The Efficacy and Safety of Duloxetine in a Multidrug Regimen for Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Antonella Giannantoni, Massimo Porena, Marilena Gubbiotti, Stefania Maddonni, and Savino M. Di Stasi

OBJECTIVE To evaluate the efficacy and safety of duloxetine hydrochloride in the treatment of patients affected by chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).

METHODS Thirty-eight CP/CPPS patients completed the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) and International Index of Erectile Function-Erectile Function-5 (IIEF-5) questionnaires, uroflowmetry, and evaluation of psychologic status using Hamilton Anxiety Scale (HAM-A) and Hamilton Depression Scale (HAM-D). Patients were randomly assigned to 2 treatments groups. Treatment in group 1 consisted of a simultaneous oral administration of tamsulosin (0.4 mg/d, 60 mg/d), saw palmetto (320 mg/d), and duloxetine (60 mg/d). Treatment in group 2 consisted of tamsulosin (0.4 mg/d) and saw palmetto (320 mg/d). NIH-CPSI and IIEF-5 questionnaires, uroflowmetry, and evaluation of the psychological status were repeated at 16 weeks of follow-up.

RESULTS At 16 weeks, a significant improvement in NIH-CPSI pain subscore, NIH-CPSI quality of life subscore, and NIH-CPSI total score were observed in group 1 patients compared with those in group 2 ($P < .01$, respectively), together with a significant improvement in HAM-A and HAM-D scores ($P < .01$, respectively). Patients in group 2 showed a significant improvement in NIH-CPSI total score, in the urinary symptoms subscore, and in the HAM-A total score. No significant differences were observed in IIEF-5 scores in the 2 groups. Maximum flow rate significantly increased in both groups. In group 1, 20% of patients stopped the study due to adverse effects.

CONCLUSION The use of duloxetine in a multimodal treatment with an α-blocker medication and a saw palmetto extract allowed better results in controlling clinical symptoms, psychologic status and quality of life patients affected by CP/CPPS. UROLOGY 83: 400–405, 2014. © 2014 Elsevier Inc.

Category III chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is characterized by pelvic pain for more than 3 of the previous 6 months, urinary symptoms, and painful ejaculation, without documented urinary tract infections from uropathogens.[1] CP/CPPS affects about 10%-15% of the male population, is associated with high rate of mental disorders, such as anxiety and depression, and has a dramatic effect on quality of life (QoL).[2,3] The etiology of the syndrome is still poorly understood, and it is not clear whether CP/CPPS is a disease of the prostate gland or a voiding dysfunction, a myofascial pain syndrome, or a functional somatic syndrome.[4] Recently, symptoms of CP/CPPS have been considered as the result of an interaction among psychologic factors and dysfunction in the immune, neurologic, and endocrine systems.[4]

Deterioration of the psychoemotional status frequently accompanies urologic symptoms and pain in patients with CP/CPPS.[5,6] Indeed, depression is commonly detected in patients with the disease,[5,6] and many studies have reported that anxiety and depression frequently coexist in patients with chronic pain. In addition, chronic pain and depressive symptoms in patients with CP/CPPS, alone or in combination, are associated with a risk of diminished physical functioning and deterioration of QoL. The most frequent therapies for CP/CPPS include single or sequential treatments or multimodal approaches with antibacterial, analgesics, and anti-inflammatory drugs, α-blockers, and pelvic floor rehabilitation to treat dysfunctional voiding, but very few studies have been performed in which anxiolytic or antidepressant medications, or

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From the Department of Urology and Andrology, University of Perugia, Ospedale Santa Maria della Misericordia, Perugia, Italy; and the Department of Urology, Tor Vergata University, Rome, Italy

Reprint requests: Antonella Giannantoni, M.D., Ph.D., Department of Urology and Andrology, University of Perugia, Ospedale Santa Maria della Misericordia, Perugia Italy. E-mail: agianton@libero.it

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both, have been used to control psychologic problems.[7] To date, no studies have used duloxetine hydrochloride to modulate pain and changes in the psychoemotional status in patients affected by CP/CPPS.

The aim of the present study was to evaluate the efficacy and safety of a multimodal treatment including duloxetine hydrochloride in the treatment of patients affected by CP/CPPS and to compare the obtained results with a conventional multimodal therapeutic strategy.

PATIENTS AND METHODS

The study was approved by the Institutional Review Board, and patients gave their written consent. All procedures were conducted in accordance with the Declaration of Helsinki.

Patients

Between January 2009 and December 2012, 38 patients affected by CP/CPPS were prospectively included in the study. Diagnosis of the disease was performed according to the National Institutes of Health (NIH) criteria,[1] and included pelvic/perineal pain with urinary frequency, urgency, and voiding difficulties.

Inclusion Criteria

We included patients aged at least 18 years, with pelvic or perineal pain, or both, and sexual dysfunction during at least 3 of the previous 6 months, with a score of at least 15 on the NIH Chronic Prostatitis Symptom Index (NIH-CPSI).

Exclusion Criteria

We excluded patients affected by bacterial prostatitis, urethritis, urethral stricture, neurogenic bladder, those previously treated with antidepressants, with hepatic insufficiency, a history of alcohol use or evidence of chronic liver disease, and severe orthostatic hypotension.

Urologic Investigation

All patients underwent detailed history, physical examination, urinalyses and culture, analysis of prostatic secretion, NIH-CPSI questionnaire,[8] International Index Erectile Function-5 questionnaire (IIEF-5),[9] uroflowmetry with postvoid residual volume (PVR) measurement, cystoscopy, and evaluation of their psychologic status. The NIH-CPSI questionnaire measures the 3 key domains of CP/CPPS: pain (location, frequency, and severity; possible score, 0-21); urinary symptoms (irritative and obstructive; possible score, 0-10), and impact/QoL (possible score, 0-12), for a total score of 0-43. A 4-point decrease in NIH-CPSI score has been shown to be clinically perceptible in previous clinical trials of men with CP/CPPS.[10]

Psychologic Assessment

Included were details of schooling and employment. The Hamilton Anxiety Rating Scale (HAM-A) with 14 items was used to assess anxiety.[11] Each item is evaluated on a 5-point scale ("absent", "light", "moderate", "severe", "very severe"), with scores ranging from 0-56, and a total score of 18 is considered pathologic. We focused on Somatic Anxiety (items 7-13) and Psychic Anxiety (items 1-6, and 14), and the total score. The Hamilton Depression Rating Scale (HAM-D) was used to assess symptoms of depression.[12] HAM-D has 21 graduated items, scoring to 3 (0-2), 4 (0-3), or 5 (0-4) levels of severity. Cutoffs are severe depression, ≥25; moderate depression, 18-24; slight depression, 8-17; and absence of depression, ≤7. The factors mainly used are: Anxiety/Somatization, Weight, Cognitive Disorders, Diurnal Variations, Deceleration, Slowing Down, and Sleeping Disorders.

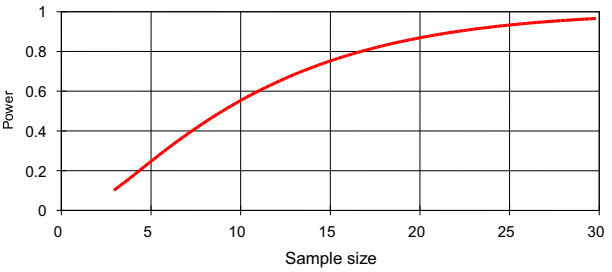

Figure 1. Number of subjects per group needed to reach a power of 80%. (Color version available online.)

Study Design and Treatment

Patients were randomly assigned by using a block randomization procedure to receive a multimodal treatment (group 1) with the addition of duloxetine hydrochloride, or a conventional multimodal treatment (group 2) for 16 weeks. All patients were counseled about the objectives of the study and the proposed treatments and were aware of their treatment allocation.

Treatment in group 1 consisted of a simultaneous administration of oral tamsulosin (0.4 mg/d; Astella Pharma, Italy), saw palmetto (320 mg/d; Pierre Fabre Pharma, Italy), and oral duloxetine hydrochloride (60 mg/d; Eli Lilly Pharma, Italy). A dose-escalation to reach the standard dose of duloxetine (60 mg/d) was used in the first 15 days. Treatment in group 2 consisted of oral tamsulosin (0.4 mg once daily) and saw palmetto (320 mg/d). NIH-CPSI and IIEF-5 questionnaires, uroflowmetry, and evaluation of psychologic status were repeated at 16 weeks of follow-up.

The primary outcome was the response, defined as a decrease in the NIH-CPSI score of at least 4 points, from baseline observation to week 16.

Secondary outcomes were improvement in anxiety and depression as assessed by HAM-A and HAM-D, improvement in IIEF-5 scores and in uroflowmetry parameters (increase in maximum urine flow [Qmax], reduction in PVR volume) from the baseline observation to week 16.

Statistical Analysis

Assuming a difference after treatments of 4 points with a standard deviation (SD) of 4 in the NIH-CPSI score, 10 pairs of subjects per group should have been able to reject the null hypothesis that this response of difference is 0 with a probability (power) of 0.8. The type I error probability associated with this test of this null hypothesis was 0.05 (PS-Power and Sample Size Calculation 3.0 software; 2009). Assuming the same effect size in the NIH-CPSI score (mean difference of 4 ± 4 SD) between the treatments groups (test for independent data), 17 subjects per group were considered enough to reach a power of 80%, as shown in Figure 1.

Statistical analysis was performed using Friedmann, Wilcoxon, and Mann-Whitney tests for nonparametric data. The Bonferroni correction was applied to post hoc multiple comparisons and the procedure of Cuzick was used to calculate the z test for trends. Statistical significance was set at $P < .05$.

Table 1. Primary outcome measures at baseline and 16 wks after treatment in patients with chronic prostatitis/chronic pelvic pain syndrome randomized into 2 treatment groups

Domains	Baseline Mean (SD)	P*	16 Wks Mean (SD)	P*	P†
NIH-CPSI subscores					
Pain					
Group 1	11.9 (3.1)	NS	6.1 (3.3)	<.01	<.05
Group 2	12.3 (3.0)		10.6 (4.2)		.06
Urinary symptoms					
Group 1	4.5 (2.3)	NS	3.8 (2.6)	.07	<.01
Group 2	4.4 (2.2)		3.4 (2.1)		<.01
QoL					
Group 1	8.7 (2.3)	NS	5.8 (3.0)	<.01	<.01
Group 2	8.8 (2.2)		7.4 (4.5)		.04
NIH-CPSI total score					
Group 1	25.1 (3.7)	NS	14.17 (2.2)	<.01	<.01
Group 2	24.25 (8.4)		20.14 (3.6)		<.05

NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; NS, not significant; QoL, quality of life; SD, standard deviation.
* Group 1 vs group 2.
† 16 wk vs baseline.

All data analyses were performed using SPSS 13.0 software (SPSS Inc).

RESULTS

The treatments groups were well balanced in baseline characteristics. The mean (SD) age of patients in group 1 was 47 (13.0) years compared with 46.6 (12.2) years for patients in group 2. There was no difference in educational level or employment status between the 2 treatment groups. Mean duration of symptoms since diagnosis was 5.7 (8.1) years for patients in group 1 and 6.5 (7.3) years for patients in group 2. At 16 weeks of follow-up, we observed a significant amelioration, compared with baseline, in the NIH-CPSI total score and subscores of pain, urinary symptoms, and QoL in patients in group 1. Patients in group 2 showed a significant improvement in NIH-CPSI total score and in the urinary symptoms subscore. We detected a significant improvement in the NIH-CPSI pain subscore, QoL subscore, and total score in patients in group 1 compared with those in group 2. Table 1 reports the results for the 2 groups allocated to the 2 different treatments and the results between groups at baseline and at 16 weeks of follow-up.

Sexual Function Results

We could not detect any significant change in IIEF-5 scores in the 2 groups between the baseline observation and 16 weeks of follow-up. IIEF-5 total (SD) scores were 15.1 (6.4) in group 1 and 14.3 (5.2) in group 2 at baseline and were 14.8 (6.4) in group 1 and 15.3 (7.3) in group 2 at 16 weeks of follow-up.

Uroflowmetry and PVR Results

We detected a significant improvement in Qmax (SD) in both treatment groups, from 8.6 (4.2) mL/s at baseline to 14.2 (6.3) mL/s at 16 weeks of follow-up in group 1 ($P < .01$) and from 7.9 (5.1) mL/s at baseline to 13.8 (7.0) mL/s ($P < .01$) at 16 weeks of follow-up in group 2. We did not detect any significant change in PVR between baseline and 16 weeks of follow-up in either treatment group. The mean (SD) PVR volume was 56 (38.4) mL in group 1 and 49.3 (24.5) mL in group 2 at baseline and was 51.3 (26.7) mL in group 1 and 50.9 (31.2) in group 2 at 16 weeks of follow-up.

Psychologic Results

At baseline, 10 patients in group 1 and 9 in group 2 (50%) had pathologic HAM-A scores (Table 2). Overall, 26 patients (68.4%) showed depressive symptoms on HAM-D (14 patients in group 1 and 11 in group 2; Table 2). At 16 weeks of follow-up, the mean total HAM-A scores decreased significantly in patients in group 1, particularly mean Psychic Anxiety and Somatic Anxiety scores, whereas we detected a significant improvement in the HAM-A total score in patients in group 2 (Table 2). In addition, a significant difference was observed in Psychic Anxiety and Somatic Anxiety scores between group 1 and group 2 patients, with the best improvements in those who also took duloxetine (Table 2). The HAM-D total score and scores related to Anxiety/Somatization, Cognitive Disorders, and Daily Variations significantly improved in group 1 patients. We did not observe any significant difference between HAM-D scores at baseline and at 16 weeks in patients in group 2 (Table 3).

Follow-up, Adherence, and Adverse Effects

All patients but 4 completed the 16 weeks of follow-up. Of the 38 patients, 34 reported taking 100% of their allocated therapy. Four patients in group 1 stopped taking duloxetine due to intolerable adverse effects (nausea, sleep disturbances, sedation) within 1 month after the beginning of the study. They continued with the remaining assigned drugs but dropped out of the study. Five group 1 patients complained of a worsening of libido and sexual activity. Four group 1 patients and five group 2 patients reported ejaculation disorders. Seven patients in group 1 and 9 in group 2 complained of orthostatic

Table 2. Secondary outcome measures: Hamilton Anxiety Scale results before and 16 wks after treatment in patients with chronic prostatitis/chronic pelvic pain syndrome randomized into 2 treatment groups

	Group 1 (n = 20)				Group 2 (n = 18)			
Domains	Baseline Mean (SD)	16 Wks Mean (SD)	*z*	*P*	Baseline Mean (SD)	16 Wks Mean (SD)	*z*	*P*
Psychic Anxiety	10.57 (5.43)*	4.71 (3.43)†	−2.67	<.01	9.85 (4.469)	7.24 (4.19)	−1.52	NS
Somatic Anxiety	10.14 (4.24)*	3.21 (3.19)†	−3.18	<.01	10.07 (4.33)	7.99 (5.06)	−2.16	<.05
Total score	20.61 (8.9)*	7.93 (6.54)†	−3.11	<.01	19.82 (9.6)	15.72 (10.11)	−2.87	<.05

Abbreviations as in Table 1.
* Between group 1 and group 2: P = NS.
† Between group 1 and group 2: P <.01.

Table 3. Secondary outcome measures: Hamilton Depression Scale results before and 16 wks after treatment in patients with chronic prostatitis/chronic pelvic pain syndrome randomized into 2 treatment groups

	Group 1 (n = 20s)				Group 2 (n = 18)			
Domains	Baseline Mean (SD)	16 Wks Mean (SD)	*z*	*P*	Baseline Mean (SD)	16 Wks Mean (SD)	*z*	*P*
Anxiety/Somatization	7.07 (3.67)	3.26 (2.44)	−2.65	<.01	7.91 (4.01)	7.06 (3.9)	−0.216	NS
Cognitive Disorders	2.34 (1.86)	0.71 (0.65)	−3.06	<.01	2.04 (1.52)	2.19 (1.88)	−0.312	NS
Diurnal Variations	1.47 (1.27)	0.21 (0.08)	−2.94	<.01	1.83 (1.23)	1.51 (1.34)	−0.262	NS
Retardation	4.59 (1.78)	2.78 (1.80)	−2.48	<.05	4.23 (2.01)	4.19 (1.96)	−0.102	NS
Weight	1.04 (1.09)	0.71 (0.09)	−0.379	NS	1.17 (1.19)	1.02 (0.19)	−0.322	NS
Sleeping Disorders	2.18 (1.26)	1.64 (1.63)	−1.42	NS	1.99 (1.44)	1.17 (0.17)	−1.26	NS
Total score	17.56 (4.75)	9.71 (5.26)	−3.19	<.01	16.97 (6.35)	16.82 (0.15)	−0.209	NS

Abbreviations as in Table 1.

hypotension at the beginning of treatment but continued to take the medications.

COMMENT

This study demonstrated that the addition of duloxetine hydrochloride to an α-blocker medication and a saw palmetto extract was superior in relieving pain and improving psychologic status and QoL compared with a conventional treatment including the 2 drugs alone in patients affected by CP/CPPS. Particularly, a combination treatment with duloxetine (60 mg/d), tamsulosin (0.4 mg/d), and saw palmetto (320 mg/d) was able to significantly improve the NIH-CPSI total score and subscores (pain, urinary symptoms, and QoL) and also the anxiety and depression scores in HAM-A and HAM-D. Treatment in group 2 with tamsulosin (0.4 mg/d) and saw palmetto (320 mg/d) significantly improved the HAM-A total score, NIH-CPSI urinary symptoms subscore, and Qmax, but did not have a significant effect on pain and depression. Because patients were aware of their treatment assignment, these results should be interpreted with caution, which represents a limitation of the study.

The combination treatment that included duloxetine in our study was chosen to target the most frequent clinical symptoms in CP/CPPS, which were present in our patients: pain, voiding difficulty, and deterioration of their psychoemotional status. Indeed, 50% of CP/CPPS patients in the present study were affected by anxiety, and approximately 65% presented with depressive symptoms, as assessed by HAM-A and HAM-D scales. Depression has been commonly detected in patients with CP/CPPS,[5,6] and many studies have reported that anxiety and depression frequently coexist in patients with chronic pain.[13,14] Approximately 60% of patients with chronic abacterial prostatitis show symptoms related to a major depression disorder.[15]

Patients with CP/CPPS have been shown to present not only with depression but also with anxiety, hysteria, and hypochondria.[16,17] Psychologic stress may contribute to prostate disease, and the prostate gland responds to emotional stimulation through the autonomic nervous system.[18] Moreover, autonomic fibers have been identified in the prostate gland, and their stimulation may induce prostatic fluid secretion and muscular contraction.[10] Patients affected by depression and stress can have reduced levels of interleukin-10 in circulating mononuclear cells compared with controls.[19] However, very few studies to date have focused on the efficacy of antidepressants (selective serotonin receptor inhibitors and tricyclics) in CP/CPPS. One nonrandomized study that used fluoxetine in the treatment of CP/CPPS showed this agent was effective in improving symptoms and QoL in CP/CPPS patients, without any adverse events.[20]

Duloxetine belongs to serotonin–norepinephrine reuptake inhibitors and is currently approved by the U.S. Food and Drug Administration for the management of diabetic peripheral neuropathic pain.[21] It is also used for the treatment of major depressive disorder, generalized anxiety, and fibromyalgia. In addition, duloxetine is approved in Europe for the treatment of stress urinary incontinence.[22] Serotonin is a crucial neurotransmitter in the pathogenesis of depression and anxiety and an important modulator of descending inhibitory pain pathways in the central nervous system.[22,23] The beneficial effect on pain we detected in CP/CPPS patients who

received duloxetine treatment could be due to a true pain reduction as a direct effect from the drug, but also to a secondary effect due to improvement in mood. The drug was able to strongly modulate mood disorders in our patients, with somatoform symptoms, cognitive performance, and circadian variations appearing most improved. Worth noting: 20% of the patients in our study stopped taking duloxetine due to intolerable side effects (mainly nausea), and 26.3% complained of worsening of libido and sexual activity. Indeed, discontinuation for adverse events, most commonly nausea, has been observed to occur in up to one-third of patients in the short-term trials for generalized anxiety disorders.[24]

The reduction in the HAM-A total score we observed in both groups could be due to the amelioration in pain and urinary symptoms, the latter effect was also observed in group 2 patients. The concomitant use of the 2 other conventional drugs, saw palmetto, with anti-inflammatory properties, and tamsulosin, with effects in reducing bladder neck tone, could have helped to modulate local inflammation and bladder emptying. Although α-blockers have traditionally been postulated to inhibit over-activation of bladder neck smooth muscle, thus increasing urine flow, and have been recently implicated in blocking proliferation and inducing prostatic apoptosis,[25] their effect in controlling CP/CPPS symptoms is modest and still controversial,[7] mostly due to the high heterogeneity of published studies. Indeed, a recent systematic review with a meta-analysis showed that among 8 randomized controlled trials in which α-blockers were compared with placebo, an average total NIH-CPSI score reduction of −4.8 (95% confidence interval, −7.1 to −2.6) and an average pain reduction of −2.1 points (95% confidence interval, −3.1 to −1.2), were observed, but with high heterogeneity among the studies. Neither antibiotics nor nonsteroidal anti-inflammatory drugs resulted in significant improvement in the NIH-CPSI total score and NIH-CPSI pain subscore compared with placebo.[26]

Saw palmetto belongs to the phytotherapy family, which also includes pollen extracts and quercetin. Unfortunately, until now phytotherapy has never been compared with conventional medical therapy in a head-to-head, randomized controlled trial. Pollen extracts have the most compelling evidence, with 2 randomized clinical trials and smaller, nonrandomized studies demonstrating some durable benefits associated with the use of these agents.[27] The assessments of saw palmetto extract studies for CP/CPPS are far fewer than those for benign prostatic hyperplasia, but at least 3 clinical trials suggest a beneficial effect of this natural compound in chronic prostatitis,[28] which induced us to include it in our multidrug regimen for CP/CPPS.

In the present study we did not investigate the potential interactions between the different pharmacologic properties of duloxetine, an α-1-adrenoceptor agonist, and tamsulosin, a well known α-1-adrenoceptor blocker. Nevertheless, no relevant clinical adverse cardiovascular effects (strong reduction of blood pressure or severe modification in pulse rate) were observed in patients simultaneously taking the 2 drugs. Cardiovascular adverse effects occur only rarely in the standard therapeutic dose of tamsulosin (0.4 mg/d). The pharmacokinetic profie of tamsulosin has been thoroughly reviewed recently,[29] and its metabolism involves cytochrome P450 2D6 (CYP2D6) and 3A4. Duloxetine is a moderate inhibitor of CYP2D6. In line with the role of CYP2D6 in the metabolism of tamsulosin, coadministration of strong CYP2D6 inhibitors, such as paroxetine, could increase tamsulosin exposure. To date, no studies have investigated the pharmacodynamic or pharmacokinetic interactions of tamsulosin-duloxetine, which potentially reduce the otherwise good tolerability of the α-blocker.

The concept of using a multidrug regimen emerges also from the more recent literature. Randomized controlled trials of combinations of drugs (eg, combination of antibiotics and α-blockers) produced the greatest effect on symptoms, and benefits appear to be more significant when multimodal therapy is individualized according to the patient's clinical phenotype.[30] A limitation of the present study is that it is impossible to determine if duloxetine as a single agent would be clinically effective. This investigation could be the objective of a further study.

Until the exact etiology and pathophysiology of CP/CPPS is clarified, we need to control pain, the most crucial parameter affecting CP/CPSS patients. Taking into account the superior effect of such a multimodal treatment for CP/CPPS patients obtained in the short-term follow-up, we need other studies with a long-term follow-up and with the application of individualized treatments.

CONCLUSIONS

The inclusion of duloxetine hydrochloride in a multimodal treatment with an α-blocker medication and a saw palmetto extract allowed better results in controlling clinical symptoms, psychological status, and QoL in patients affected by CP/CPPS.

References

1. Krieger JN, Nyberg L Jr, Nickel JC. NIH consensus definition and classification of prostatitis. *JAMA*. 1999;282:236-237.
2. Murphy AB, Macejko A, Taylor A, Nadler RB. Chronic prostatitis: management strategies. *Drugs*. 2009;69:171-184.
3. Clemens JQ, Brown SO, Calhoun EA. Mental health diagnoses in patients with interstitial cystitis/painful bladder syndrome and chronic prostatitis/chronic pelvic pain syndrome: a case/control study. *J Urol*. 2008;180:378-382.
4. Pontari MA, Ruggieri MR. Mechanisms in prostatitis/chronic pelvic pain syndrome. *J Urol*. 2008;179:61-67.
5. De la Rosette JJ, Ruijgrok MC, Jeuken JM, et al. Personality variables involved in chronic prostatitis. *Urology*. 1993;42:654-662.
6. Berghuis JP, Heiman JR, Rothman I, et al. Psychological and physical factors involved in chronic idiopathic prostatitis. *J Psychosom Res*. 1996;41:313-325.
7. Strauss AC, Dimitrakov JD. New treatments for chronic prostatitis/chronic pelvic pain syndrome. *Nat Rev Urol*. 2011;7:127-135.

8. Giubilei G, Mondaini N, Crisci A, et al. Italian version of the National Institutes of Health Chronic Prostatitis Symptom Index. *Eur Urol*. 2005;47:105-111.
9. Rosen RC, Riley A, Wagner G, et al. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology*. 1997;49:22-30.
10. Propert KJ, Mayer RD, Wang Y, et al. Interstitial Cystitis Clinical Trials Group, Responsiveness of symptom scales for interstitial cystitis. *Urology*. 2006;7:55-59.
11. Hamilton M. The assessment of anxiety states by ratings. *Brit J Med Psychol*. 1959;32:50-55.
12. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62.
13. Lovibond PF, Lovibond SH. The structure of negative emotional states: comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behav Res Ther*. 1995;3:35-43.
14. Krishnan KR, France RD, Pelton S, et al. Chronic pain and depression. II. Symptoms of anxiety in chronic low back pain patients and their relationship to subtypes of depression. *Pain*. 1985; 22:89-94.
15. Egan KJ, Krieger JN. Psychological problems in chronic prostatitis patients with pain. *Clin J Pain*. 1994;10:218-226.
16. Ku JH, Jeon YS, Kim ME, et al. Psychological problems in young men with chronic prostatitis-like symptoms. *Scand J Urol Nephrol*. 2002;36:296-301.
17. Mehik A, Hellstrom P, Sarpola A, et al. Fears, sexual disturbances and personality features in men with prostatitis: a population-based cross-sectional study in Finland. *BJU Int*. 2001;88:35-38.
18. Clarck LC Jr, Treichler P. Psychic stimulation of prostate secretion. *Psychosom Med*. 1950;12:261-263.
19. Borish L, Schmaling K, DiClementi JD, et al. Chronic fatigue syndrome: identification of distinct subgroups on the basis of allergy and psychological variables. *J Allergy Clin Immunol*. 1998;102: 222-230.
20. Xia D, Wang P, Chen J, et al. Fluoxetine ameliorates symptoms of refractory chronic prostatitis/chronic pelvic pain syndrome. *Chin Med J*. 2011;124:2158-2161.
21. Zilliox L, Russell JW. Maintaining efficacy in the treatment of diabetic peripheral neuropathic pain: role of duloxetine. *Diabetes Metab Syndr Obes*. 2010;3:7-17.
22. Goldstein DJ, Lu Y, Detke MJ, et al. Effects of duloxetine on painful physical symptoms associated with depression. *Psychosomatics*. 2004; 45:17-28.
23. Goldstein DJ, Lu Y, Detke MJ, et al. Duloxetine vs. placebo in patients with painful diabetic neuropathy. *Pain*. 2005;116:109-118.
24. Carter NJ, McCormack PL. Duloxetine: a review of its use in the treatment of generalized anxiety disorder. *CNS Drugs*. 2009;23: 523-541.
25. Anglin IE, Glassman DT, Kyprianou N. Induction of prostate apoptosis by alpha1-adrenoceptor antagonists: mechanistic significance of the quinazoline component. *Prostate Cancer Prostatic Dis*. 2002;5:88-95.
26. Cohen JM, Fagin AP, Hariton E, et al. Therapeutic intervention for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS): a systematic review and meta-analysis. *PLoS One*. 2012;7:41941.
27. Herati AS, Moldwin RM. Alternative therapies in the management of chronic prostatitis/chronic pelvic pain syndrome. *World J Urol*. 2013;31:761-766.
28. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. *Natl Health Stat Report*. 2008;12:1-23.
29. Franco-Salinas G, de la Rosette JJMCH, Michel MC. Pharmacokinetics and harmacodynamics of tamsulosin in its modified-release and oral-controlled absorption system formulations. *Clin Pharmacokin*. 2010;49:177-188.
30. Thakkinstian A, Attia J, Anothaisintawee T, Nickel JC. α-blockers, antibiotics and anti-inflammatories have a role in the management of chronic prostatitis/chronic pelvic pain syndrome. *BJU Int*. 2012; 110:1014-1022.