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دانشگاه علوم پزشکی گلستان
معاونت تحقیقات و فناوری

عنوان

Male Chronic Pelvic Pain and CP/ CPP

نویسندگان

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NIH – CPSI Classification

According to the National Institutes of Health (NIH) prostatitis classification system, prostatitis is classified as:

1. Acute bacterial Prostatitis (category I),

2. Chronic bacterial Prostatitis (category II),

3. Chronic Pelvic Pain Syndrome (CPPS, category III)

3a. inflammatory

3b. non-inflammatory

4. Asymptomatic Prostatitis (category IV)

The NIH-Chronic Prostatitis Symptom Index (NIH-CPSI) is a commonly used 13-item questionnaire for the assessment of symptom severity in men with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).

- Research guidelines define CP/CPPS as chronic pelvic pain for at least three of the preceding six months in the absence of other identifiable causes, often associated with urinary symptoms and/or sexual dysfunction.
- CP/CPPS is sometimes referred to as either inflammatory or non-inflammatory; however, the distinction is generally for research purposes only, as there is no evidence that patients in the two subgroups have different symptoms or respond differently to therapy.

The **type of chronic prostatitis/chronic pelvic pain syndrome** (CP/CPPS) is more common in the younger and middle-aged men.

With a prevalence of 2.5–16%, CP/CPPS is considered as the most common urological disease in males aged <50 years.

It manifests as a chronic pain in a variety of areas such as perineum, penis, testicles, and pelvic floor muscles.

In addition, CP/CPPS patients may complain of burning urination, painful ejaculation, and a slow urine flow.

The CP/CPPS can severely impair quality of life of these patients.

The assessment of patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) in everyday practice and clinical studies relies on National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) scores for symptom appraisal, inclusion criteria for clinical trials, follow-up, and response evaluation.

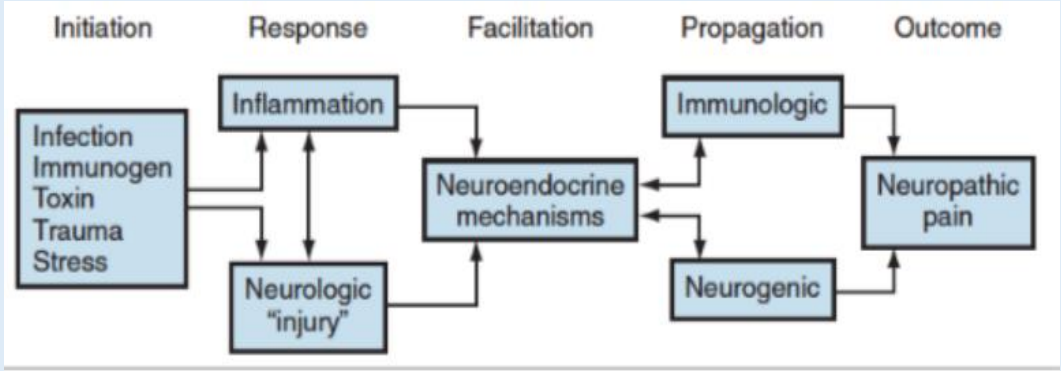
Pain severity categories results for NIH-CPSI item 4 (0–10 numerical rating scale for average pain) were mild, 0–3; moderate, 4–6; severe, 7–10; CPSI pain domain (0–21): mild, 0–7; moderate, 8–13; and severe, 14–21.

Definition of CCPS

- Chronic or recurring symptoms of perineal, testicular, penile pain or discomfort, sometimes associated with symptoms of voiding dysfunction and sexual dysfunction in the absence of infection.
- CP/CPPS show heterogeneity of clinical manifestations
- Arising from the variety of possible underlying etiologies
- Symptoms can vary between patients or fluctuate over time

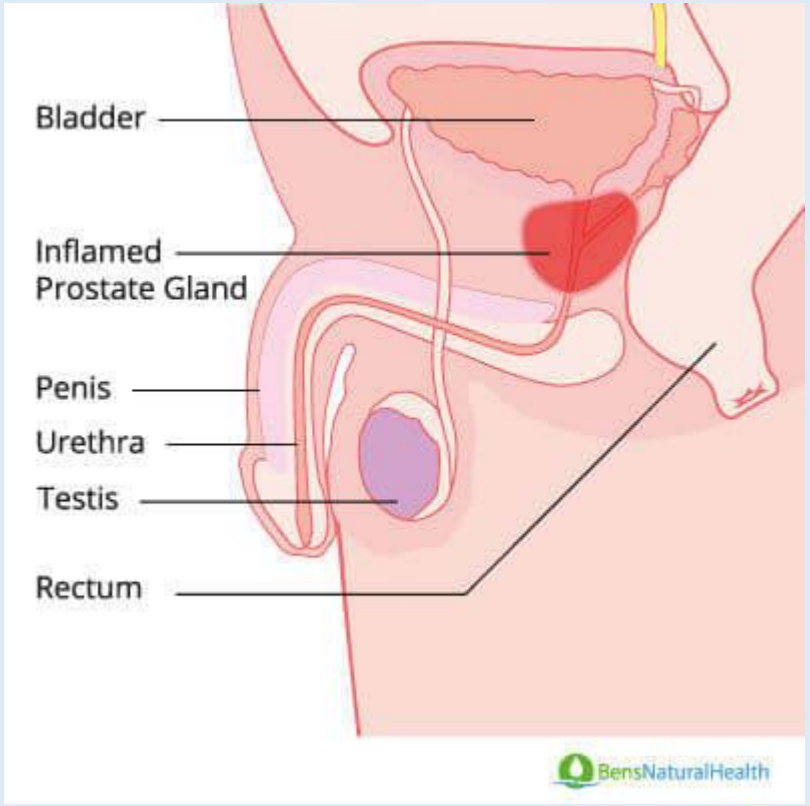
Etiology

- No single aetiological explanation
- Infection
- – E Coli, Enterococcus
- – Altered prostatic host defense
- Pelvic floor muscle abnormalities
- Genetic, anatomical, neuromuscular, endocrine
- Psychological mechanism



CPPS clinical characteristics

Symptoms	% in 764 patients
Pain	82
Urinary	68
Abdominal	63
Sexual	40



4 Symptom Domains

- The four main symptom domains associated with CP/CPPS are:
- 1. Urogenital pain
- 2. LUTS
- 3. Psychological issues
- 4. Sexual dysfunction

Primary evaluation

- Detailed pain history – site(s), predominate site, duration, type, severity, continues
- or intermittent, frequency, radiation, how long it lasts, impact of the pain on
- daily/work life.
- Initial trigger
- Aggravating and relieving factors (including triggers i.e., alcohol, spices etc)
- Ejaculatory and erectile pain
- Other regional pain syndromes (FM, constipation, IBS)

Primary evaluation

- LUTS – Storage, voiding , post mic symptoms
- Hematuria and Hematospermia
- Sexual function
- Healthcare utilization for this problem
- Sexual history and PSTD
- Recreation drug use/Alcohol/Smoking
- Social history/ Exercise history
- Domestic abuse/sexual violence/PTSD
- Psychiatric/Psychology
- PMH/Medicine/Allergy

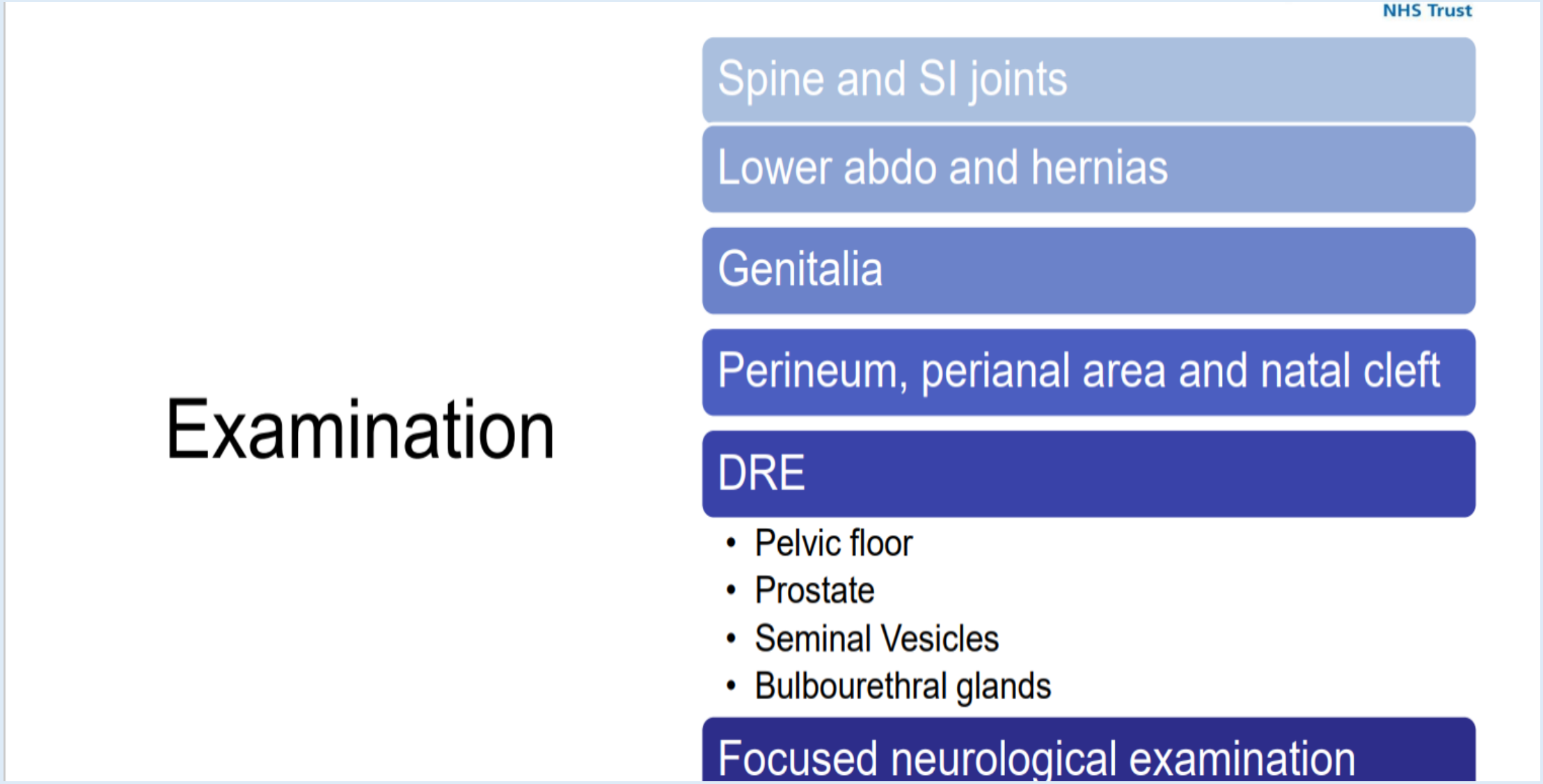
Special Investigations

- Urinalysis and culture
- STI screen
- Specialized evaluation
- Meares-stamey four glass test
- Pre and post-massage two glass test
- Semen culture
- Transrectal ultrasound
- Urodynamic studies (only if lower urinary tract symptoms or outflow
- obstruction present)

Special Investigations

- New/optional evaluation
- Serum prostate-specific antigen
- Cystoscopy
- Computerized tomography
- Intra-anal electromyography
- Pelvic floor ultrasound

- The exclusive diagnostic algorithms of CP/CPPS start with low abdominal pain and/or abnormal urination (so-called alarming signs), prostate palpating, and two basic laboratory examinations, that is, urine macroscopic test and ultrasound of low abdomen region.
- These examinations give the care providers a clue to exclude abnormal results that may be caused by other disorders such as tumors, tuberculosis, urolithiasis, nephropathy, and bladder infection.
- Age is another phenotype to consider at initial visits of patients with associated symptoms.
- Patients under 50 years of age are more likely to suffer from CP/CPPS than those over 50 years whose symptoms are likely caused by other diseases.
- Prostate-specific antigen (PSA) is usually ordered for patients >50 years old in the exclusive diagnostic procedure for CP/CPPS.



A digital rectal exam (DRE) is a test that examines a person's lower rectum, pelvis, and lower belly.

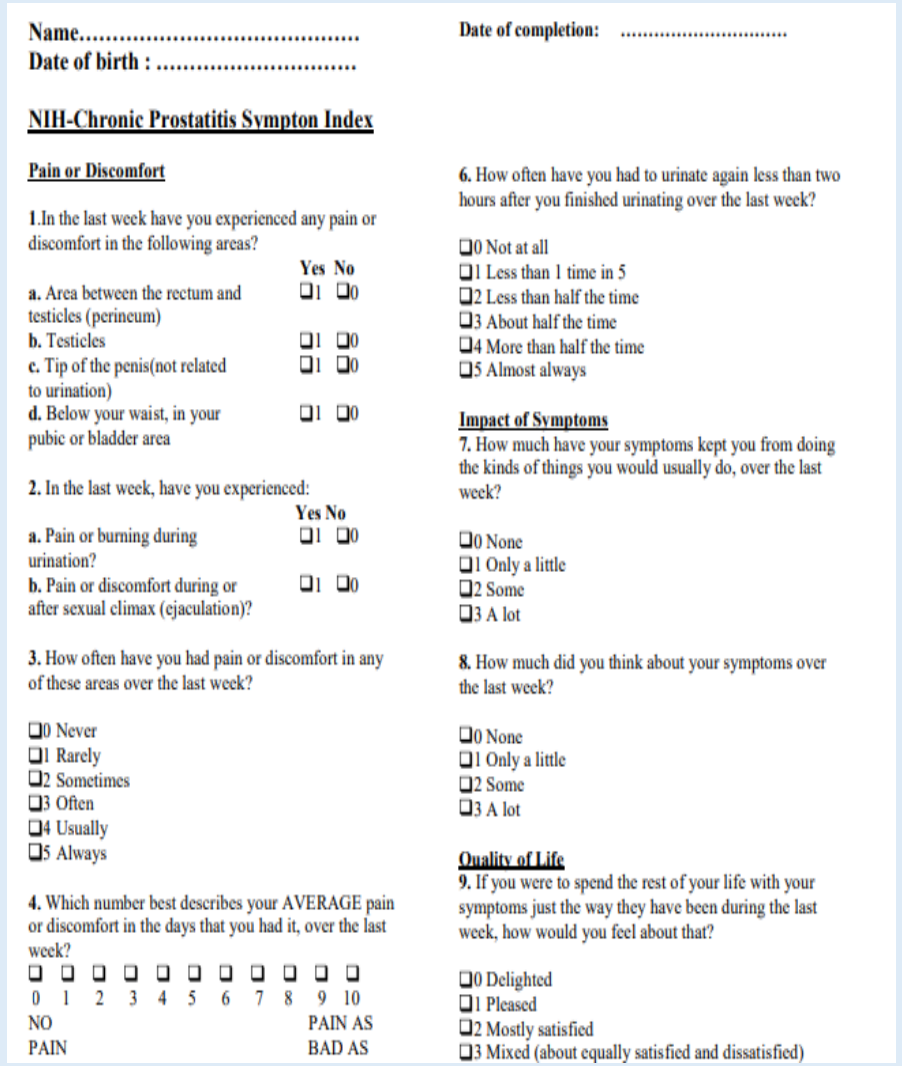
- A taxonomy provided by the International Association for the Study of Pain (IASP) recommended that pain in the pelvic region should be considered as a multidisciplinary issue including
- urologic,
- gastrointestinal,
- musculoskeletal,
- neurologic, and/or rheumatologic etiology with psychosocial aspects

(Doggweiler et al., 2017).

- In addition, the European Association of Urology (EAU) guidelines subdivide chronic pelvic pain (CPP) into conditions that are associated with pain and those with non-pain syndromes (Engeler et al., 2019).
- The non-pain syndromes have well-recognized pathology (e.g., infection, neuropathy, or inflammation), whereas the conditions that are associated with pain do not have a clear etiology. Although the EAU classification deals primarily with urological disorders, it can be applied to all conditions associated with pain perception within the pelvis.

Measures and scales

- The terminology of CPPS published by ICS is usually used for measuring scales and locations of pain (pain mapping; Doggweiler et al., 2017).
- The NIH-Chronic Prostatitis Symptom Index (NIH-CPSI) and the consensus guideline by the Prostatitis Expert Reference Group are also useful instruments for initial evaluation of symptom severity and follow-up of treatment results of CP/CPPS (Collins et al., 2001; Litwin et al., 1999; Rees et al., 2015).
- NIH Chronic Prostatitis Symptom Index useful to gauge and track symptoms



Name.....
Date of birth : .....

Date of completion: .....

NIH-Chronic Prostatitis Sympton Index

Pain or Discomfort

1. In the last week have you experienced any pain or discomfort in the following areas?

	Yes	No
a. Area between the rectum and testicles (perineum)	❑1	❑0
b. Testicles	❑1	❑0
c. Tip of the penis(not related to urination)	❑1	❑0
d. Below your waist, in your pubic or bladder area	❑1	❑0

2. In the last week, have you experienced:

	Yes	No
a. Pain or burning during urination?	❑1	❑0
b. Pain or discomfort during or after sexual climax (ejaculation)?	❑1	❑0

3. How often have you had pain or discomfort in any of these areas over the last week?

❑0 Never
❑1 Rarely
❑2 Sometimes
❑3 Often
❑4 Usually
❑5 Always

4. Which number best describes your AVERAGE pain or discomfort in the days that you had it, over the last week?

❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑
0 1 2 3 4 5 6 7 8 9 10
NO PAIN — PAIN AS BAD AS

6. How often have you had to urinate again less than two hours after you finished urinating over the last week?

❑0 Not at all
❑1 Less than 1 time in 5
❑2 Less than half the time
❑3 About half the time
❑4 More than half the time
❑5 Almost always

Impact of Symptoms

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

❑0 None
❑1 Only a little
❑2 Some
❑3 A lot

8. How much did you think about your symptoms over the last week?

❑0 None
❑1 Only a little
❑2 Some
❑3 A lot

Quality of Life

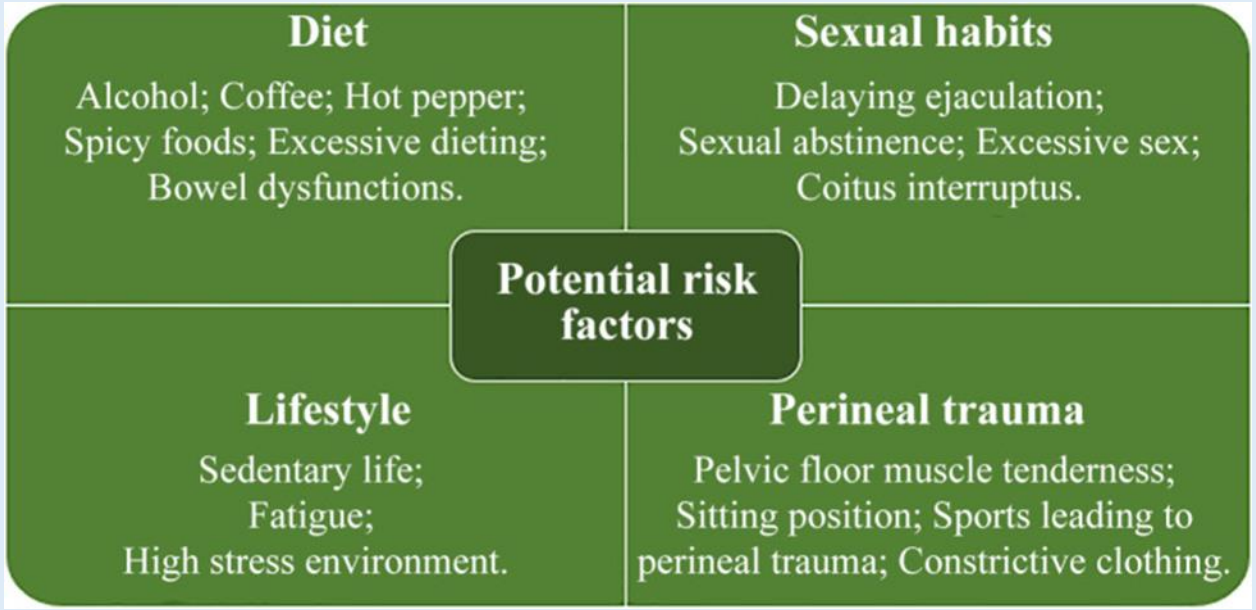
9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

❑0 Delighted
❑1 Pleased
❑2 Mostly satisfied
❑3 Mixed (about equally satisfied and dissatisfied)

NIH-Chronic Prostatitis Symptom Index (NIH-CPSI)

- Pain severity categories results for NIH-CPSI item 4 (0–10 numerical rating scale for average pain) were mild, 0–3; moderate, 4–6; severe, 7–10; CPSI pain domain (0–21): mild, 0–7; moderate, 8–13; and severe, 14–21.

Potential risk factors associated with chronic prostatitis and chronic pelvic pain syndrome.



Phenotyping CPPS

- CPPS comprises a heterogeneous group of patients with very different etiologies, symptom complexes, and progression trajectories

Phenotypically directed multimodal management: UPOINTS

- Aims to stratify patients into specific symptom-led phenotypes.

Measures urinary symptoms, psychosocial dysfunction, organ-specific findings, infection, neurological/systemic routes, and tenderness of muscles and sexual function.

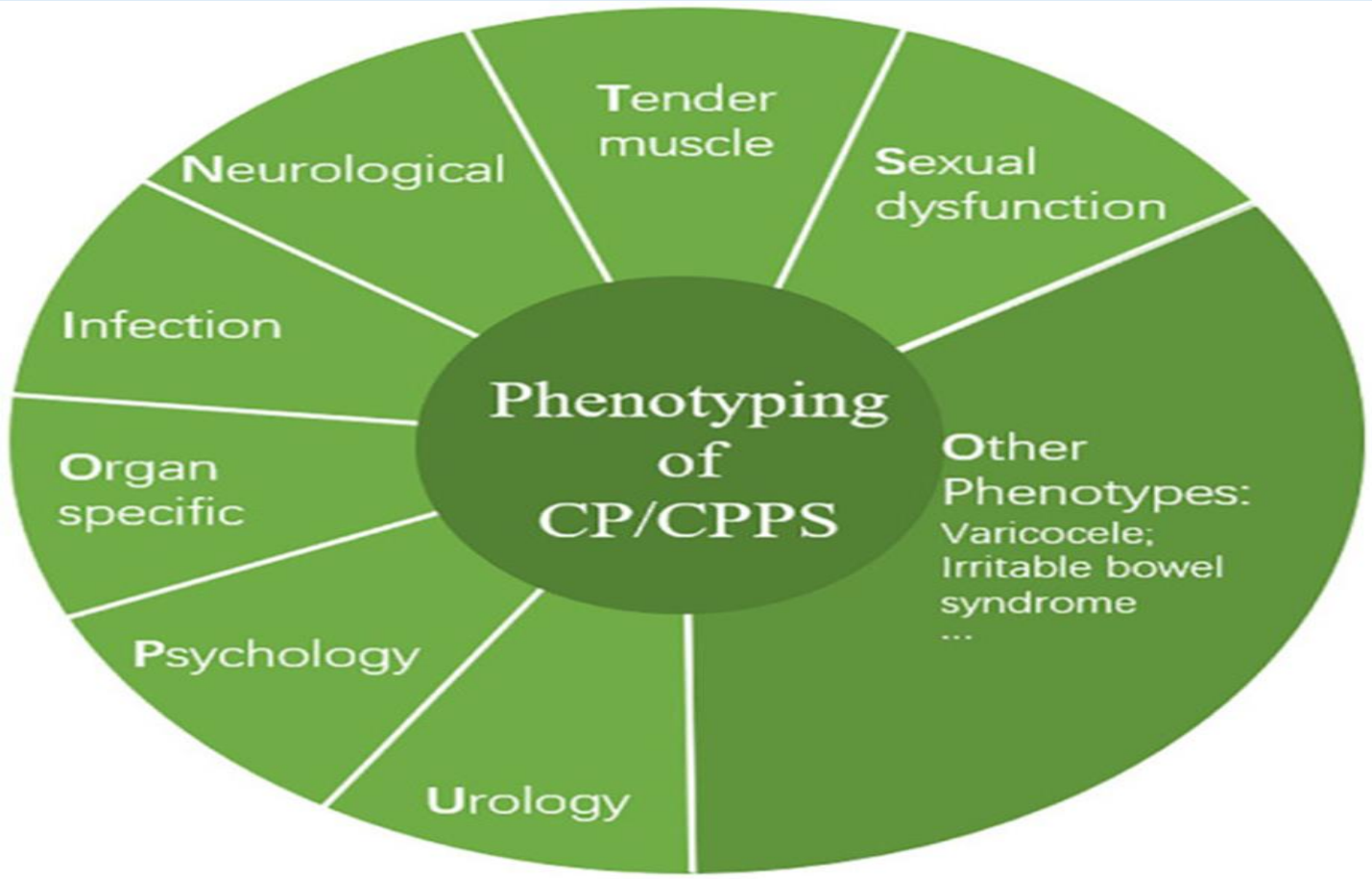
The UPOINT phenotype system

- UPOINT is more meaningful for urology care providers in evaluating associated symptoms of CP/CPPS than the evidence-based diagnostic guideline.
- Associated symptoms may be linked to other disorders such as varicocele, irritable bowel syndrome, and melena (Li et al., 2002; Lotti et al., 2009; Pavone et al., 2000; Vicari et al., 2011, 2014).
- Once a diagnosis of CP/CPPS has been made, a multimodal approach that addresses a patient's phenotype (based on his specific complaints) can be formulated.
- the UPOINT system for the clinical phenotyping of chronic pelvic pain, classifies patients into six domains (Urinary, Psychosocial, Organ Specific, Infectious, Neurological/systemic, and Tenderness of skeletal muscles)+ Sexual function.

The UPOINT phenotype system

- Based on patient evaluation including patient complaints, physical examination findings, laboratory tests and NIH-CPSI scores and thus guides appropriate therapy.
- The number of positive domains in the UPOINT system has been shown to correlate with increasing NIH-CPSI .
- As patients may be grouped into multiple domains, each patient's overall treatment can vary.

Phenotypes possibly associated with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).



Those phenotypes need to be ruled out in the diagnosis of CP/CPPS.

The UPOINT phenotype system

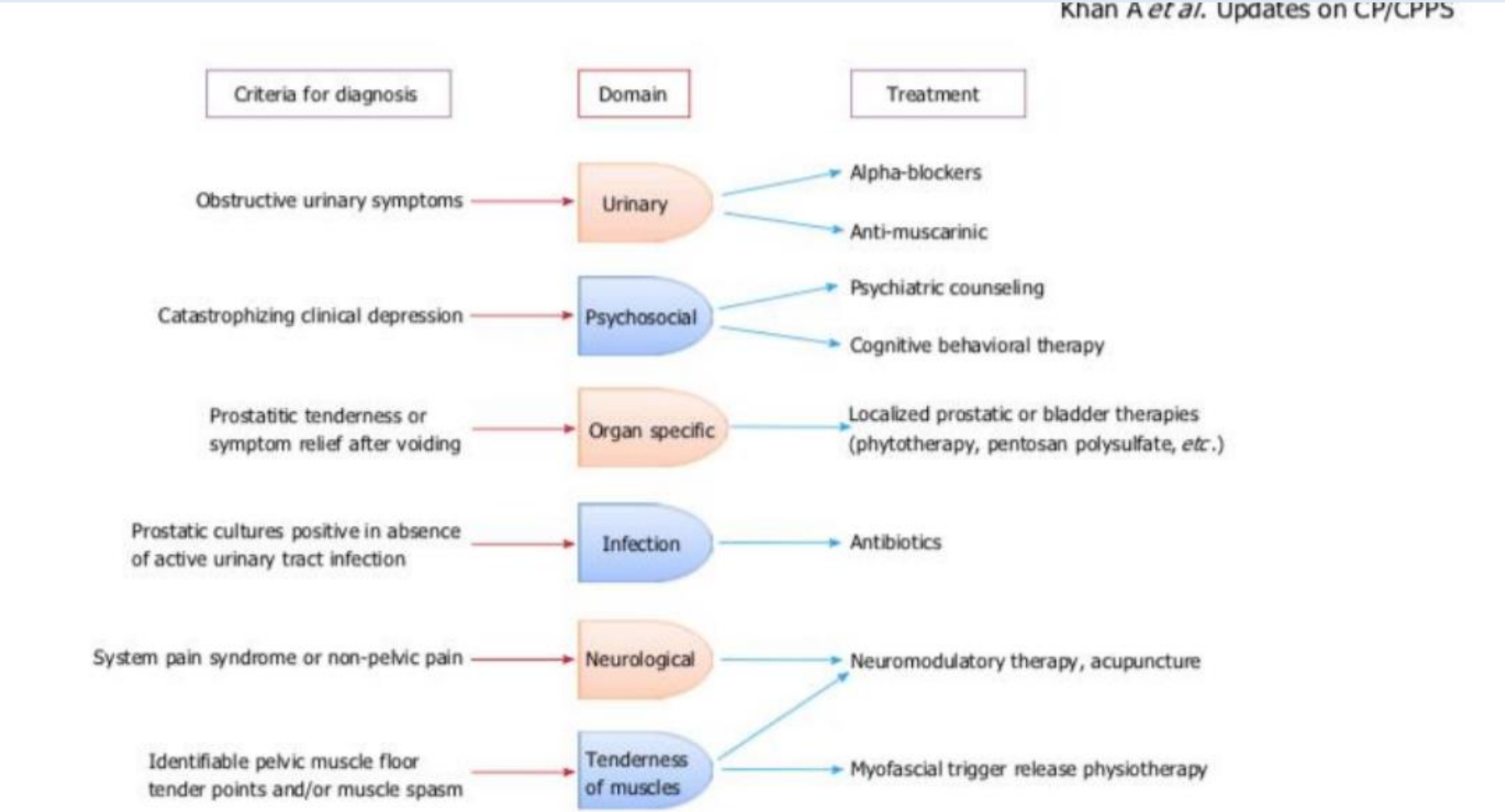


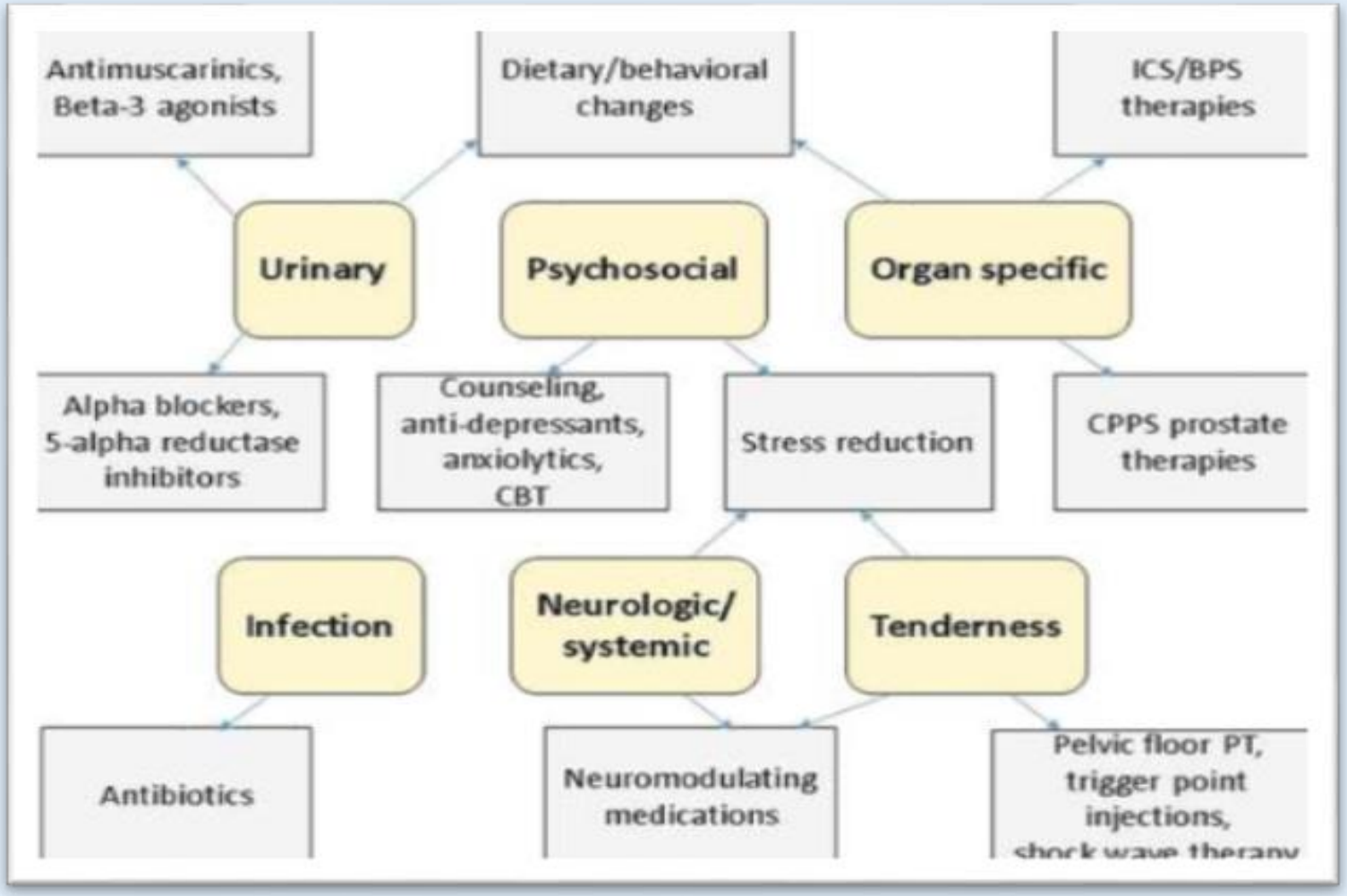
Figure 3 Multimodal therapy based on clinical phenotype (urinary, psychosocial, organ specific, infection, neurological, tenderness of muscle) approach for chronic prostatitis/chronic pelvic pain syndrome.

Multimodal treatment strategy

- Most clinical trials conducted so far speak in favor of the extended UPOINT approach. First studies suggested that the multimodal management guided by UPOINT leads to a significant improvement of symptoms and quality of life.
- There have been myriad studies that have evaluated various monotherapies in the treatment of CP/CPPS.
- Franco et al. in two Cochrane reviews of pharmacological and non-pharmacological interventions for the treatment of CP/CPPS, respectively, found low-quality evidence that some monotherapies may provide a small decrease in symptoms, rarely with a decrease in NIH-CPSI score of >6 and the majority with limited long-term outcomes. Even for the helpful therapies, such **as α-blockers**, large multicenter trials have failed to show benefit, likely because of phenotypic diversity of this syndrome.

The UPOINT phenotype system treatment guide

CBT: cognitive behavioural therapy; IC/BPS: interstitial cystitis/bladder pain syndrome; PT: physical therapy



- Patients with the '**Urinary' phenotype** complain of LUTS, including bothersome nocturia, daytime frequency or urinary urgency, may have an NIH-CPSI urinary score >4 and may have incomplete emptying of the bladder.
- The 'Urinary' domain is often among the most commonly positive domains in men with CPPS, ranging from 60–72% of CPPS populations.
- **A post-void bladder scan** should be obtained in these patients to evaluate for elevated residual urine or urinary retention.
- Treatments can include behavior modifications (timed voiding, fluid intake limitation and dietary changes, such as avoiding caffeine) and medications (such as α-blockers, 5α-reductase inhibitors, antimuscarinics and β3 agonists) with drug choice based on the predominant urinary complaint.

- Patients in the ‘Psychosocial’ domain often have depression or depressive symptoms, anxiety, stress and poor coping/adjustment mechanisms; patients may also catastrophize, characterized by a sense of helplessness and hopelessness about the condition and rumination about their symptoms.
- Patients with CP/CPPS have a high prevalence of psychological issues and may have a history of sexual or other physical abuse, which is associated with poorer quality of life .
- Treatments should include referral to appropriate psychological therapy (including cognitive behavioural therapy), counselling, antidepressants and anxiolytics (prescribed by a mental health specialist), and stress reduction techniques.

- The ‘Organ-specific’ patients have complaints that implicate the prostate and/or bladder as symptom drivers.
- Prostate-related symptoms can include prostate tenderness to palpation, white blood cells in EPS(Expressed prostate secretion), hematospermia and prostate calcifications; treatments can include anti-inflammatory phytotherapies such as quercetin, flower pollen and cernilton .
- Bladder-related symptoms can include pain with bladder filling that improves with voiding and Hunner lesions seen on cystoscopy. These symptoms suggest a diagnosis of interstitial cystitis/bladder pain syndrome; treatments should follow the algorithm in the AUA guideline on Interstitial Cystitis/Bladder Pain Syndrome.

- Patients with CP/CPPS are often prescribed empiric antibiotics, which are rarely effective at improving symptoms .
- The ‘Infection’ domain refers to instances where patients have uropathogenic bacteria in urine, EPS or urethra without meeting criteria for UTI or Category I or II prostatitis .
- Mycoplasma and Ureaplasma may be such pathogens present that are not commonly tested .
- In the absence of infection, antibiotics will not be helpful; however, for patients in this domain, culture-directed antibiotics are indicated.

- The ‘Neurological/systemic’ patients can be characterized by pain outside the lower abdomen, genitals and pelvis, fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and/or other systemic pain complaints.
- For these patients, neuromodulators, such as tricyclic antidepressants (amitriptyline), duloxetine, gabapentin and pregabalin, are recommended. Cannabinoids can also be used.
- Chronic opioids should be avoided.
- Patients in the ‘Tenderness’ domain have spasm, tenderness and/or trigger points of the pelvis or abdominal muscles diagnosed on DRE and genital and abdominal examinations. First-line treatments for these patients are stress reduction and pelvic floor physical therapy. Additionally, muscle relaxants, trigger point injections, acupuncture and low-intensity shockwave therapy can be helpful.

Sexual dysfunction and UPOINT ‘S

- Sexual dysfunction, including ED, ejaculatory dysfunction, orgasmic dysfunction and decreased libido, is a common complaint of men with CP/CPPS.
- As such, Magri et al. in a study assessing the correlation of positive UPOINT domains to NIH-CPSI scores showed that adding a ‘Sexual Dysfunction’ domain, thus creating a UPOINT ‘S’ system, improved the correlation and better characterized the symptom profile in patients with CP/CPPS.
- A case–control study involving men with CP/CPPS demonstrated that this group was more likely to have evidence of arterial stiffness associated with nitric oxide-mediated vascular endothelial dysfunction compared to asymptomatic controls .
- Decreased arterial inflow may also be related to extrinsic compression from pelvic floor spasm.

Effectiveness of Extended-release Bupropion and Duloxetine on Pelvic Pain among Patients with Chronic Prostatitis / Chronic Pelvic pain

Accepted for publication in Advanced Biomedical Research

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Abstract

- Finding an effective treatment for chronic pain, reduced quality of life, sexual dysfunction, and psychological consequences in patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is important.
- To compare the efficacy of the two antidepressants; duloxetine and bupropion, on complications of CP/CPPS patients, a single blind clinical trial was conducted.
- Sixty eight patients randomly assigned to receive extended release bupropion (150 mg/day) or duloxetine (30 mg/day) for 12 weeks (each group N=34).

Effectiveness of Extended-release Bupropion and Duloxetine on Pelvic Pain among Patients with Chronic Prostatitis / Chronic Pelvic pain

- The pain, quality of life, depression, anxiety, and sexual dysfunction scores were compared by Short Form of the McGill Pain, Short-Form Health Survey, Hospital Anxiety and Depression Scale (HADS) and Arizona Sexual Experiences Scale, at baseline, 4, 12 and 16 weeks follow-up session.
- The results showed pelvic pain scores were significantly lower in duloxetine group after 12, and 16 weeks (P value <0.05). The mean HADS and quality of life scores significantly improved through time of intervention in both group (P time<0.001). Sexual dysfunction scores were higher in the duloxetine group after 4 and 12 (P value <0.05), and more improved after 16 weeks in bupropion group (P time× group <0.001).Our findings suggest that adding bupropion and duloxetine to current treatment of CP/CPPS patients is useful .

Lay summary
and
take home message

- For choosing an effective medication for reduction of pain and discomfort in 68 patients with chronic prostatitis a study conducted using duloxetine or bupropion in a sixteen -week trial. Results indicated although both antidepressants work in pain relief, duloxetine is slightly more effective. Depression and anxiety relived, by receiving both medications. Sexual dysfunction scores were higher in the duloxetine group after 4 and 12 and more improved after 16 weeks in bupropion group. Our findings suggest that adding bupropion or duloxetine to current treatment of chronic prostatitis patients is useful.

KEY WORDS

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS); Duloxetine; Bupropion; Depression, Pain; Sexual function; Quality of life.

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