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Chronic Prostatitis/Chronic Pelvic Pain Syndrome: Role of Alpha Blocker Therapy

Abstract

Introduction: This article reviews the rationale and data supporting alpha blocker therapy for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), the most common and difficult prostatitis syndrome. **Methods:** Systematic review identified ten clinical trials evaluating alpha blocker therapy for patients with CP/CPPS, including five open-label or small prospective studies and five double-blinded and placebo-controlled clinical trials. **Results:** Encouraging results in uncontrolled and small clinical trials led to the development of reasonably powered, double-blinded, placebo-controlled, randomized clinical trials evaluating terazosin, doxazosin, tamsulosin, and alfuzosin. **Conclusions:** Current data suggest that treatment-naïve and/or newly diagnosed patients appear more likely to respond than long-term, chronic refractory patients. Longer courses of treatment (12 weeks to 6 months) appear superior to shorter courses, and less selective agents appear superior to more selective alpha₁ blockers. These observations outline important questions that must be answered to define optimal treatment strategies for patients with CP/CPPS.

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Introduction

Alpha blockers represent a common therapy for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) [1–3], the most common and difficult prostatitis category. Patients with CP/CPPS experience considerable morbidity from symptoms of chronic prostatitis but have no evidence of active infection or other urological disorders [4]. This article reviews the rationale for alpha blockers in patients with CP/CPPS. We explain the current terminology and pharmacology, emphasizing that these agents have many common features but also important differences. From a pharmacological standpoint, the alpha blockers used in urology are not interchangeable. These drugs may work by different mechanisms and with different efficacy in patients with lower urinary tract symptoms related to benign prostatic hyperplasia (BPH) and in those with symptoms of CP/CPPS.

In the following, we summarize the literature supporting the use of alpha blockers for the treatment of CP/CPPS, starting with the initial clinical observations. These preliminary studies resulted in the development of high-quality randomized clinical trials. Strengths and limitations of the available data are then used to develop current recommendations for alpha blocker therapy for patients with symptoms of prostatitis.

Table 1. Summary of α_1 receptor subtypes

Native ¹	Cloned receptor nomenclature		Anatomic distribution
	old ²	new ^{3, 4}	
α_{1A}	α_{1c}	α_{1a}	urethral smooth muscle, heart, arterial smooth muscle, prostate
α_{1B}	α_{1b}	α_{1b}	prostate epithelium, venous smooth muscle
α_{1D}	$\alpha_{1a}, \alpha_{1d}, \alpha_{1a/d}$	α_{1d}	bladder detrusor muscle, bladder neck, sacral spinal cord, spleen, lung

¹ α_1 adrenoceptor nomenclature.

² Molecular cloning techniques have identified three distinct members of α_1 -adrenoceptor gene products. However, the nomenclature was not consistent, leading to the introduction of a new scheme [58].

³ The nomenclature follows the recommendations of the International Union of Basic and Clinical Pharmacology Sub-committee on Adrenoceptors.

⁴ The pharmacological subtype is expressed in capital letters, in contrast to the molecular biological subtype which is expressed in lowercase letters.

Rationale for Alpha Blocker Therapy for Patients with CP/CPPS

The original rationale for alpha blocker treatment was based on four clinical observations: (1) some patients with prostatitis were believed to suffer from dysfunctional voiding and/or bladder outflow obstruction related to prostatic hypertrophy [5, 6]; (2) alpha blockers have proven effective for many patients with voiding dysfunction and bladder outflow obstruction; (3) some patients experiencing both prostatitis symptoms and lower urinary tract symptoms appear to benefit substantially from alpha blocker therapy [6–8], and (4) urologists have considerable experience with alpha blockers for other indications. These observations resulted in the empiric use of alpha blockers to treat patients with symptoms of CP/CPPS. Clinically, many patients appeared to improve following therapy.

Pharmacology of Alpha Blockers in the Lower Urinary Tract

Alpha and beta receptor sites can be found in many tissues, such as blood vessels, spinal cord, prostate, bladder, and detrusor muscle. The high density of alpha receptor sites in the genitourinary tract resulted in the development of specific pharmacological agents to treat genitourinary problems. Molecular structural studies demonstrated two alpha receptor families, namely α_1 (with three subtypes: α_{1a} , α_{1b} , and α_{1d}) and α_2

(also with three subtypes: α_{2a} , α_{2b} , and α_{2c}) [9]. Alpha receptors from both families are members of the G-protein-linked receptor family. Alpha agonists alter cell activities through second messenger systems to change catecholamine levels and induce a broad range of responses. The α_1 -adrenergic receptors are located predominantly in postsynaptic cells in smooth muscles, heart, vas deferens, brain, and prostate [10–12] (table 1).

Improved understanding of alpha blocker pharmacology and pharmacokinetics resulted in the development of agents that have proven effective for the treatment of genitourinary disorders, especially BPH (table 2). In addition, these agents offered potential benefit for patients with other urological disorders, including CP/CPPS. The critical point is that the available alpha-blocking agents work at varied pharmacological sites and cannot be presumed to be clinically equivalent.

Data and Debate

The observations supporting alpha blocker therapy for CP/CPPS have become subject to heated debate.

Role of Bladder Outflow Obstruction and Voiding Disorders in Patients with CP/CPPS

The most controversial statement is that patients with CP/CPPS often have evidence of bladder outflow obstruction and/or dysfunctional voiding that can be improved by alpha blocker therapy.

Table 2. Alpha blockers evaluated clinically for treating lower urinary tract symptoms

Category	Agents	Site of action	Main indications	Major side effects
Non-selective	phentolamine phenoxybenzamine labetalol α -difluoromethyl-orthinine	peripheral alpha receptors, vascular smooth muscle	hypertension	orthostatic hypotension, reflex tachycardia, nasal, stuffiness, retrograde ejaculation
Selective α_1	terazosin doxazosin alfuzosin ¹	bladder trigone, urethra, prostatic capsule	BPH, hypertension	orthostatic hypotension
Selective α_{1a}	tamsulosin [59]	prostate capsule	BPH	retrograde ejaculation
Selective α_{1d}	naftopidil [60]	bladder smooth muscle	BPH	orthostatic hypotension

¹ The primary effect of alfuzosin is on the prostatic capsule, resulting in clinical 'uroselectivity' [61, 62].

Beginning in the early 1970s, a number of authors suggested that urodynamic studies could identify patients with chronic prostatitis caused by bladder neck dysfunction and/or obstruction [13–22]. The concept was that dysfunctional voiding led to high pressure, turbulent urine flow, intraprostatic reflux of urine into the prostatic ducts, or intraprostatic antibody deposition leading to pain and other symptoms [17, 19, 23–27]. Uncontrolled studies concluded that such patients could benefit substantially from procedures, such as endoscopic incision, transurethral resection of the prostate, transtrigonal posterior prostatectomy, or balloon dilation of the prostate [18, 19, 25, 28–31]. Such patients were also considered to be candidates for alpha blocker therapy.

Other authors drew dramatically different conclusions, finding that alpha blockers provided minimal benefit, because patients with urodynamic evidence of obstruction often responded poorly to treatment [25, 29]. Mayo et al. [32] evaluated the possibility that articles suggesting that high rates of obstruction in prostatitis patients might reflect referral of patients to urodynamics centers. They compared 201 men aged 18–50 years presenting to their urodynamic unit with lower tract symptoms with the findings in 123 prostatitis clinic patients. Only 37 of the 201 urodynamics unit patients (18%) had significant pain and might have been diagnosed as having chronic prostatitis, including 4 patients (11%) with definite obstruction. Fewer of the 123 prostatitis patients had obstruction (definite in 2 patients or 1.6% and equivocal in 1 patient or 0.8%; $p = 0.03$). Consistent with this report, a recent large, randomized clinical trial comparing alpha blocker with placebo therapy for CP/CPPS

found no correlation between clinical response and urodynamic parameters [33].

Other data suggest that alpha-blocking agents might prove effective in treating CP/CPPS by mechanisms besides improvement of the urodynamic parameters. Certain α_1 blockers work at sites other than prostate and bladder neck. These sites may prove important for treating CP/CPPS [33]. Mehik et al. [34] suggested that men with CP/CPPS often have an increased intraprostatic pressure. These researchers compared 42 patients with chronic nonbacterial prostatitis with 12 men without urological complaints. The intraprostatic tissue pressure proved higher in the prostatitis patients ($p < 0.001$). These authors hypothesized that an elevated intraprostatic pressure may reflect increased tissue resistance or poor tissue microcirculation. In theory, alpha blockers might improve such pathophysiological processes without effecting voiding.

Uncontrolled and Small Prospective Studies of Alpha Blocker Therapy for Patients with Chronic Prostatitis Symptoms

The identification of alpha receptors in the urinary tract raised the possibility that patients with prostatitis symptoms related to dysfunctional voiding might benefit from pharmacological therapy. Early studies employed agents such as phentolamine [35], phenoxybenzamine [36–38], or α -difluoromethylornithine [37]. The nonspecific alpha-blocking agents available in the early 1980s had side effect profiles that severely limited their clinical utility for treating patients with symptoms of prostatitis [39].

Table 3. Open-label and small prospective studies evaluating alpha blocker therapy for chronic prostatitis symptoms

First author year	Alpha-blocker (classification)	Study design	Active therapy, follow-up after therapy	Total participants	Primary outcome
Osborn 1981 [36]	phenoxybenzamine (nonselective alpha blocker)	open label	4 weeks	27	48% of the patients improved ¹
de la Rosette 1992 [43]	alfuzosin (selective alpha-1)	2-arm multicenter	6 weeks	20	p = 0.01
Neal 1994 [40]	terazosin (selective alpha-1)	open label	4 weeks	25	76% of the patients improved ¹
Lacquaniti 1999 [45]	terazosin (selective alpha-1) or tamsulosin (selective alpha-1 _{a/d})	3-arm multicenter	8 weeks	18	terazosin, p = 0.0002 ² tamsulosin, p = 0.001 ³
Evliyaoglu 2002 [46]	doxazosin (selective alpha-1)	2-arm, single center	12 weeks	60	p = 0.001 ⁴

¹ The response rate was defined as complete symptom resolution.

² Significance for terazosin versus placebo therapy.

³ Significance for tamsulosin versus placebo therapy.

⁴ The primary end point was defined using the change from pre- and posttreatment values of the International Prostate Symptom Score.

The development of more selective alpha₁ agents with fewer side effects led to uncontrolled, open-label trials [40–42] and some small randomized prospective studies [36, 43]. Encouraging results were reported for alpha₁ blockers in trials evaluating: terazosin [44, 45], doxazosin [46], and alfuzosin [43] (table 3). These observations were extended in other uncontrolled investigations of multimodal programs incorporating alpha blockers in various combinations with antibiotics, anti-inflammatory drugs, prostatic massage, anti-inflammatory phytotherapy, and neuromuscular agents [41, 47–49]. Such observations led to the development of reasonably powered, randomized clinical trials evaluating alpha blocker therapy [50].

Randomized Clinical Trials of Alpha Blocker Therapy for CP/CPPS

Meta-Analysis of Randomized Clinical Trials Employing Alpha Blockers

Four clinical trials met evidence-based criteria for inclusion in a meta-analysis of CP/CPPS therapies (table 4) [33, 51–54]. Pooled estimates from these randomized clinical trials were created using statistical modeling [52]. The authors concluded that these investigations provided evidence for efficacy, since the pooled relative risk for improvement was 0.57 (95% confidence interval 0.24–0.91,

p = 0.10). Although this analysis demonstrated a 42% increase in the likelihood of improvement with alpha blocker therapy, the amount of improvement was modest.

Limitations

These four studies represent the best available data. A fifth high-quality randomized clinical trial [55] will soon be completed to add to the body of high-quality data. The studies employed three different alpha blockers. These agents differ in their precise sites and mechanisms of action. Further, there were important differences in study designs, duration of therapy, and patient populations evaluated. These issues limit the value of combining the available data in a statistical analysis. Below, we consider each study separately.

Tamsulosin

Two trials evaluated tamsulosin, an alpha_{1a/d} subtype selective blocker, for treating patients with symptoms of CP/CPPS.

Comparison of Tamsulosin with Placebo Therapy

Nickel et al. [51] completed a multicenter study comparing tamsulosin with placebo treatment.

Population. The study included 58 patients with CP/CPPS. All participants in this multicenter trial were younger than 55 years old and had moderate or severe

Table 4. Double-blinded, placebo-controlled, randomized clinical trials evaluating alpha blocker therapy for patients with CP/CPPS

First author year	Alpha blocker (classification)	Study design	Active therapy, follow-up after therapy	Participants	Significance, primary outcome
Nickel 2004 [51]	tamsulosin (selective alpha-1 _{a/d})	2-arm, multicenter	6 weeks	58 referral patients	p = 0.04
Alexander 2004 [53]	tamsulosin (selective alpha-1 _{a/d})	4-arm factorial design, multicenter	6 weeks	174 heavily pretreated, tertiary referral ¹	p > 0.2 ²
Mehik 2003 [54]	alfuzosin (selective alpha-1)	three-arm, two centers ³	6 months 6 months	66 ⁴	p = 0.01
Pontari, in progress [55]	alfuzosin (selective alpha-1)	2-arm, multicenter	12 weeks	270 alpha-blocker-naïve patients with symptoms for < 2 years	in progress
Cheah 2003, 2004 [33, 57]	terazosin (nonselective alpha-1)	2 arm, single center	14 weeks 38 weeks	100 newly diagnosed, treatment-naïve patients	p = 0.03

¹ This study included 174 evaluable patients, including: 132 treated with placebo, tamsulosin alone, ciprofloxacin alone, or the combination of tamsulosin plus ciprofloxacin.

² p value for tamsulosin compared to no tamsulosin therapy.

³ Randomized clinical trial of alfuzosin or placebo plus 'control or standard arm' (sitz baths and anti-inflammatory therapy, as needed).

⁴ The 66 evaluable patients included 37 patients in the randomized clinical trial and 29 patients in the standard/control arm.

symptoms. Details of previous treatment are not provided, but it appears likely that many subjects were referred for management of chronic, refractory prostatitis symptoms.

Study Design. This trial design was double-blind, randomized, and placebo controlled. Following a 2-week washout period, the study participants received either tamsulosin (0.4 mg daily) or placebo for 6 weeks. Assessments were on days 15 and 45 using the National Institutes of Health Chronic Prostatitis Symptoms Index (NIH-CPSI) scoring. The primary end point was the change in NIH-CPSI total score from baseline to day 45.

Results. Tamsulosin proved superior to placebo. On day 45, the participants receiving active therapy had larger decreases in their NIH-CPSI total scores (treatment effect -3.6, p = 0.04). Tamsulosin therapy proved most effective for participants with higher total NIH-CPSI scores at baseline. Tamsulosin was more effective than placebo for participants with higher total NIH-CPSI scores at baseline (treatment effect -8.3, p < 0.01), higher pain domain scores (treatment effect -2.9, p = 0.02), higher urinary domain scores (treatment effect -2.3, p < 0.01), and worse quality-of-life domain scores (treatment effect -2.1, p = 0.02). The benefit of tamsulosin increased with

time (no significant difference between tamsulosin and placebo after 15 days of therapy).

Summary. Tamsulosin was more effective than placebo in relieving CP/CPPS symptoms. Although the patients did not benefit significantly after 2 weeks, there was a significant benefit after 6 weeks of therapy. The overall benefit of tamsulosin was modest, but patients more severe symptoms were more likely to benefit from the treatment.

Tamsulosin, Ciprofloxacin, Combination, or Placebo Therapy

The NIH Chronic Prostatitis Clinical Research Network conducted one of the most interesting studies [50, 53].

Population. The study participants were from a heavily pretreated, tertiary referral population. Their mean duration of symptoms was 6.2 years [53]. More than 90% of the subjects had failed previous therapy with either or both of the agents evaluated before they entered the study [2].

Study Design. This multicenter study employed a 2 × 2 factorial design to evaluate four treatments: placebo, tamsulosin hydrochloride (0.4 mg daily) only, ciprofloxacin (500 mg twice daily) only, and tamsulosin hy-

drochloride combined with ciprofloxacin [50]. Since there were relatively few subjects for the design, this study had limited power to evaluate potential interactions between the treatments. Stated another way, the study had very little ability to determine whether one active therapy inhibited or enhanced the other. Participants receiving the combination therapy were included in the comparisons of both individual drugs to the placebo treatment.

The primary response criterion was a 4-point decrease in the NIH-CPSI total score from baseline to week 6. Other outcomes included: NIH-CPSI domain scores, a patient-reported global assessment, and mental summary scores on the Medical Outcomes Study 12-Item Short-Form Health Survey.

Results. The study highlighted important design issues. The NIH-CPSI scores improved significantly in all four treatment groups (by approximately 3–6 points), consistent with other randomized clinical trial results. These observations support the need for blinding and placebo therapy groups in CP/CPPS treatment trials. Because test results for treatment-by-treatment interaction for the primary end point were not considered significant ($p = 0.075$), the primary analysis considered the two main treatment comparisons separately. This is an important study design issue, because the authors might have interpreted this borderline p value as suggesting an interaction between the treatments.

In contrast to the other published high-quality clinical trials, this study found no significant difference in the primary outcome for ciprofloxacin versus no ciprofloxacin ($p = 0.15$) or for tamsulosin versus no tamsulosin ($p > 0.2$). The best result was for the 42 participants in the ciprofloxacin-only group who reported an average 6.2 ± 7.3 -point decrease in NIH-CPSI total score versus a mean decrease of 3.4 ± 5.0 points for the 45 men in the placebo group. The 45 participants treated with tamsulosin only had an average 4.4 ± 6.3 -point decrease in NIH-CPSI scores. The worst outcomes were noted for the 42 participants receiving combination therapy who had an average 4.1 ± 6.1 -point decrease in NIH-CPSI scores. There was no significant difference among treatments for any secondary outcome.

Summary. This study highlights important issues for the design of future clinical trials. Although the trial results identified no benefit from any treatment, the authors were careful to emphasize that patients who had received less pretreatment may have responded differently. The authors also noted that a longer course of therapy might result in better outcomes.

Alfuzosin

Alfuzosin is an α_{1a} blocker that has been termed ‘uroselective’, because most α_{1a} receptors are in the prostate [56]. One randomized treatment trial of alfuzosin therapy has been published [54], while another important trial is in progress.

Population. Mehik et al. [54] screened 120 consecutive Finnish men who presented to two hospital clinics for treatment of CP/CPPS. The patients were offered a variety of treatment options.

Study Design. The patients were encouraged to enroll in a double-blind placebo-controlled pilot study or a ‘positive-control/standard-therapy group’. In addition, patients could receive treatment without enrolling in a study.

The participants who agreed to the randomized clinical trial received alfuzosin (5 mg twice daily) or placebo for 6 months with an additional 6 months of follow-up. The patients who agreed to participate but not to be randomized received ‘control or standard’ therapy (‘traditional hot sitz baths and anti-inflammatories’). No participant in the randomized trial or the standard-therapy group received alpha blockers, antibiotics, or 5α -reductase inhibitors. Outcome measures included changes from baseline in the total and domain scores of the Finnish NIH-CPSI. Improvement was defined as $>33\%$ decrease from the baseline evaluation.

Results

The 66 evaluable subjects included 37 men in the randomized clinical trial and 29 men who received control/standard treatment. Of the 37 participants in the clinical trial, 17 received alfuzosin therapy, and 20 received placebo therapy.

After 6 months of treatment, the alfuzosin group had a greater decrease in total NIH-CPSI scores than the placebo and control/standard groups (mean 9.9-, 3.8-, and 4.3-point decreases, respectively; $p = 0.01$). Greater improvement occurred in the NIH-CPSI pain domain in the alfuzosin group at 6 months than in the placebo and control/standard treatment groups ($p = 0.01$), but there was no difference in voiding or quality-of-life domains among the three groups.

Of 17 participants receiving alfuzosin, 11 (65%) had $>33\%$ improvement in their mean NIH-CPSI total scores as compared with 5 (25%) of 20 receiving placebo and 9 (32%) of 29 receiving control/standard treatment ($p = 0.02$). At 12 months, the symptom scores in all NIH-CPSI domains decreased in the alfuzosin and placebo groups, but not in the control/standard group (mean to-

tal NIH-CPSI score decreases of 3.5, 0.1, and 5.6 points, respectively).

Summary

In this report, 6 months of alfuzosin treatment resulted in a modest improvement, particularly in the NIH-CPSI pain domain, as compared with placebo and standard/traditional treatment. This benefit required several months of treatment and decreased 6 months after treatment was discontinued.

Ongoing Studies

The NIH Chronic Prostatitis Clinical Research Network is conducting a randomized clinical trial comparing alfuzosin (10 mg daily) to placebo treatment for alpha-blocker-naïve patients who have had CP/CPPS symptoms for 2 years or less [55]. Treatment is for 12 weeks. The participants may have had considerable previous treatment, provided this treatment did not include alpha blockers.

The enrollment goal is 270 participants from eleven clinical centers. This trial is progressing well with more than half of the total patients enrolled. This placebo-controlled randomized clinical trial should provide important information on the benefit of this selective α_{1a} blocker for treatment-naïve CP/CPPS patients.

Terazosin

Terazosin is considered a nonselective α_1 blocker that represents the least selective alpha blocker evaluated in high-quality randomized clinical trials. Cheah et al. [33] enrolled 100 20- to 50-year-old subjects who met the NIH consensus criteria for CP/CPPS in this clinical trial.

Study Population

This study was limited to newly diagnosed patients who had received minimal prior treatment. No participant had received previous alpha blockers. Thus, the participants were substantially different from the heavily pretreated tertiary referral patients evaluated in most studies from North America.

Study Design

This double-blinded randomized clinical trial compared terazosin (with dose escalation from 1 to 5 mg daily) to placebo therapy for 14 weeks. The primary outcome was the NIH-CPSI quality-of-life item, with a score of 2 or less ('delighted to mostly satisfied') for response. The secondary criterion for response was a >50% reduction

in the NIH-CPSI pain subscore after 14 weeks. Other outcomes included NIH-CPSI total and domain scores, International Prostate Symptom Score, peak urinary flow rate, and postvoid residual urine.

Results

Initial Response. Terazosin proved superior to placebo in this population of alpha-blocker-naïve patients. In the terazosin group, 24 of 43 evaluable participants (56%) met the primary response criterion as compared with 14 of 43 participants (36%) in the placebo group ($p = 0.03$). For the secondary criterion, 26 of 43 evaluable subjects (60%) responded in the terazosin group as compared with 16 of 43 participants (37%) in the placebo group ($p = 0.03$). The terazosin group experienced greater reductions ($p < 0.05$) in NIH-CPSI total score, individual domain scores, and International Prostate Symptom Score than the placebo group. There was no difference in peak urinary flow rate or postvoid residual urine between responders and nonresponders. In the terazosin group 18 patients (42%) had side effects versus 9 patients (21%) in the placebo group ($p = 0.04$), as one might predict.

Long-Term Results. During follow-up of the initial trial groups, nonresponders and responders who subsequently relapsed were treated with terazosin or other medications (open label) [57]. The same criterion for response as in the initial report was employed (a score of 0–2 on the NIH-CPSI quality-of-life item). The long-term response was evaluated after a median of 38 (range 34–42 weeks), regardless of additional therapy. A durable response was defined as an initial response (after the initial 14-week treatment period) without additional treatment. Long-term responses were reported by 23 of 41 evaluable subjects (56%) treated with terazosin initially as compared with 12 of 38 evaluable subjects (32%) treated with placebo ($p = 0.03$). Of the nonresponders and initial responders who relapsed, 7 of 17 subjects (41%) responded to terazosin as compared with 7 of 34 (21%) who received other treatments ($p = 0.12$). Durable responses were reported by 18 of the 41 patients (44%) treated with terazosin initially as compared with 6 of 38 patients (16%) treated with placebo initially ($p = 0.01$).

Summary

Newly diagnosed alpha-blocker-naïve participants treated for 14 weeks with terazosin were more likely to have initial, long-term, and durable responses than participants treated with placebo.

Conclusions and Clinical Questions

Alpha blockers represent one of the few treatments for CP/CPPS, supported by high-quality randomized clinical trials. Clinically, many patients respond to therapy with these agents. Current data support the following conclusions:

(1) Critical study design outcomes and issues have been resolved, facilitating the development of additional high-quality treatment studies.

(2) Treatment-naïve and/or newly diagnosed patients appear more likely to respond than long-term, chronic refractory patients.

(3) Longer courses of treatment (12 weeks to 6 months) appear to be superior to shorter courses of treatment (6 weeks).

(4) Less selective agents appear generally to be superior to more selective α_1 blockers for treating patients with CP/CPPS.

There are four major questions concerning the role of alpha blockers for patients with CP/CPPS:

(1) We need to define sites and receptors responsible for the benefit of alpha blockers in CP/CPPS. Such sites may be in the prostate, in the bladder, in the spinal cord, or other anatomical locations. These sites and receptors may well differ from the sites and receptors mediating lower urinary tract symptoms related to BPH.

(2) We need to define the optimal alpha-blocking agents and duration of treatment.

(3) We need to define whether alpha blockers should be used as monotherapy or as part of a combination therapy program.

(4) We need to define the optimal time to employ alpha blockers during the natural history of CP/CPPS. Should these agents be used as initial therapy, as second-line treatment perhaps after antimicrobial or other therapy, or after multiple courses of other agents?

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