World J Urol (2013) 31:755–760
DOI 10.1007/s00345-013-1075-6

TOPIC PAPER

Classification and treatment of men with chronic prostatitis/chronic pelvic pain syndrome using the UPOINT system

Daniel A. Shoskes · J. Curtis Nickel

Received: 26 February 2013 / Accepted: 3 April 2013 / Published online: 16 April 2013

Abstract Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common condition; however, many of the traditional therapies used in clinical practice fail to show efficacy when subjected to large randomized placebo-controlled trials. This may be because CP/CPPS is a heterogeneous syndrome rather than a specific disease which would explain the failure of "one size fits all" therapy. In order to direct appropriate therapy, we have developed a six-point clinical phenotyping system to evaluate patients with chronic urologic pelvic pain. The clinical domains are urinary symptoms, psychosocial dysfunction, organ-specific findings, infection, neurologic/systemic, and tenderness of muscles, which produces the acronym UPOINT. Each domain is diagnosed clinically and is associated with specific therapies. This approach is simple and has proven effective in our hands for patients even after many years of failed therapies.

Keywords Prostatitis · Pelvic pain · Phenotype · Multimodal therapy

Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common and prevalent condition with significant impact on quality of life and financial burden [1]. Multiple factors may play a role in the pathophysiology of CPPS including initial urinary tract infection, intra-prostatic urinary reflux [2], cytokines [3], pelvic floor spasm [4], generalized neuropathic or neuroendocrine associations [5], or psychologic traits [6]. However, none of these factors has been determined as the sole cause in majority of cases. Rather, a combination of these factors is likely contributing to CPPS, and therefore, therapy must likely be directed toward individual patient's clinical phenotype. Our current best understanding of the etiologies is illustrated in Fig. 1. In this opinion article, we will review the genesis of the development of the UPOINT phenotyping system for CPPS, its practical application, and the results we have obtained.

D. A. Shoskes (✉)
Department of Urology, Glickman Urological and Kidney Institute, Cleveland Clinic Foundation, 9500 Euclid Avenue, Suite Q10, Cleveland, OH 44195, USA
e-mail: dshoskes@mac.com

J. C. Nickel
Department of Urology, Queens University, Kingston, ON, Canada

Monotherapies

Different types of treatments have been used to treat CPPS. These include alpha-blockers, antibiotics, hormonal therapy, anti-inflammatory medications, phytotherapy, antispasmotics, and non-pharmacological therapies. While many of these therapies have shown promise in single center or small studies, large multicenter studies have usually failed to prove the utility of monotherapy. Several α-blockers have been studied with conflicting results. Some of the differences among randomized controlled trials (RCTs) include different α-blockers, populations, duration of therapies, and outcomes. These RCTs have had anywhere from 19 to 138 patients in the treatment group, with treatment duration from 6 to 24 weeks. Benefit has been shown with terazosin [7], alfuzosin [8], and silodosin [9]. Two multicenter studies, however, were negative. Alexander et al. [10] studied the effect of 6 weeks of tamsulosin on total National Institutes of Health-Chronic Prostatitis

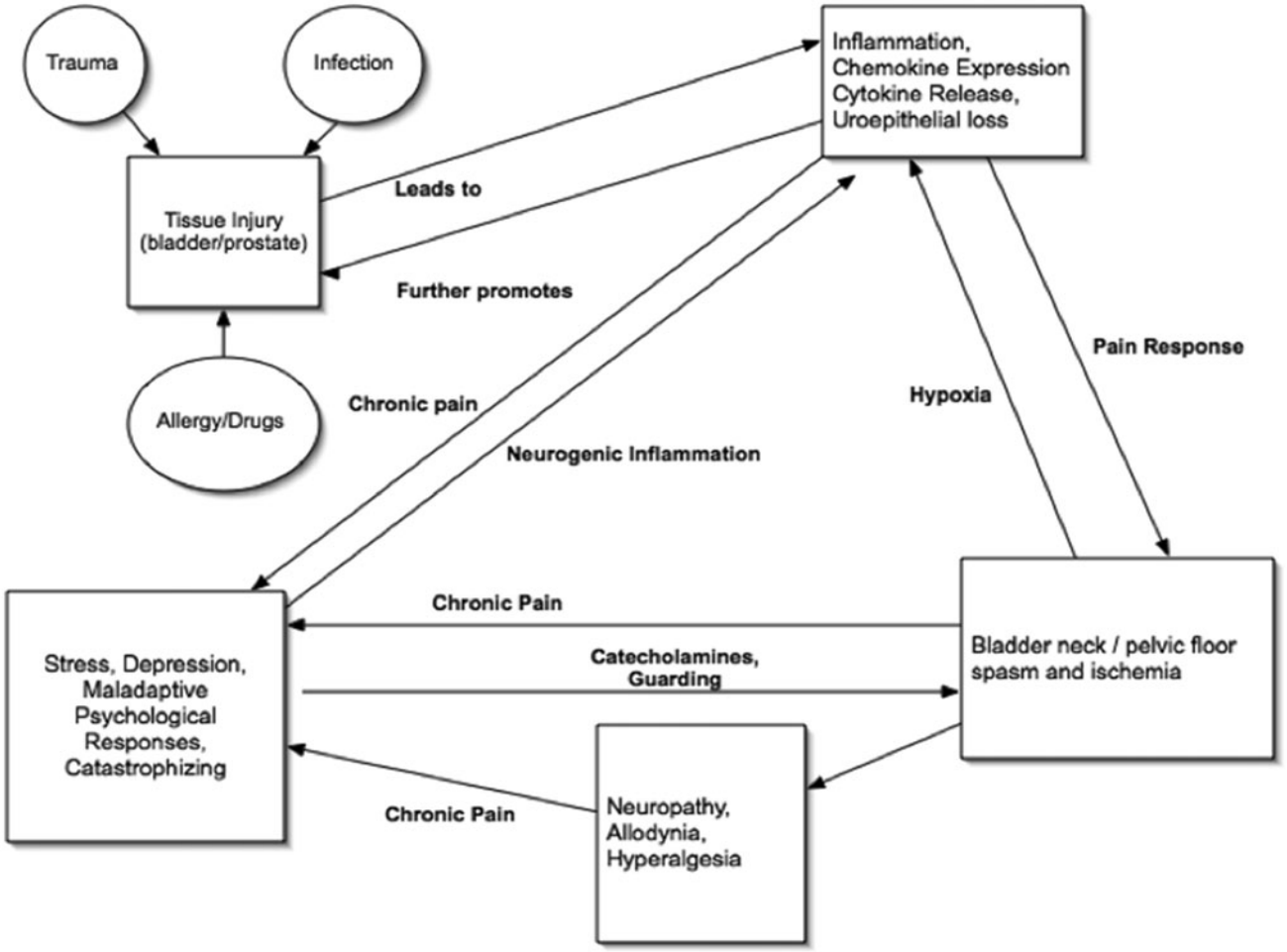

Fig. 1 Multifactorial etiology of chronic pelvic pain syndrome

Symptom Index (NIH-CPSI). There was no significant benefit of an α-blocker on total NIH-CPSI scores. Some of the drawbacks of this trial were that patients had long-standing symptoms and had prior exposure to α-blockers. Furthermore, the 2 × 2 trial design was not powered to show efficacy for each individual study arm. Therefore, another trial was designed to investigate alfuzosin use in patients with shorter duration of symptoms and without prior exposure to this class of drugs [11]. There was still no clear benefit of treatment with the α-blocker.

Antibiotics are often used in patients with pelvic pain for presumed bacterial prostatitis despite negative cultures [12]. A randomized controlled trial studied the efficacy of levofloxacin for 6 weeks compared to placebo [13]. Although patients did better in terms of total NIH-CPSI scores in both groups over time, there was no significant difference between groups. Similarly, in an NIDDK-sponsored trial, ciprofloxacin was evaluated for efficacy and was not found to be superior to placebo, although this arm of the study was underpowered [10].

Anti-inflammatory medications have been used as a therapeutic option for CPPS with variable results. A study done in China with celecoxib demonstrated improvement but the benefit deteriorated in 2 weeks after finishing therapy [14]. Pentosan polysulfate sodium, a glycosaminoglycan drug used in interstitial cystitis, was evaluated in a randomized controlled trial, which showed no significant benefit in Clinical Global Improvement and total NIH-CPSI scores [15]. A small study from UK showed no benefit for zafirlukast, a leukotriene antagonist [16].

Phytotherapy has been found to be of benefit to men with CPPS. Quercetin is a natural bioflavonoid found in fruits, vegetables, leaves, and grains. It is thought to help in CPPS because of its antioxidant and anti-inflammatory properties. In a randomized, double-blind, placebo-controlled trial, patients taking quercetin had a mean decrease in NIH-CPSI scores of 7.9 points compared to a decrease of 1.4 points in the placebo group ($P = 0.003$). An improvement of at least 25 % was seen in 67 % of men in the treatment group versus 20 % of men in the placebo

group [17]. In another study of pollen extract, 22 of 30 patients had improvement in pain and lower urinary tract symptoms on a symptom questionnaire compared to 10 out of 28 men in the placebo group [18]. In a randomized controlled trial, cernilton, a pollen extract, was found to be clinically and statistically significantly better than placebo [34]. A decrease of at least 25 % or 6 points in total NIH-CPSI scores was seen in 70.6 and 50.0 % of patients in the pollen extract and placebo group ($P = 0.01$), respectively [19].

Pregabalin is commonly used for neuropathic pain. One randomized controlled trial showed no statistically significant improvement in primary outcome of 6 point decrease in total NIH-CPSI scores between groups [20]. However, 47.2 versus 35.8 % patients had a 6-point decrease in treatment and placebo groups ($P = 0.07$), respectively. There was a significant improvement in secondary outcome of total NIH-CPSI scores. A decrease of 6.6 points was seen in the pregabalin arm and 4.2 points in the placebo arm ($P = 0.01$). However, 59 % of the patients in the pregabalin arm experienced adverse effects, most being mild to moderate.

Myofascial trigger point release is a type of physical therapy which targets the taut bands or tender nodules that provide relief by therapeutic manipulation. Anderson et al. [21] showed that myofascial trigger point release and paradoxical relaxation training had a moderate to marked improvement in symptoms in 72 % of patients. Conduction of a randomized, double-blind, placebo-controlled trial is limited by the fact that sham therapy and blinding of both patients and operators is difficult. An NIH sponsored pilot study evaluated the feasibility of performing a larger trial by comparing myofascial release physical therapy and global therapeutic massage in 48 patients including men with CPPS or women with interstitial cystitis [22]. The study did show that it was feasible to conduct a larger trial. There was a clinically important difference in NIH-CPSI in the 10 CP/CPPS men treated with directed physiotherapy (−14.1) compared to the 11 CP/CPPS men treated with global massage (−7.6); however, the treatment effect (7.6) was not statistically significant, presumably because of the small sample size.

Development and utility of UPOINT

The understanding of CPPS has evolved since the NIH classification. The major barrier in treating men with CPPS is the heterogenous nature of this syndrome. The therapies discussed above have had minimal or no success because they target a single mechanism for every patient with CPPS, whereas each patient should be evaluated individually to assess the nature of symptoms and then be treated appropriately.

In order to direct appropriate therapy, we have developed a six-point clinical phenotyping system to evaluate patients with chronic urologic pelvic pain [23]. The clinical domains are urinary symptoms, psychosocial dysfunction, organ-specific findings, infection, neurologic/systemic, and tenderness of muscles, which produces the acronym UPOINT (Fig. 2). Each patient is evaluated clinically for involvement of each domain, and symptom severity is assessed using the NIH-CPSI. This is followed by a multimodal therapeutic approach toward positive domains.

We have shown that there is a stepwise increase in the total NIH-CPSI score with increase in the number of positive domains. In addition, the number of positive domains also correlates with longer duration of symptoms [24]. We have also shown that the domains with the greatest contribution of symptom severity were urinary, psychosocial, and tenderness [25]. In a Swedish study, the correlation between the number of positive domains and NIH-CPSI was verified [26]. The UPOINT clinical phenotyping system may provide a useful and clinically relevant framework for multimodal therapy for the treatment of CPPS.

A European study evaluated the inclusion of a sexual dysfunction domain to the UPOINT clinical phenotyping system [27]. In this study, 937 men from Italy and 290 men from Germany with CPPS were retrospectively classified into a modified UPOINTS system (S = sexual dysfunction domain). The regular UPOINT system correlated well with symptom severity in the Italian but not in the German cohort. The modified clinical phenotyping system (UPOINTS) with an additional sexual dysfunction domain correlated significantly with NIH-CPSI scores in the German cohort. Similarly, a recent Canadian study found addition of a sexual dysfunction domain improved correlation with quality of life [28].

This finding was further studied in a population of one hundred patients at our institution [29]. Twenty-eight percent of men with CPPS were found to have bothersome erectile dysfunction. However, addition of the sexual domain decreased the correlation between the clinical phenotyping system and symptom severity. Total NIH-CPSI scores, pain subscores, and quality of life measures were unaffected by erectile dysfunction. Therefore, inclusion of a sexual domain did not appear to add value to our patient population.

The development of UPOINT would have limited utility unless it actually improved treatment outcomes. A recent prospective study offered multimodal therapy based on the UPOINT phenotype (e.g. urinary: alpha blocker or antimuscarinic, psychosocial: stress reduction/psychologic support, organ specific: quercetin; infection: antibiotic; neurologic/systemic: amitriptyline or pregabalin, tenderness: pelvic floor physical therapy) and measured response

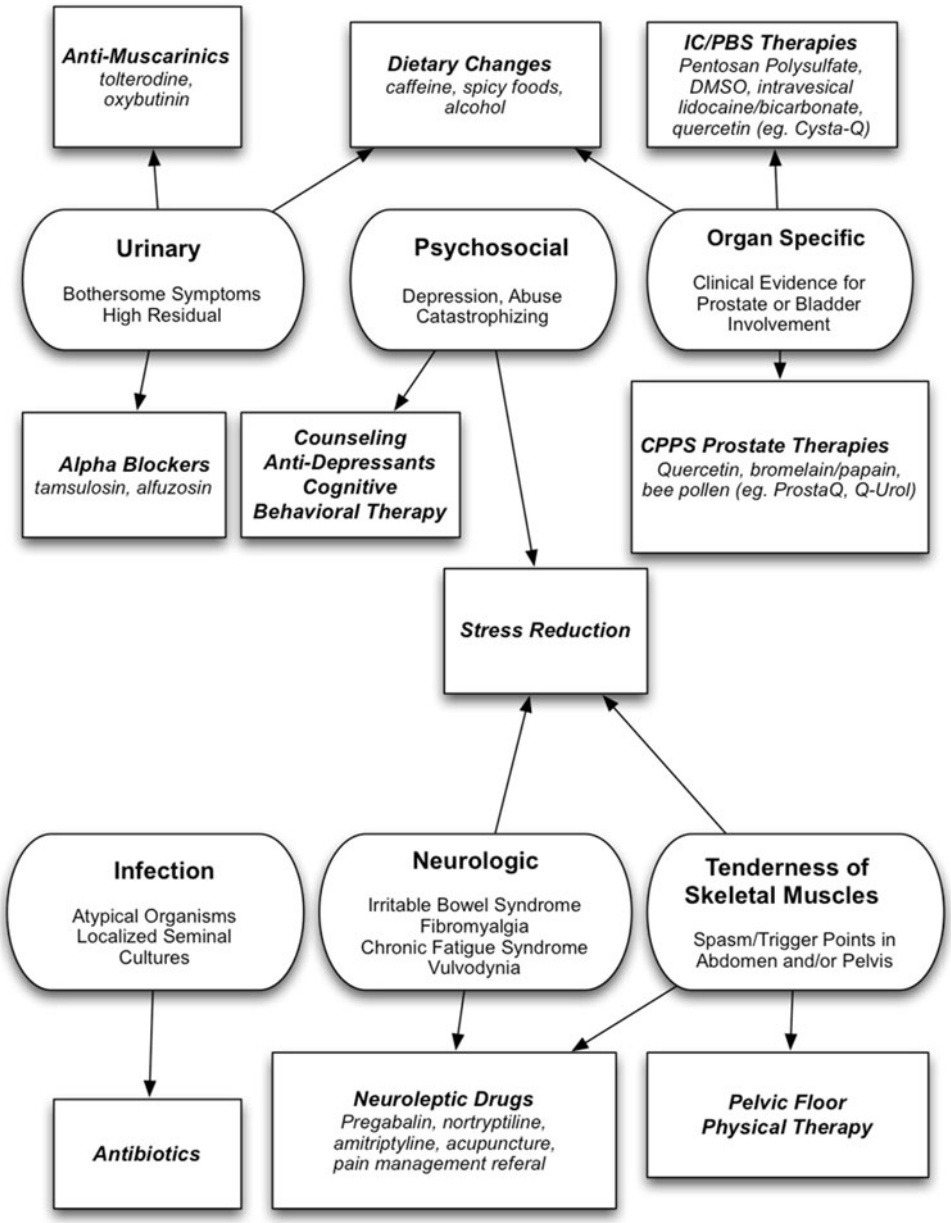

Fig. 2 UPOINT domains and associated therapies

after at least 6 months [30]. The primary endpoint was a minimum 6-point drop in total NIH-CPSI score. One hundred patients, with a mean age of 46 years, median symptom duration of 24 months, and a median of 3 positive UPOINT domains, were followed for an average of 50 weeks. 84 % of patients had at least a 6-point decrease in CPSI, with an average drop of 12 points. Fifty-one patients had a 50 % or greater improvement in total CPSI, while 84 patients had at least a 25 % or greater improvement. All CPSI subscores were significantly improved from baseline. Number of positive domains, initial CPSI scores, and symptom duration did not predict outcome. Though this study was not a placebo-controlled trial, the results were significantly better than all prior large trials with monotherapy.

UPOINT directed therapy is an attractive approach that simplifies treatment in patients with the challenging diagnosis of CPPS. An online resource has been made available for use by urologists, where one enters patient data and is given the UPOINT clinical phenotype with suggested therapies. A Web-based algorithm is available at http://www.upointmd.com. The diagnostic criteria and typical therapies for each domain are summarized in Table 1. Again, each domain is classified as positive or negative by clinical criteria, and for each positive domain, therapy is offered. For example, a patient with urinary and

Table 1 Diagnostic criteria for UPOINT phenotypes and treatments

Domain	Diagnostic criteria	Potential treatments
Urinary	Bothersome irritative or obstructive urinary symptoms	Alpha-blockers Antimuscarinics
	High postvoid residual	
Psychosocial	Clinical depression	Psychologic or Psychiatric counseling
	Catastrophizing (verbalized helplessness and hopelessness)	Cognitive behavioral therapy
Organ specific (bladder or prostate)	Specific prostate tenderness	Quercetin (e.g., Prosta-Q)
	Hematospermia	
	Symptom relief with voiding	Pollen extract (e.g., Q-Urol)
		Pentosan polysulfate
Infection	Positive cultures of prostatic fluid in absence of UTI	Antibiotics
	Concomitant urethritis	
Neurologic/ systemic	Pain outside pelvis	Pregabalin
	Systemic pain syndrome	Amitriptyline
Tenderness	Pelvic floor spasm	Pelvic physical therapy
	Muscle trigger points	
		Myofascial Release

organ specific may be treated with an alpha-blocker and quercetin, while another with neurologic and tenderness may be treated with pregabalin and pelvic floor physical therapy.

References

1. Shoskes DA (2008) Chronic prostatitis/chronic pelvic pain syndrome. Humana Press
2. Persson BE, Ronquist G (1996) Evidence for a mechanistic association between nonbacterial prostatitis and levels of urate and creatinine in expressed prostatic secretion. J Urol 155:958
3. He L, Wang Y, Long Z, Jiang C (2010) Clinical significance of IL-2, IL-10, and TNF-alpha in prostatic secretion of patients with chronic prostatitis. Urology 75:654
4. Westesson KE, Shoskes DA (2010) Chronic prostatitis/chronic pelvic pain syndrome and pelvic floor spasm: can we diagnose and treat? Curr Urol Rep 11:261
5. Pontari MA, McNaughton-Collins M, O'leary MP, Calhoun EA, Jang T, Kusek JW, Landis JR, Knauss J, Litwin MS (2005) A case-control study of risk factors in men with chronic pelvic pain syndrome. BJU Int 96:559
6. Tripp DA, Nickel JC, Wang Y, Litwin MS, McNaughton-Collins M, Landis JR, Alexander RB, Schaeffer AJ, O'Leary MP, Pontari MA, Fowler JEJ, Nyberg LM, Kusek JW (2006) Catastrophizing and pain-contingent rest predict patient adjustment in men with chronic prostatitis/chronic pelvic pain syndrome. J Pain 7:697
7. Cheah PY, Liong ML, Yuen KH, Teh CL, Khor T, Yang JR, Yap HW, Krieger JN (2003) Terazosin therapy for chronic prostatitis/chronic pelvic pain syndrome: a randomized, placebo controlled trial. J Urol 169:592
8. Nickel JC, Elhilali M, Emberton M, Vallancien G (2006) The beneficial effect of alfuzosin 10 mg once daily in 'real-life' practice on lower urinary tract symptoms (LUTS), quality of life and sexual dysfunction in men with LUTS and painful ejaculation. BJU Int 97:1242
9. Nickel JC, O'Leary MP, Lepor H, Caramelli KE, Thomas H, Hill LA, Hoel GE (2011) Silodosin for men with chronic prostatitis/chronic pelvic pain syndrome: results of a phase II multicenter, double-blind, placebo controlled study. J Urol 186:125
10. Alexander RB, Propert KJ, Schaeffer AJ, Landis JR, Nickel JC, O'Leary MP, Pontari MA, McNaughton-Collins M, Shoskes DA, Comiter CV, Datta NS, Fowler JEJ, Nadler RB, Zeitlin SI, Knauss JS, Wang Y, Kusek JW, Nyberg LMJ, Litwin MS (2004) Ciprofloxacin or tamsulosin in men with chronic prostatitis/chronic pelvic pain syndrome: a randomized, double-blind trial. Ann Intern Med 141:581
11. Nickel JC, Krieger JN, McNaughton-Collins M, Anderson RU, Pontari M, Shoskes DA, Litwin MS, Alexander RB, White PC, Berger R, Nadler R, O'Leary M, Liong ML, Zeitlin S, Chuai S, Landis JR, Kusek JW, Nyberg LM, Schaeffer AJ (2008) Alfuzosin and symptoms of chronic prostatitis-chronic pelvic pain syndrome. N Engl J Med 359:2663
12. Shoskes DA (2001) Use of antibiotics in chronic prostatitis syndromes. Can J Urol 8(Suppl 1):24
13. Nickel JC, Downey J, Clark J, Casey RW, Pommerville PJ, Barkin J, Steinhoff G, Brock G, Patrick AB, Flax S, Goldfarb B, Palmer BW, Zadra J (2003) Levofloxacin for chronic prostatitis/chronic pelvic pain syndrome in men: a randomized placebo-controlled multicenter trial. Urology 62:614
14. Zhao WP, Zhang ZG, Li XD, Yu D, Rui XF, Li GH, Ding GQ (2009) Celecoxib reduces symptoms in men with difficult chronic pelvic pain syndrome (Category IIIA). Braz J Med Biol Res 42:963
15. Nickel JC, Forrest JB, Tomera K, Hernandez-Graulau J, Moon TD, Schaeffer AJ, Krieger JN, Zeitlin SI, Evans RJ, Lama DJ, Neal DEJ, Sant GR (2005) Pentosan polysulfate sodium therapy for men with chronic pelvic pain syndrome: a multicenter, randomized, placebo controlled study. J Urol 173:1252
16. Goldmeier D, Madden P, McKenna M, Tamm N (2005) Treatment of category III A prostatitis with zafirlukast: a randomized controlled feasibility study. Int J STD AIDS 16:196
17. Shoskes DA, Zeitlin SI, Shahed A, Rajfer J (1999) Quercetin in men with category III chronic prostatitis: a preliminary prospective, double-blind, placebo-controlled trial. Urology 54:960
18. Elist J (2006) Effects of pollen extract preparation Prostat/Poltit on lower urinary tract symptoms in patients with chronic nonbacterial prostatitis/chronic pelvic pain syndrome: a randomized, double-blind, placebo-controlled study. Urology 67:60
19. Wagenlehner FM, Schneider H, Ludwig M, Schnitker J, Brahler E, Weidner W (2009) A pollen extract (Cernilton) in patients with inflammatory chronic prostatitis-chronic pelvic pain syndrome: a multicentre, randomised, prospective, double-blind, placebo-controlled phase 3 study. Eur Urol 56:544
20. Pontari MA, Krieger JN, Litwin MS, White PC, Anderson RU, McNaughton-Collins M, Nickel JC, Shoskes DA, Alexander RB, O'Leary M, Zeitlin S, Chuai S, Landis JR, Cen L, Propert KJ, Kusek JW, Nyberg LMJ, Schaeffer AJ (2010) Pregabalin for the treatment of men with chronic prostatitis/chronic pelvic pain syndrome: a randomized controlled trial. Arch Intern Med 170:1586

21. Anderson RU, Wise D, Sawyer T, Glowe P, Orenberg EK (2011) 6-day intensive treatment protocol for refractory chronic prostatitis/chronic pelvic pain syndrome using myofascial release and paradoxical relaxation training. J Urol 185:1294
22. FitzGerald MP, Anderson RU, Potts J, Payne CK, Peters KM, Clemens JQ, Kotarinos R, Fraser L, Cosby A, Fortman C, Neville C, Badillo S, Odabachian L, Sanfield A, O'Dougherty B, Halle-Podell R, Cen L, Chuai S, Landis JR, Mickelberg K, Barrell T, Kusek JW, Nyberg LM (2009) Randomized multicenter feasibility trial of myofascial physical therapy for the treatment of urological chronic pelvic pain syndromes. J Urol 182:570
23. Shoskes DA, Nickel JC, Rackley RR, Pontari MA (2009) Clinical phenotyping in chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis: a management strategy for urologic chronic pelvic pain syndromes. Prostate Cancer Prostatic Dis 12:177
24. Shoskes DA, Nickel JC, Dolinga R, Prots D (2009) Clinical phenotyping of patients with chronic prostatitis/chronic pelvic pain syndrome and correlation with symptom severity. Urology 73:538
25. Samplaski MK, Li J, Shoskes DA (2012) Clustering of UPOINT domains and subdomains in men with chronic prostatitis/chronic pelvic pain syndrome and contribution to symptom severity. J Urol 188:1788
26. Hedelin HH (2009) Evaluation of a modification of the UPOINT clinical phenotype system for the chronic pelvic pain syndrome. Scand J Urol Nephrol 43:373
27. Magri V, Wagenlehner F, Perletti G, Schneider S, Marras E, Naber KG, Weidner W (2010) Use of the UPOINT chronic prostatitis/chronic pelvic pain syndrome classification in European patient cohorts: sexual function domain improves correlations. J Urol 184:2339
28. Davis SN, Binik YM, Amsel R, Carrier S (2013) Is a sexual dysfunction domain important for quality of life in men with urological chronic pelvic pain syndrome? Signs "UPOINT" to yes. J Urol 189:146
29. Samplaski MK, Li J, Shoskes DA (2011) Inclusion of erectile domain to UPOINT phenotype does not improve correlation with symptom severity in men with chronic prostatitis/chronic pelvic pain syndrome. Urology 78:653
30. Shoskes DA, Nickel JC, Kattan MW (2010) Phenotypically directed multimodal therapy for chronic prostatitis/chronic pelvic pain syndrome: a prospective study using UPOINT. Urology 75:1249