluating α-Blockers in Men With Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Study	Intervention	Design	N	Outcome
Osborn et al, 1981[18]	Phenoxybenzamine	RCT	37	Satisfactory response: 50% vs 8% with placebo
Dunzendorfer et al, 1983[19]	Phenoxybenzamine	RCT	39	Decrease in pain compared with placebo ($P < .05$)
de la Rosette et al, 1992[20]	Alfuzosin	RCT	20	Modest symptom score improvement compared with placebo ($P = .01$)
Neal and Moon, 1994[17]	Terazosin	Uncontrolled	24	19 subjects (76%) showed significant improvement in symptom score
Barbalias et al, 1998[16]	Terazosin or alfuzosin	Uncontrolled	163	105 subjects (64%) had satisfactory symptom response
Lacquaniti et al, 1999[21]	Terazosin or tamsulosin	RCT	18	Symptom score improvement compared with baseline, but not in placebo group
Gül et al, 2001[22]	Terazosin	RCT	91	Symptom score improvement compared with placebo ($P = .001$)
Cheah et al, 2003[24]	Terazosin	RCT	100	57% response compared with 36% in placebo group ($P = .03$) at 14 weeks
Mehik et al, 2003[25]	Alfuzosin	RCT	70	65% response compared with 24% in placebo group ($P < .001$) at 6 months
Nickel et al, 2004[26]	Tamsulosin	RCT	58	52% response compared with 33% in placebo group ($P = .04$) at 6 weeks

RCT, randomized controlled trial.

reduced symptom score from baseline (P = .0002 and P = .001, respectively), whereas placebo had no effect on symptoms. The study was too small and not powered to show a significant difference in treatment effect between the α-blockers and placebo.

In a study by Gül and colleagues,[22] 91 men who had received a diagnosis of CPPS were randomized to treatment with terazosin (2 mg/d) or placebo. At 3 months, 69 patients (terazosin [n = 39], placebo [n = 30]) returned for evaluation employing an unvalidated pain-specific symptom index. Although the investigators noted a statistically significant (P = .001) treatment effect (the difference in the change from pre- to post-treatment scores between the terazosin and placebo groups), they concluded that a longer duration of treatment would be necessary to obtain a better clinical effect.

Validated outcome index. Assessing patient response to α-blockers from these early trials was difficult. The researchers employed different definitions of prostatitis symptoms, used variable inclusion/exclusion criteria, and did not have available a validated outcome parameter, such as a symptom index. In 1999, the NIH Chronic Prostatitis Collaborative Research Network (CPCRN) developed and then validated the NIH-CPSI.[14] This index can be used to obtain a total score (0 to 43), or the 3 major domains of the prostatitis experience can be scored separately. The pain domain (score, 0 to 21) measures the location, frequency, and severity of the pain/discomfort; the voiding domain (score, 0 to 10) measures the obstructive and irritative voiding symptoms; and the impact/quality-of-life domain (score, 0 to 12) measures the specific impact of prostatitis on patient quality of life. The emergence of this validated symptom index stimulated a flurry of research activity as many therapeutic options (including α-blockers) were evaluated in well-designed, randomized, placebo-controlled trials.[23]

Cheah and colleagues[24] randomized 100 patients with chronic prostatitis to either terazosin or placebo for 14 weeks; 86 subjects completed follow-up assessments. Subjects who received terazosin had a 57% reduction in mean symptom score, compared with a 36% reduction in subjects who received placebo (P = .03). Terazosin therapy resulted in modest but significant improvement in all domains (pain, urinary, and quality-of-life) of the NIH-CPSI.

Mehik and colleagues[25] evaluated 70 CP/CPPS patients in a unique, randomized, placebo-controlled trial. In this study, 21 subjects were randomized to 6 months of alfuzosin therapy; 19 subjects were randomized to 6 months of placebo; and 30 subjects elected to be followed concurrently on standard therapy. Compared with both the placebo and standard-therapy groups, patients who received alfuzosin had a significant amelioration of symptoms, which was evident at 4 months and became even more clinically significant by 6 months. At the end of the 6-month active treatment phase, symptoms scores quickly deteriorated back to baseline in the patients who had received placebo. Symptom scores also deteriorated in the patients who had received alfuzosin, but not to the same extent, and these patients were still better off at 12 months than those who had received placebo. This important trial demonstrates that long-term α-blocker therapy is required before significant symptom amelioration occurs and that the duration of α-blocker therapy may have to be longer than was originally believed (>6 months).

Nickel and colleagues[26] designed and implemented a 6-week, double-blind pilot study of tamsulosin versus placebo in patients with chronic nonbacterial prostatitis/CPPS. Results of the study were presented by Narayan and colleagues[27] at the 2002 Annual Meeting of the American Urological Association. Fifty-eight men with CP/CPPS were randomized to receive tamsulosin, 0.4 mg, or placebo after a 2-week placebo run-in. The principal study outcome parameter was the NIH-CPSI (total score and domain subscores). Primary analysis included mean change in the NIH-CPSI from baseline in quartiles of symptom severity. At 6 weeks, the subjects who received tamsulosin demonstrated a statistically significant treatment effect (−3.6 points; P = .04) compared with those who received placebo. No significant treatment effect was observed in patients who had mild symptoms (25th percentile, −1.6 points; P = .53). Patients with severe symptoms (75th percentile) had a statistically and clinically significant response compared with those who received placebo (treatment effect, −8.3 points; P < .01). This pilot study showed tamsulosin to be significantly more effective than placebo, particularly in men with moderate or severe CP/CPPS. This effect was noted in both the total score and domain subscores of the NIH-CPSI. There was no difference in adverse events in the

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subjects who received tamsulosin versus those who received placebo, suggesting that tamsulosin is well tolerated in men with CP/CPPS. This study suggests a real treatment effect that occurs after only 6 weeks of tamsulosin therapy.

The NIH CPCRN conducted a randomized, controlled, phase 3 trial comparing placebo, ciprofloxacin, tamsulosin, and ciprofloxacin plus tamsulosin in men with CP/CPPS.[28] This trial, which enrolled long-term, heavily pretreated patients, failed to show any improvement in patients treated with tamsulosin (with or without ciprofloxacin) when compared to patients treated with placebo. The lessons learned from these very well designed and implemented studies were that symptom amelioration with α-blockers occurs only after more than 6 weeks of therapy in less heavily pretreated patients, who have experienced recent onset of moderate to severe symptoms.

Table 3
Rationale for the Clinical Use of α-Blocker Therapy for the Prostatitis Syndromes

Category	Clinical Utility of α-Blocker Therapy
National Institutes of Health Prostatitis Categories	
I: Acute bacterial prostatitis	Adjuvant therapy (with antibiotics) to improve obstructive urinary symptoms
II: Chronic bacterial prostatitis	Adjuvant therapy (with antibiotics) to reduce recurrence rate
III: Chronic prostatitis/chronic pelvic pain syndrome	Long-term monotherapy or combination multimodal therapy for amelioration of symptoms
IV: Asymptomatic inflammatory prostatitis	No clinical utility
Iatrogenic Treatment-Induced Prostatitis	
TUMT-induced	Neoadjuvant and adjuvant therapy to decrease posttreatment irritative voiding symptoms and risk of AUR
Radiation therapy–induced	Neoadjuvant and adjuvant therapy to decrease risk of AUR; may be used to treat radiation cystoprostatourethritis

TUMT, transurethral microwave thermal therapy; AUR, acute urinary retention.

Category IV: Asymptomatic Inflammatory Prostatitis

At the present time, there is no indication for the use of α-blockers for the treatment of category IV asymptomatic inflammatory prostatitis.

Other Prostatitis Syndromes: Iatrogenic Heat- and Radiation-Induced Prostate Inflammation

TUMT is associated with long-term symptom amelioration in patients with BPH. However, many weeks are needed for symptoms to resolve and, in many patients, there is an increase of irritative and obstructive voiding symptoms and an appreciable risk of AUR after the procedure. In a study by Djavan and colleagues,[29] 81 patients were randomized to receive TUMT alone (n = 41) or TUMT plus tamsulosin (n = 40). Tamsulosin was employed in a neoadjuvant and adjuvant setting (2 weeks before and 12 weeks after therapy). Tamsulosin combined with TUMT in this manner improved the velocity of symptom relief in the 6 to 12 weeks following therapy. In addition, patients who received tamsulosin experienced less AUR after the procedure (2%) compared with those who received TUMT alone (12%).

Radiation therapy for prostate cancer induces prostatourethritis in many patients. Symptoms include nocturia, frequency, hesitancy, and decreased flow. It is estimated that prostatourethritis occurs in 50% of patients who receive conformal external beam radiation therapy and 95% of patients who receive interstitial radiation therapy. Usually, this process is self-limited and the patient's symptoms improve over time without therapy; however, in many cases, the symptoms severely affect patient quality of life in the posttreatment period. In a study by Prosnitz and colleagues,[30] 26 patients with radiation-induced prostatourethritis received tamsulosin, 0.4 mg or 0.8 mg. Twenty subjects (77%) achieved control of their symptoms with tamsulosin therapy. Of these subjects, 10 required a 0.4-mg dose and 10 required a 0.8-mg dose for symptomatic control. This perceived benefit of α-blocker therapy after radiation should be evaluated in a prospective, randomized, placebo-controlled trial.

Almost all patients develop storage/voiding symptoms after prostate brachytherapy for prostate cancer. It is estimated that 3% to 22% of these patients develop AUR, and the risk of AUR correlates with the severity of the preimplant symptom score. Merrick

and colleagues[31] initiated tamsulosin therapy in 156 (92%) of 170 patients undergoing transperineal ultrasound-guided prostate brachytherapy for stage T1C through T3A prostate cancer. Eighty-eight percent of patients had the catheter successfully removed on the day of brachytherapy. The International Prostate Symptom Score returned to preimplant levels at a median of 6 weeks (mean, 13.3 weeks). This study suggests that neoadjuvant and adjuvant α-blockade may benefit patients undergoing brachytherapy, especially those suffering from moderate to severe BPH-like symptoms. This perceived benefit should be assessed in a randomized, placebo-controlled trial.

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Future Considerations

Prostatitis, particularly the chronic prostatitis syndromes, is a difficult clinical condition to treat. α-Blockers benefit patients suffering from the prostatitis syndromes but, like many other treatments, do not produce spectacular cure rates. A trend toward combination therapy is developing, not only for the treatment of BPH (as in the Medical Therapy of Prostatic Symptoms trial[32]) but also for the treatment of prostatitis.[33] The combination of an α-blocker and a 5-α-reductase inhibitor for the treatment of BPH results in more significant short- and long-term benefits than does either agent alone. Combination or multimodal therapy for prostatitis with α-blockers and other potentially beneficial agents that have independent actions (eg, anti-inflammatory agents, 5-α-reductase inhibitors, phytotherapeutic agents) should be evaluated in prospective, randomized, placebo-controlled trials.

Summary

α-Blockers have a role in the treatment of the prostatitis syndromes (Table 3). In patients with acute bacterial prostatitis (category I), α-blockers possibly ameliorate obstructive and irritative voiding symptoms. In men with chronic bacterial prostatitis (category II), α-blockers appear to reduce the risk of clinical and bacteriologic recurrence. In patients with CP/CPPS (category III), α-blockers ameliorate symptoms and improve quality of life. This has now been demonstrated in at least 3 independent, randomized, placebo-controlled trials employing similar inclusion/exclusion criteria and validated outcome parameters. α-Blockers also appear to ameliorate the symptoms and reduce the risk of AUR in patients with heat- or radiation-induced prostatic inflammation. Additional trials of longer duration employing combination therapies are needed to better evaluate the role of α-blocker therapy for the management of the prostatitis syndromes. ■

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Main Points

- The prostatitis syndromes result in lower urinary tract symptoms as well as pain and discomfort. These syndromes are among the most frustrating clinical challenges for urologists in outpatient practice.
- The National Institutes of Health classifies the prostatitis syndromes into 4 categories: category I, acute bacterial prostatitis; category II, chronic bacterial prostatitis; category III, chronic prostatitis/chronic pelvic pain syndrome; and category IV, asymptomatic inflammatory prostatitis.
- α-Blocker therapy has been suggested to ameliorate obstructive voiding symptoms in men with category I prostatitis who do not have obvious acute urinary retention (AUR).
- In patients with category II prostatitis, the combination of α-blockers and antibiotics appears to reduce the risk of recurrence compared with antibiotic therapy alone.
- In patients with category III prostatitis, α-blockers have been shown to ameliorate symptoms and improve quality of life.
- α-Blockers are not indicated for category IV prostatitis.
- α-Blocker therapy appears to reduce the voiding symptoms and risk of AUR that may occur after transurethral microwave thermal therapy, as well as the prostatourethritis that may be induced by brachytherapy.

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