Treatment Response to Conventional and Novel Therapies in Chronic Prostatitis

Daniel A. Shoskes, MD, MSc

Address
Department of Urology, Section of Renal Transplantation, Cleveland Clinic Florida, 2950 Cleveland Clinic Blvd., Weston, FL 33331, USA.
E-mail: uro@dshoskes.com

Current Urology Reports 2003, **4:**311–315
Current Science Inc. ISSN 1527-2737

Chronic prostatitis is a common and poorly understood condition that significantly impacts quality of life. Conventional therapy usually consists of prolonged courses of antibiotics; however, the efficacy of this approach is defined better by clearance of bacteria than by improvement in symptoms. Newer therapies with some evidence for efficacy include α blockers, anti-inflammatory drugs, phytotherapy (quercetin, bee pollen), physiotherapy, neuroleptics, and others with unique actions (finasteride, pentosan polysulfate). The National Institutes of Health Chronic Prostatitis Symptom Index is a validated symptom score that, in preliminary use, appears to be responsive to patient improvement. As more well-designed clinical trials in chronic prostatitis and chronic pelvic pain syndrome come to completion, physicians will be able to make rational treatment choices for patients with this common and frustrating condition.

Introduction

Chronic prostatitis is a common condition, but its etiology and appropriate therapy are still controversial. Approximately 5% of patients with chronic prostatitis have the true syndrome of chronic bacterial prostatitis (National Institutes of Health [NIH] classification, category II), with recurrent cystitis and positive cultures of expressed prostatic secretions (EPS) for uropathogens in between cystitis episodes. Most men with symptomatic chronic prostatitis do not have bacterial cystitis and may or may not have bacteria recovered from EPS. The more appropriate term, chronic pelvic pain syndrome (CPPS), is used to describe this syndrome, further subdivided by the presence of inflammation in the EPS or semen (category IIIa) or not (category IIIb). Many theories have been suggested for the etiology of CPPS, including infection, inflammation, autoimmunity, and neuromuscular spasm. Therapies aimed at these specific etiologies have met with variable success, which may reflect the multifactorial nature of the syndrome.

Until recently, there have been very few well-designed, randomized, placebo-controlled clinical trials examining treatment outcomes in this condition. Therapy typically has consisted of empiric antibiotics based on the assumption that bacteria are the cause in all of the cases and whether cultures are positive (or even performed). Analysis of outcomes also has been hampered by the lack of a validated symptom score/outcome measure. The NIH Chronic Prostatitis Symptoms Index (CPSI) is available and validated [1] and appears to be responsive [2].

Category II: Chronic Bacterial Prostatitis

The mainstay of therapy for chronic bacterial prostatitis is antibiotics [3]. Using canine models, antibiotics with lipid solubility and a high pKa were determined to have the best prostatic penetration [4]. These antibiotics include quinolones, sulphas, macrolides, tetracyclines, and aminoglycosides [5]. Numerous studies have been done examining the effects of antibiotics on chronic bacterial prostatitis, but they focus typically on a bacteriologic cure rather than on symptom improvement. In one study of antibiotics in chronic prostatitis, the patients with positive cultures had the least symptom benefit [6•]. In a typical recent study, 40 men with chronic bacterial prostatitis secondary to *Escherichia coli* were treated with ciprofloxacin for 4 weeks. EPS was sterile in 92% of the patients 3 months after therapy and in 80% 2 years after therapy [7]. In a multicenter study of men with chronic bacterial prostatitis that resulted from any organism, treatment with ciprofloxacin for 28 days eradicated the infection in 89% of the patients at 1 month; however, only 59% were infection-free after 9 months [8]. Twenty-nine percent of the men experienced at least one adverse event.

Alternative routes of antibiotic delivery have been employed to try to improve antibiotic penetration into the prostate. Several studies have examined intraprostatic injection of antibiotics, typically using an aminoglycoside; bacteriologic cure rates of approximately 45% have been reported [9], even in those patients who have failed previous oral therapy [10]. In the latter study, the suprapubic transvesical

route of delivery was less painful than the transperineal approach. It is unclear whether intraprostatic injection is superior to intravenous systemic therapy; however, the use of sustained-release microspheres may hold promise in the future [11].

When the administration of antibiotics alone is not effective, some patients may benefit from combination therapy including α blockers [12] or repetitive prostatic massage [13,14].

Category III: Chronic Pelvic Pain Syndrome

Chronic pelvic pain syndrome is the most common category of chronic prostatitis, but causes the greatest controversy regarding appropriate therapy. This controversy stems from the relative lack of published conclusive trials and from the unclear nature of the disorder itself. There is evidence for infection, inflammation, autoimmunity, and neuromuscular spasm as etiologies for this syndrome and many patients with identical presenting symptoms may improve with different therapies that target each of these causes. Again, prior studies have been hampered by the lack of a validated outcome measure and a dearth of randomized, placebo-controlled studies.

Supportive measures

Standard supportive measure for men with prostatitis include sitz baths and avoidance of spicy foods, caffeine, and alcohol. Efficacy has not been established in clinical trials. Although some men have exacerbation of symptoms with ejaculation, others have a reduction in symptoms with regular ejaculation [15]. Stress reduction also can be effective for the degree of symptoms and for dealing with their sequelae [16].

Antibiotics

The most commonly used therapy for CPPS is antibiotics, despite the fact that full localization studies are seldom done. The usual rationale for the use of antibiotics is that patients may have difficult-to-culture bacteria such as chlamydia [17], mycoplasma [18], or ureaplasma [19] and that direct therapy is simpler than extensive cultures, which possibly are inconclusive. There is evidence that empiric antibiotics may help some patients with CPPS. Nickel *et al.* [6•] performed a multicenter study of 102 patients with prostatitis (II, IIIa, and IIIb) who were treated with ofloxacin for 12 weeks. Overall, 57% of the patients felt moderate to marked improvement. Perhaps most surprisingly, there was no difference in response by culture results, antibacterial antibody status, or white blood cell count. In addition, none of the patients who were not improved by 4 weeks of therapy had a positive response in the subsequent 8-week course. The results of a similar study that is randomized and placebo-controlled is expected shortly. In addition, the NIH has sponsored a randomized, placebo-controlled study of ciprofloxacin with or without tamsulosin in men with CPPS, which is completed and expected to be published soon.

Prostatic massage

Prostate massage (drainage) was the mainstay of therapy for chronic prostatitis before the advent of broad spectrum oral antibiotics. Many patients derive immediate symptomatic relief from the first massage. There has been a recent resurgence of interest in this technique, which usually is combined with antibiotics [13]. In the author's experience, patients who benefit the most share at least one of the following features: symptom relief with the first massage, large volume of EPS, often with clumps that are suggestive of seminal vesicle contents, and persistent positive EPS cultures despite culture-specific antibiotics. In these selected patients, durable improvement is achieved in approximately 40% [14]. Benefit from prostatic massage may come from relief of prostatic congestion, improved blood flow with better antibiotic penetration, disruption of bacterial biofilm, or massage of neuromuscular trigger points along the pelvic side wall.

α Blockers

There is evidence that α blockers can help the urinary symptoms and the pain of CPPS. Some men with CPPS have high resistance to flow at the bladder neck and the internal or external sphincter [20], although this is not a universal finding on urodynamic evaluation [21]. Nevertheless, many studies have shown positive results with α blockers [12]. In an open-label study, terazosin resolved symptoms in 76% of men after 1 month of therapy and the effect persisted 3 months later in 58% [22]. Similar results have been reported with tamsulosin [23] and alfuzosin [24]. α Blockers also may have a direct effect on pain. Inflammation of the prostate can lead to substance P-mediated changes in pain perception regions of the spinal cord, which are blocked by tamsulosin [25].

Anti-inflammatory therapy

There is a growing body of evidence showing that men with CPPS have an inflammatory or autoimmune condition [26] with elevated levels of cytokines [27] and oxidative stress [28,29] found in semen and EPS [30•]. The beneficial effects of antibiotics in CPPS may be caused by their direct inhibition of inflammatory cytokines [31] rather than by their antibacterial properties.

Nonsteroidal anti-inflammatory drugs have been used extensively to control the symptoms of prostatitis and epididymitis [32]. A randomized, placebo-controlled study (unpublished) of rofecoxib in CPPS showed symptomatic improvement after 1 month with high-dose therapy, but changes in the CPSI did not reach statistical significance, primarily because of an unusually large placebo effect. Limited case reports suggest that some patients may benefit from therapy with steroids [33,34] or full immunosuppression [35], although the side effects may be unacceptably high if the patient does not require these drugs for another concomitant problem. Two open-label studies have shown efficacy of pentosan polysulfate (Elmiron; Alza, Mountainview, CA) in CPPS [36,37], although long-term therapy

often is required. The beneficial effects of Elmiron may be anti-inflammatory through inhibition of mast cells [38]. Several phytotherapeutic agents (discussed in the next section) likely act primarily as anti-inflammatories.

Phytotherapy

Alternative herbal-based therapies are prevalent and popular in urologic disease (in general and prostatic disorders, in particular) [39]. Phytotherapy has been used most commonly in CPPS and evidence for efficacy is actually more compelling than for other standard therapies. There is no evidence in any study of CPPS that patients in category IIIa have significantly different responses to therapy than those in category IIIb.

Cernilton (Graminex, Saginaw, MI), an extract of bee pollen, has been used in prostatic conditions for its presumed anti-inflammatory and antiandrogenic effects. In a small open-label study, 13 of 15 patients reported symptomatic improvement. In a larger, more recent open-label study, 90 patients received one tablet of Cernilton N three times daily for 6 months [40]. Patients with complicating factors (prostatic calculi, urethral stricture, bladder neck sclerosis) had minimal response, with only one of 18 showing improvement. However, in the "uncomplicated" patients, 36% were cured of their symptoms and 42% improved.

Quercetin is a polyphenolic bioflavonoid commonly found in red wine, green tea, and onions [41]. It has documented antioxidant and anti-inflammatory [42] properties and inhibits inflammatory cytokines, such as interleukin-8, implicated in the pathogenesis of CPPS [43]. In a preliminary small, open-label study, 500 mg of quercetin administered twice daily gave significant symptomatic improvement to most patients, particularly those with negative EPS cultures [44]. This was followed by a prospective, double-blind, placebo-controlled trial of 500 mg of quercetin administered twice daily for 4 weeks, using the NIH-CPSI as the primary endpoint [45]. Patients taking placebo had a mean improvement in NIH-CPSI from 20.2 to 18.8; those taking quercetin had a mean improvement from 21.0 to 13.1 ($P = 0.003$). Twenty percent of patients taking placebo and 67% of patients taking the bioflavonoid had an improvement of symptoms of at least 25%. A third group of patients received Prosta-Q (Farr Labs, El Segundo, CA), a commercial formulation containing quercetin with bromelain and papain, which are digestive enzymes known to increase the intestinal absorption of quercetin. In this group, 82% of the patients showed a significant improvement in symptoms. Side effects are rare, although gastrointestinal side effects can occur if taken on an empty stomach.

Several mechanisms may contribute to the beneficial effects of quercetin in CPPS. CPPS is associated with elevated oxidative stress in EPS and semen, and patients who improve with quercetin have a reduction in oxidative stress metabolite F2-isoprostane in their EPS [28]. Furthermore, quercetin therapy reduces inflammation, which is measured by prostaglandin E2 levels in EPS, and increases the levels of prostatic β-endorphins [29].

Saw palmetto is the most commonly used phytochemical for lower urinary tract symptoms and benign prostatic hyperplasia, and some of the clinical studies with entry criteria based on symptoms likely included patients with CPPS. Although commercially promoted as "herbal Proscar," it is unclear whether the beneficial effects are from dihydrotestosterone blockade, α-1 receptor blockade, or some other unknown mechanism. There have been no published studies of saw palmetto use for the treatment of CPPS. A poster presented at the 2001 American Urological Association meeting (Volpe *et al*. abstract 115) compared therapy with saw palmetto or finasteride in CPPS patients for 1 year. Although there was some improvement seen in the finasteride group, there was no improvement in the saw palmetto group.

Neuromuscular therapy

Many patients with CPPS have pain and spasm of the pelvic floor muscles. This may be secondary to infection or inflammation in the prostate or the primary inducing problem. Although no large published clinical trials exist, preliminary evidence suggests potential efficacy of biofeedback and bladder retraining in alleviating symptoms [46]. Amytriptyline can be effective for pain from chronic muscle spasm [47] and has been found to be helpful in the management of CPPS. We also have used gabapentin, which has been used in the treatment of other neuropathic pain syndromes [48] alone or in combination with amitriptyline [49]. Conservative measures such as sitz baths and sitting on a cushion also may help with persistent muscle spasm.

Treatment algorithm

There is still much controversy regarding the appropriate therapy for chronic prostatitis, particularly CPPS. At the Cleveland Clinic in Weston, Florida, a stepwise approach is used addressing infection, inflammation, and neuromuscular spasm in turn (Fig. 1). In a study of 54 patients using this approach, 90.7% had initial improvement with at least one of the therapies. At a median of 1-year follow-up, 80% of the patients reported continued improvement, with a mean change in CPSI of 22.7 to 13.2 ($P < 0.0001$) [50].

Conclusions

Chronic prostatitis remains a controversial condition with little agreement regarding the best treatment options. The past few years have produced studies of standard and novel therapies using placebo controls and validated symptom score outcomes that can begin to guide the clinician toward efficacious therapies. When used in a rational stepwise manner, we have found that therapies can be effective for most patients with prostatitis, even for those with long-standing symptoms.

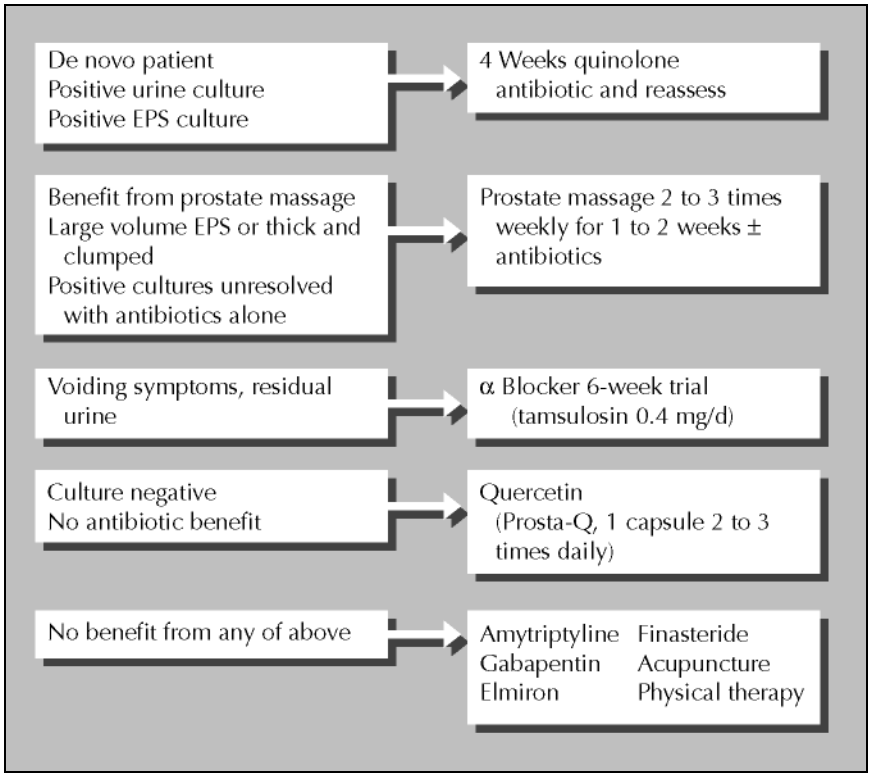

Figure 1. Algorithm for the treatment selection used at the Cleveland Clinic in Weston, Florida. EPS—expressed prostatic secretions.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Litwin MS: **A review of the development and validation of the National Institutes of Health Chronic Prostatitis Symptom Index.** *Urology* 2002, **60:**14–18.
2. Turner JA, Ciol MA, Von Korff M, Berger R: **Validity and responsiveness of the national institutes of health chronic prostatitis symptom index.** *J Urol* 2003, **169:**580–583.
3. Pfau A: **The treatment of chronic bacterial prostatitis.** *Infection* 1991, **19:**S160–S164.
4. Barza M, Cuchural G: **The penetration of antibiotics into the prostate in chronic bacterial prostatitis.** *Eur J Clin Microbiol* 1984, **3:**503–505.
5. Goto T, Makinose S, Ohi Y, *et al.*: **Diffusion of piperacillin, cefotiam, minocycline, amikacin and ofloxacin into the prostate.** *Int J Urol* 1998, **5:**243–246.
6. • Nickel JC, Downey J, Johnston B, *et al.*: **Predictors of patient response to antibiotic therapy for the chronic prostatitis/chronic pelvic pain syndrome: a prospective multicenter clinical trial.** *J Urol* 2001, **165:**1539–1544.

The first study to demonstrate that improvement with antibiotic therapy in chronic prostatitis is unrelated to culture results or the presence of inflammation in the seminal fluids.

7. Weidner W, Ludwig M, Brahler E, Schiefer HG: **Outcome of antibiotic therapy with ciprofloxacin in chronic bacterial prostatitis.** *Drugs* 1999, **58:**103–106.
8. Naber KG, Busch W, Focht J: **Ciprofloxacin in the treatment of chronic bacterial prostatitis: a prospective, non-comparative multicentre clinical trial with long-term follow-up.** *Int J Antimicrob Agents* 2000, **14:**143–149.
9. Jimenez-Cruz JF, Tormo FB, Gomez JG: **Treatment of chronic prostatitis: intraprostatic antibiotic injections under echography control.** *J Urol* 1988, **139:**967–970.
10. Yavascaoglu I, Camlikiyi H, Oktay B, *et al.*: **Percutaneous suprapubic transvesical route: a new and comfortable method of intraprostatic injection.** *Urol Int* 1998, **60:**229–234.
11. Bahk JY, Hyun JS, Lee JY, *et al.:* **Concentration of ofloxacin in canine prostate tissue and prostate fluid after intraprostatic injection of biodegradable sustained-releasing microspheres containing ofloxacin.** *J Urol* 2000, **163:**1560–1564.
12. Barbalias GA, Nikiforidis G, Liatsikos EN: **Alpha-blockers for the treatment of chronic prostatitis in combination with antibiotics.** *J Urol* 1998, **159:**883–887.
13. Nickel JC, Alexander R, Anderson R, *et al.:* **Prostatitis unplugged? Prostatic massage revisited.** *Tech Urol* 1999, **5:**1–7.
14. Shoskes DA, Zeitlin SI: **Use of prostatic massage in combination with antibiotics in the treatment of chronic prostatitis.** *Prostate Cancer Prostatic Dis* 1999, **2:**159–162.
15. Yavascaoglu I, Oktay B, Simsek U, Ozyurt M: **Role of ejaculation in the treatment of chronic non-bacterial prostatitis.** *Int J Urol* 1999, **6:**130–134.
16. Miller HC: **Stress prostatitis.** *Urology* 1988, **32:**507–510.
17. Mutlu N, Mutlu B, Culha M, *et al.*: **The role of Chlamydia trachomatis in patients with non-bacterial prostatitis.** *Int J Clin Pract* 1998, **52:**540–541.
18. Taylor-Robinson D: **Mycoplasma genitalium: an update.** *Int J STD AIDS* 2002, **13:**145–151.
19. Potts JM, Sharma R, Pasqualotto F, *et al.:* **Association of ureaplasma urealyticum with abnormal reactive oxygen species levels and absence of leukocytospermia.** *J Urol* 2000, **163:**1775–1778.
20. Kaplan SA, Santarosa RP, D'Alisera PM, *et al.:* **Pseudodyssynergia (contraction of the external sphincter during voiding) misdiagnosed as chronic nonbacterial prostatitis and the role of biofeedback as a therapeutic option.** *J Urol* 1997, **157:**2234–2237.
21. Mayo ME, Ross SO, Krieger JN: **Few patients with "chronic prostatitis" have significant bladder outlet obstruction.** *Urology* 1998, **52:**417–421.

22. Neal DE Jr, Moon TD: **Use of terazosin in prostatodynia and validation of a symptom score questionnaire.** *Urology* 1994, **43:**460–465.
23. Lacquaniti S, Destito A, Servello C, *et al.:* **Terazosine and tamsulosin in non bacterial prostatitis: a randomized placebo-controlled study.** *Arch Ital Urol Androl* 1999, **71:**283–285.
24. de la Rosette JJ, Karthaus HF, van Kerrebroeck PE, *et al.:* **Research in 'prostatitis syndromes': the use of alfuzosin (a new alpha 1-receptor-blocking agent) in patients mainly presenting with micturition complaints of an irritative nature and confirmed urodynamic abnormalities.** *Eur Urol* 1992, **22:**222–227.
25. Ishigooka M, Nakada T, Hashimoto T, *et al.*: **Spinal substance P immunoreactivity is enhanced by acute chemical stimulation of the rat prostate.** *Urology* 2002, **59:**139–144.
26. Pontari, MA: **Inflammation and anti-inflammatory therapy in chronic prostatitis.** *Urology* 2002, **60:**29–33.
27. Nadler RB, Koch AE, Calhoun EA, *et al.:* **Il-1beta and TNF-alpha in prostatic secretions are indicators in the evaluation of men with chronic prostatitis.** *J Urol* 2000, **164:**214–218.
28. Shahed AR, Shoskes DA: **Oxidative stress in prostatic fluid of patients with chronic pelvic pain syndrome: correlation with gram positive bacterial growth and treatment response.** *J Androl* 2000, **21:**669–675.
29. Shahed AR, Shoskes DA: **Correlation of beta-endorphin and prostaglandin e2 levels in prostatic fluid of patients with chronic prostatitis with diagnosis and treatment response.** *J Urol* 2001, **166:**1738–1741.
30.• John H, Barghorn A, Funke G, *et al.*: **Noninflammatory chronic pelvic pain syndrome: immunological study in blood, ejaculate and prostate tissue.** *Eur Urol* 2001, **39:**72–78.

This study demonstrates the presence of inflammation in patients with CPPS, even if conventional microscopy of EPS is negative.

31. Galley HF, Dhillon JK, Paterson RL, Webster NR: **Effect of ciprofloxacin on the activation of the transcription factors nuclear factor kappaB, activator protein-1 and nuclear factor-interleukin-6, and interleukin-6 and interleukin-8 mRNA expression in a human endothelial cell line.** *Clin Sci (Lond)* 2000, **99:**405–410.
32. Canale D, Scaricabarozzi I, Giorgi P, *et al.*: **Use of a novel non-steroidal anti-inflammatory drug, nimesulide, in the treatment of abacterial prostatovesiculitis.** *Andrologia* 1993, **25:**163–166.
33. Bates S, Talbot M: **Short course oral prednisolone therapy in chronic abacterial prostatitis and prostatodynia: case reports of three responders and one nonresponder.** *Sex Transm Infect* 2000, **76:**398–399.
34. Talbot M, Bates S: **Variability of the symptoms of chronic abacterial prostatitis/chronic pelvic pain syndrome during intermittent therapy with rectal prednisolone foam for ulcerative colitis.** *Int J STD AIDS* 2001, **12:**752–753.
35. Palapattu GS, Shoskes DA: **Resolution of the chronic pelvic pain syndrome after renal transplantation.** *J Urol* 2000, **164:**127.
36. Wedren H: **Effects of sodium pentosanpolysulphate on symptoms related to chronic non-bacterial prostatitis: a double-blind randomized study.** *Scand J Urol Nephrol* 1987, **21:**81–88.
37. Nickel JC, Johnston B, Downey J, *et al.*: **Pentosan polysulfate therapy for chronic nonbacterial prostatitis (chronic pelvic pain syndrome category IIIA): a prospective multicenter clinical trial.** *Urology* 2000, **56:**413–417.
38. Chiang G, Patra P, Letourneau R, *et al.*: **Pentosanpolysulfate inhibits mast cell histamine secretion and intracellular calcium ion levels: an alternative explanation of its beneficial effect in interstitial cystitis.** *J Urol* 2000, **164:**2119–2125.
39. Shoskes DA: **Phytotherapy in chronic prostatitis.** *Urology* 2002, **60:**35–37.
40. Rugendorff EW, Weidner W, Ebeling L, Buck AC: **Results of treatment with pollen extract (Cernilton N) in chronic prostatitis and prostatodynia.** *Br J Urol* 1993, **71:**433–438.
41. Hollman PC, Katan MB: **Bioavailability and health effects of dietary flavonols in man.** *Arch Toxicol Suppl* 1998 **20:**237–248.
42. Guardia T, Rotelli AE, Juarez AO, Pelzer LE: **Anti-inflammatory properties of plant flavonoids: effects of rutin, quercetin and hesperidin on adjuvant arthritis in rat.** *Farmaco* 2001, **56:**683–687.
43. Sato M, Miyazaki T, Kambe F, *et al.:* **Quercetin, a bioflavonoid, inhibits the induction of interleukin 8 and monocyte chemoattractant protein-1 expression by tumor necrosis factor-alpha in cultured human synovial cells.** *J Rheumatol* 1997, **24:**1680–1684.
44. Shoskes DA: **Use of the bioflavonoid quercetin in patients with longstanding chronic prostatitis.** *J Am Neutraceutic Assoc* 1999, **2:**18–21.
45. Shoskes DA, Zeitlin SI, Shahed A, Rajfer J: **Quercetin in men with category III chronic prostatitis: a preliminary prospective, double-blind, placebo-controlled trial.** *Urology* 1999, **54:**960–963.
46. Nadler RB: **Bladder training biofeedback and pelvic floor myalgia.** *Urology* 2002, **60:**42–43.
47. Holroyd KA, O'Donnell FJ, Stensland M, *et al.*: **Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: a randomized controlled trial.** *JAMA* 2001, **285:**2208–2215.
48. Covington EC: **Anticonvulsants for neuropathic pain and detoxification.** *Cleve Clin J Med* 1998, **65(suppl 1):**SI21–S129.
49. Heughan CE, Sawynok J: **The interaction between gabapentin and amitriptyline in the rat formalin test after systemic administration.** *Anesth Analg* 2002, **94:**975–980.
50. Shoskes DA, Hakim L, Ghoniem G, Jackson CL: **Long-term results of multi-modal therapy for chronic prostatitis/chronic pelvic pain syndrome.** *J Urol* 2003, **169:**1406–1410.