Continuing Medical Education

Chronic Primary Pelvic Pain Syndrome in Men

Differential Diagnostic Evaluation and Treatment

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Summary

Background: Chronic primary pelvic pain syndrome in men (CPPPSm) can be associated with urogenital pain, urinary symptoms, sexual dysfunction, and emotional disturbance. Its clinical heterogeneity and incompletely understood pathogenesis make it more difficult to treat. This article is intended to familiarize the reader with basic aspects of the manifestations, pathophysiology, diagnostic evaluation, differential diagnosis, and treatment of this condition.

Method: This article is based on relevant publications retrieved by a selective search of the literature, including the current guidelines of the European Association of Urology. The features of this disease pertaining to urology, psychosomatic medicine, and pain medicine are illuminated from an interdisciplinary perspective.

Results: Chronic pelvic pain appears to arise through a complex interaction of inflammatory, infectious, neurological, musculoskeletal, and psychosomatic factors. A comprehensive diagnostic work-up should be carried out to evaluate and exclude the numerous differential diagnoses. Treatment strategies are based on the clinical phenotype. Randomized controlled trials have shown that significant relief can be achieved with a variety of drugs and non-pharmacological treatments, selected according to the manifestations of the condition in the individual case. Attention must be paid to treatment-specific adverse effects.

Conclusion: The management of patients with CPPPSm should consist of a comprehensive differential diagnostic evaluation and an individually oriented treatment strategy.

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Chronic pelvic pain (i.e., pelvic pain that persists or recurs over a period of at least 3 months) takes many different forms and is treated by physicians from multiple specialties. If there is no specific pathological process, such as an infection, underlying the constellation of clinical manifestations, it is called a primary pain syndrome. In such cases, pain is not only the main symptom, it also plays a central role in the pathophysiology of the condition. In accordance with clinical diversity of chronic pelvic pain, the European Association of Urology (EAU) has divided the chronic primary pelvic pain syndrome (CPPPS) into subtypes depending on the system that is primarily affected—urologic, gastrointestinal, or musculoskeletal (1). Pelvic pain in men is often attributed to a problem in the prostate gland, in which case it is typically associated with urinary and sexual dysfunction and emotional disturbances such as anxiety, depressive manifestations, or catastrophizing. The initial presumptive diagnosis is often of prostatitis; if no infection is detected, or the

Clinical features

Chronic primary pelvic pain syndrome in men (CPPPSm) can be associated with urogenital pain, urinary symptoms, sexual dysfunction, and emotional disturbance.

Diagnostic evaluation

The clinical heterogeneity and incompletely understood pathogenesis of this syndrome make it more difficult to treat. The initial presumptive diagnosis is often of prostatitis.

symptoms persist longer than three months, the preferred term is "primary prostate pain syndrome" once the remaining elements of the differential diagnosis have been ruled out, or else, if the pain cannot be precisely localized, "chronic primary pelvic pain syndrome of the male" (CPPPSm) (1). These terms, however, have not been employed consistently in the literature to date, and thus no reliable data on the prevalence of CPPPSm are yet available. At any rate, it is known that a 2–10% of men suffer from symptoms of prostatitis (2, 3), while only 5–10% of these cases are due to a bacterial pathogen (4–6), so it appears that many of these patients may, in fact, have CPPPSm. The condition leads not only to high costs for the health care system, but also to wider effects on society arising from these patients' psychological and social impairment (emotional burden, stress, lessened social participation, impaired ability to work, etc.).

Both the recognition and the management of CPPPSm are a challenge because of inconsistencies in terminology, the clinical heterogeneity and incomplete pathophysiological understanding of the condition, and the lack, to date, of any clear treatment strategy. This CME article, based on a selective literature review and the current EAU guidelines, is intended to broaden the understanding of CPPPSm through a presentation of the diagnostic work-up and differential diagnostic of chronic pelvic pain in men and an outline of the main therapeutic strategies. Perspectives on CPPPSm from the points of view of psychosomatic medicine and pain medicine will be included as well. We focus on prostate-related complaints here, yet we prefer to use the term CPPPSm, as pelvic pain in men is generally imprecisely localized and associated with further manifestations at a variety of anatomic sites.

Learning objectives

This CME article is intended to provide readers with a knowledge of:

- the main features of chronic primary pelvic pain syndrome in men
- its differential diagnosis
- its psychosomatic aspects
- basic elements of the treatment strategy.

Clinical features and pathophysiology

The clinical manifestations of CPPPSm are of four main types: urogenital pain, irritative and/or obstructive micturition symptoms ("lower urinary tract symptoms," LUTS), sexual dysfunction, and emotional disturbance (7). Pain often impairs these patients' quality of life (8). The pathophysiology of CPPPSm is incompletely understood, but seems to involve multiple factors (9):

- Inflammation: in a prospective study, leukocytes were found in prostate biopsies of only one-third of CPPPSm patients (10), while they were also found in prostatic secretions and urine samples from asymptomatic men (11). However, quantitative changes in pro- and anti-inflammatory cytokines were indeed found in patients with CPPPSm (12–18). Moreover, the clinical manifestations are correlated with a variety of inflammatory proteins (IgM, C3, IL8, macrophage inflammatory protein 1α) (16, 19, 20).
- Infection: Bacterial components have been inconsistently found in the prostatic secretions of men with CPPPSm (6, 21–23), but men with CPPPSm are significantly more likely than control subjects to have had nonspecific urethritis (12% vs. 4%, $p = 0.008$). This implies a possible role for chronic post-infectious processes (24).
- neural changes: Neuroimaging in men with CPPPSm has revealed microstructural changes in CNS regions associated with sensory perception and integration and with the modulation of pain (25, 26). A combination of neuropathic pain and neuroplasticity might amplify the perception of afferent stimuli and cause abnormal sensations as well as pain (27).
- Pelvic floor dysfunction: like CPPPSm, pelvic floor dysfunction is associated with pain, sexual dysfunction, and anxiety; it could be a cause and/or an effect of CPPPSm (28, 29). A cohort study revealed pelvic floor muscle tenderness in patients with CPPPSm, but not in controls (30). Increased smooth muscle tone in the prostate and bladder might be a mechanism that promotes LUTS (31, 32).
- mental/emotional aspects: A case-control study revealed that patients with CPPPSm were more than 2.5 times as likely as controls to suffer from mental illness, with an especially high frequency of anxiety/panic disorders (14.5% vs. 2.5%, $p = 0.004$) (24). Men who have experienced physical, emotional, or sexual abuse were found to be 1.7 to 3.3 times as likely to have

Prevalence

No reliable data on the prevalence of CPPPSm are yet available. 2–10% of men suffer from symptoms of prostatitis (2, 3), while only 5–10% of these cases are due to a bacterial pathogen (4–6); it appears that many of these patients may, in fact, have CPPPSm.

The clinical features are of four main types:

- urogenital pain
- irritative and/or obstructive micturition symptoms ("lower urinary tract symptoms," LUTS)
- sexual dysfunction
- emotional disturbance

CPPPSm (33). Non-traumatic stress has been found to cause mast cell degranulation and pelvic floor spasticity (34, 35), while inflammatory cytokines in seminal plasma are inversely correlated with support from a partner (15). Moreover, a supportive social environment seems to have improve the emotional state (36).

These complex pathophysiological factors must also be considered in the diagnostic and differential diagnostic evaluation. It is especially important to distinguish the changes described above that are related to CPPPSm from organ-specific pathology (such as acute infection, inflammation, or neuropathy). Pain due to an identifiable organic disease does not fall within the definition of CPPPSm.

Diagnostic evaluation

Every patient with CPPPSm should have an individually tailored diagnostic work-up, but certain basic steps should always be included *(Figure)*. All persons involved in the management of patients with chronic pelvic pain should have adequate knowledge of peripheral and central pain mechanisms (1).

General practitioners are often the first physicians to be consulted by men with chronic pelvic pain; they face the task of taking a detailed history as to the nature and time course of the patient's symptoms. Various questionnaires have been found useful for this purpose in the last few years: The National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) assesses the symptoms of CPPPSm with nine questions about pain, LUTS, and the quality of life (8, 37). The International Prostate Symptom Score (IPSS) likewise assesses LUTS-related symptoms (38). The International Index of Erectile Function (IIEF) yields information about sexual function (39). A psychosocial assessment, e.g., with the Patient Health Questionnaire 9, documents negative cognitive, emotional, social, and behavioral effects (40). After history-taking, the physical examination should cover the abdomen, genitalia, and perineum, including a digital rectal examination (DRE). The latter can reveal prostatic abnormalities that are evident on palpation, as well as rectal and pelvic floor tenderness, sometimes with reproduction of the patient's pelvic pain; it also enables the examiner to assess the contractility of the pelvic floor muscles.

Urinalysis with a 4-vial specimen according to Meares and Stamey (alternatively, a 2-vial specimen) is recommended to rule out bacterial prostatitis: in this test, a fractionated urine specimen (initial, midstream urine, expressed prostatic secretions (EPS), and urine after EPS expression) is analyzed both microbiologically and cytologically (e1, e2). 13.3% of patients with CPPPSm symptoms had positive cultures in a case-control study (e3). A neurological and musculoskeletal examination should be performed. Depending on symptoms, further studies such as urodynamics, imaging, or extended microbiological testing may be necessary.

By definition, the diagnosis of CPPPSm is confirmed when pelvic pain with or without accompanying complaints in other domains (LUTS, sexual dysfunction, emotional disturbance) has been present for at least three of the past six months and neither a urinary pathogen nor any other causal pathology can be demonstrated. If the symptoms are found to be due to a specific organ pathology, the diagnosis must be modified accordingly. For phenotypic classification, the so-called UPOINT(S) scheme has proven useful, which classically includes six domains:

- U – urinary symptoms (i.e., symptoms relating to micturition)
- P – psychosocial dysfunction
- O – organ-specific findings
- I – infection
- N – neurological or systemic pathology
- T – muscle tenderness (e4).

The UPOINT scheme has been extended to include the category of sexual dysfunction (S: e.g., erectile or ejaculatory dysfunction, post-orgasmic pain), but the added value of this has yet to be confirmed in studies (e5, e6). There is a specific evaluation for each domain *(Figure)*. For domains with positive findings, there are corresponding recommendations for targeted treatment (e7, e8).

Differential diagnosis

CPPPSm is to be regarded as a diagnosis of exclusion. The differential diagnosis of chronic pelvic pain includes disorders that are dealt with by a wide range of medical specialties, and consideration must be given to these numerous disorders at an early stage of the diagnostic evaluation. An

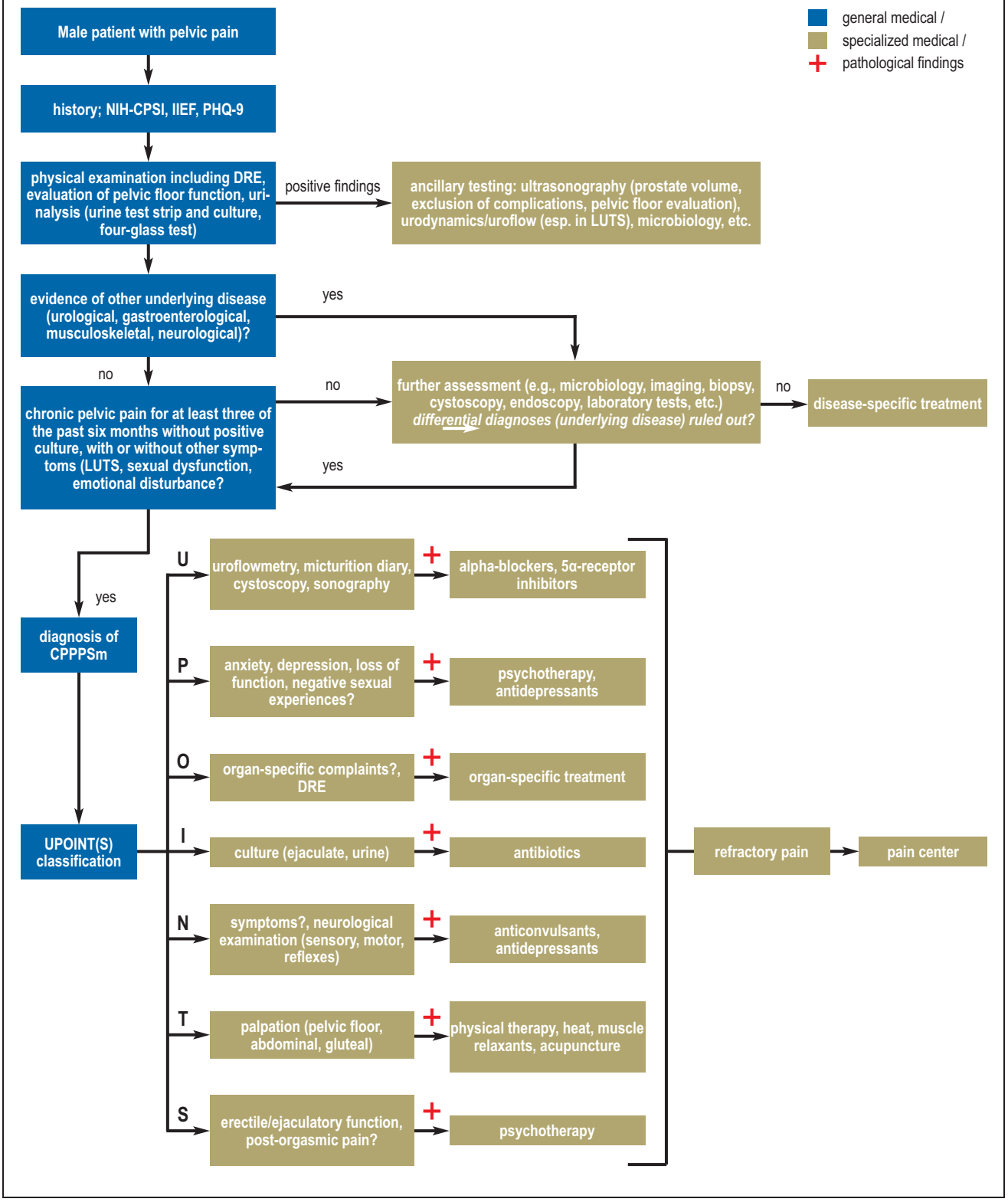
Initial steps in the diagnostic evaluation

General practitioners are often the first physicians to be consulted by men with chronic pelvic pain; they face the task of taking a detailed history as to the nature and time course of the patient's symptoms.

Available questionnaires for history-taking:

- National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI)
- International Prostate Symptom Score (IPSS)
- International Index of Erectile Function (IIEF)
- Patient Health Questionnaire 9

FIGURE



Algorithms for chronic primary pelvic pain syndrome in men (CPPPSm)

DRE, digital rectal examination; IIEF, International Index of Erectile Function; LUTS, lower urinary tract symptoms; NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; PHQ-9, Patient Health Questionnaire 9; UPOINT(S) classification, classification according to the following criteria: U = urinary, P = psychosocial, O = organ-specific, I = infectious, N = neurologic/systemic, T = pelvic muscle tenderness, S = sexual.

overview of important elements of the differential diagnosis is provided in the *eTable*.

Psychosomatic aspects

A basic psychosomatic assessment should be performed early on, in parallel with the somatic diagnostic evaluation, if there is any clinical suspicion of a psychosomatic problem. This can be done, for example, with a seemingly tangential discussion during the physical examination, so that the examiner can note the presence of any core manifestations of depression (depressed mood, reduced drive, joylessness) or of anxiety, including avoiding certain situations (e.g., prolonged sitting, sexual activity) in order not to induce symptoms. The clinician may choose this opportunity to cautiously prepare the patient for the possibility of normal physical findings. It is also helpful to ask how the patient's symptoms restrict his participation in everyday life, if at all, and to inquire about the patient's own model of the disease: "In your own subjective view, what do you think is causing your symptoms?"

The symptoms should be proactively acknowledged as legitimate complaints, and the patient should be allowed as much time as possible to describe them; this will strengthen the working relationship between the physician and the patient. It is helpful, too, not just to tell the patient about the negative physical findings, but also to communicate plausible explanatory models for CPPPSm in his case. This will help the patient feel that his suffering is being taken seriously. Many patients will rapidly feel they have been classed as "hypochondriacs" if the doctor only tells them that the physical findings are all negative. The goal is a "both, and" attitude with equal emphasis on the somatic and mental/psychosomatic perspectives.

For patients who consult doctors frequently, the giving of appointments "when needed," i.e., on demand, may reinforce the symptoms rather than diminish them. It is therefore recommended in the relevant guidelines that visits to the doctor should be regularly scheduled, e.g.., once every two to four weeks, with a clearly defined time for each appointment, even though the extent to which this might alleviate the patient's symptoms cannot be reliably quantified (e9). If the patient shows signs of an anxiety disorder or a depressive disorder, targeted psychoactive drug treatment can be considered. Pain-modulating antidepressants such as amitriptyline and duloxetine are especially suitable. For duloxetine, an initial and maintenance dose of 60 mg per day is recommended. A starting amitriptyline dose of 25 mg per day may already alleviate the symptoms; if not, it can be slowly and incrementally raised to 100 mg per day until efficacy is achieved without dose-limiting side effects. Doses of up to 150 mg have also been given in clinical trials (e10, e11).

If this strategy does not alleviate or at least stabilize the symptoms, the next step is to seek accompanying psychosomatic, psychiatric, or psychotherapeutic treatment, ideally in collaboration with a specialist in psychosomatic medicine, psychiatry, or psychotherapy.

Treatment options

According to the findings of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, the symptoms of CPPPSm tend to remain stable (e12). As the manifestations vary from patient to patient, no single treatment is best for all; treatment strategies should be multidisciplinary and individually tailored. The EAU recommends close collaboration with colleagues from multiple medical specialties (1). In this section, we will mainly discuss the treatment of prostate-associated symptoms.

In two comprehensive systematic reviews (SR), Franco and colleagues from a Cochrane research network studied the efficacy of drugs and non-drug treatments (compared to placebo or other modalities) in alleviating the symptoms of CPPPSm, as measured with the NIH-CPSI. The endpoints studied included micturition-related symptoms, sexual dysfunction, anxiety/depression, and the quality of life, as well as adverse events (e13, e14). Only randomized and controlled trials (RCTs) were evaluated. The main findings of these Cochrane analyses will be outlined here (next paragraph) and supplemented wherever possible with further, more recently published data. Outcomes are presented in detail in the *Table*. There are more treatment options than can be presented in this brief review; further ones are discussed in the EAU guidelines (1) and elsewhere.

The studies vary in design and in the inclusion criteria for patients with CPPPSm. This complicates

Phenotypic classification by the UPOINT(S) scheme

U – urinary symptoms (i.e., symptoms relating to micturition),
P – psychosocial dysfunction, O – organ-specific findings,
I – infection, N – neurological or systemic pathology,
T – muscle tenderness, (S –sexual dysfunction).

Psychosomatic aspects must be considered

A basic psychosomatic assessment should be performed . If the patient shows signs of an anxiety disorder or a depressive disorder, targeted psychoactive drug treatment can be given.

TABLE

Relevant findings of Cochrane analyses concerning drug and non-drug treatments for CPPPSm.
Effects on symptoms as measured with the NIH-CPSI and relevant side effects are listed (e13, e14), without any implication of completeness. Further treatments and their effects are discussed in systematic reviews and in the current EAU guideline (1, e13, e14).

CPPPSm symptoms (NIH-CPSI): follow-up: MD and RR [95% CI]; evidence level	Side effects: RR [95% CI]; evidence level	Sexual dysfunction (IIEF score) MD [95% CI]; evidence level	Quality of life (SF-12 HSQ) MD [95% CI]; evidence level	Anxiety and depression (Hospital Anxiety and Depression Scale) MD [95% CI]; evidence level
Treatments compared: alpha-blockers vs. placebo/no intervention				
6 wk–6 mo MD −5.01 [−7.41; −2.61] very low	6 wk–6 mo RR 1.6 [1.09; 2.34] low	6–12 wk MD 0.26 [−1,.3; 1.65] moderate	6–12 wk MD 0.15 [−2.63; 2.92] moderate	12 wk MD −1.1 [−2.54; 0.4] low
Treatments compared: antibiotics vs. placebo				
6 wk–3 mo MD −2.43 [−4.72;−0.15] low	3 wk–6 mo RR 1.01 [0.66; 1.55] moderate	6 wk MD 0.4 [−1.59; 2.39] moderate	6 wk MD −3.9 [−7.94; 0.14] moderate	–
Treatments compared: 5α-reductase inhibitors vs. placebo				
6 mo MD −4.6 [−5.43; −3.77] moderate	6–12 mo RR 0.87 [0.33; 2.3] low	–	–	–
Treatments compared: anti-inflammatory drugs vs. placebo				
6 wk–6 mo MD −2.5 [−3.74; −1.26]; low	4 wk–6 mo RR 1.27 [0.81; 2.0]; low	–	–	–
Treatments compared: phytotherapeutic drugs vs. placebo				
1–3 mo MD −5.02 [−6.81; −3,23]; low	1–3 mo RR 1.13 [0.54; 2.36]; low	3 mo MD 3.5 [2.67; 4.33]; low	–	–
Treatments compared: intraprostatic botulinum toxin A vs. sham;age > 50, NIH-CPSI baseline > 30				
intraprostatic, 6 mo: MD −25.8 [−30.15; −21.45]; low	1–6 mo: R.R 5.0 [0.25; 99.95]; low	–	–	–
Treatments compared: TCM vs. placebo				
2 wk−2 mo MD −3.13 [−4.99;−1.28]; low	4–8 wk RR 1.34 [0.22; 8.02]; low	2 wk MD + 0.27 [−1.17; 1.71]; moderate	–	2 wk MD –9.5 [−11.7; –7.3]; low
Treatments compared: acupuncture vs. sham				
6–8 wk MD −5.79 [−7.32; −4.26]; moderate	6–8 wk RR 1.33 [0.51; 3.46]; low	6 wk MD −0.5 [−3.46; 2.46]; low	–	–
Treatments compared: ESWT vs. sham/no ESWT				
12 wk MD −6.18 [−7.46; −4.9]; high	24 wk RR 1.22 [0.59; 2.51]; low	12 wk MD 3.34 [2.68; 4.0]; moderate	–	–
Treatments compared: lifestyle modification vs. no modification				
3 mo reponse to treatment (drop in the NIH-CPSI score by at least 6 points) RR 3.9 [2.2; 6.92]; very low	–	–	–	–
Treatments compared: exercise program vs. control (stretching, low activity)				
6 wk MD −2.5 [−4.69; −0.31]; low	–	–	–	6W SAI-Y score MD −2.8 [−6.78; 1.18]; very low BDIS MD 0.5 [−1.33; 2.33] very low

BDIS, Beck Depression Inventory Scale; CI, confidence interval; CPPPSm, chronic primary pelvic pain syndrome in men; EAU, European Association of Urology; ESWT, extracorporeal shock-wave therapy; IIEF, International Index of Erectile Function; mo, months; MD, mean difference; NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; RR, relative risk; SF-12 HSQ, Short Form-12 Health Status Questionnaire; TCM, traditional Chinese medicine; wk, weeks; SAI-Y, State Anxiety Inventory-Y; –, no data available

the acquisition of reliable, representative data sets in systematic reviews and makes their findings harder to interpret. Careful patient selection is highly important in the evaluation of individual treatment options in clinical practice. Adherence to the UPOINT(S) system seems to promote the success of treatment (e7, e15-e17).

Drugs

Alpha-blockers are thought to alleviate LUTS mainly by relaxing smooth muscle in the prostate and bladder neck. Many studies of their use (with much variation in study design) have yielded only low- or very low-level evidence that alpha-blockers improve symptoms, while mildly increasing side effects (e13, e18-e40).

Further studies of uniform design will be needed to yield firmer conclusions about the efficacy and tolerability of alpha-blockers in patients with CPPPSm. In particular, studies should also include elderly men, who are at increased risk for adverse events (e78).

Even though the causation of CPPPSm is not primarily infectious, it is sometimes treated with antibiotics. These drugs may alleviate the symptoms of CPPPSm (mainly pain) to a small extent (e13, e41-e46). Fluoroquinolones are commonly used, but the risk of major adverse effects (hepatotoxicity, neurotoxicity, phototoxicity; cardiac, vascular, and metabolic side effects; tendinitis, cartilage damage. etc.) should always be kept in mind. In view of the increasing resistance to antibiotics and the lack of evidence to support their use in CPPPSm, they should not be given as initial treatment unless there is a well-founded indication (e47).

Other drugs that may mildly alleviate the symptoms of CPPPSm, without any relevant increase in side effects, are 5α-reductase inhibitors (e13, e48, e49), anti-inflammatory agents (e13, e24, e34, e44, e50-e55), and phytotherapeutic drugs (e13, e32, e56-e77).

Phytotherapeutic drugs may be advantageous for use in the elderly because of their more favorable side effect profile (e78).

Botulinum toxin A (BTA) injections lessen muscle tone by decreasing the presynaptic release of acetylcholine. BTA injected into the prostate is likely to relieve the symptoms of CPPPSm comprehensively, but episodes of hematuria may occur afterward (e13, e79-e82). A prospective, controlled trial in men with medically intractable, chronic pelvic pain revealed that BTA injections alleviate the symptoms effectively (NIH-CPSI at three months, –68.2%, –20.1 points; $p < 0.0001$) (e83).

Traditional Chinese medicine (TCM) also seems to alleviate CPPPSm symptoms in the short term (up to two months), presumably without a relevant increase in side effects, without improving sexual dysfunction. TCM also seems to alleviate symptoms of anxiety and depression (e13, e84-e93).

There is also evidence that CPPPSm symptoms can be alleviated by phosphodiesterase-5-inhibitors (PDE5-I; e13, e94-e100) and mepartricin (e13, e101, e102) without any increase in side effects. PDE 5-I improve sexual dysfunction; this is, indeed, their primary indication (e13).

It bears emphasizing that the evidence supporting all of the treatments just mentioned is inadequate. To assess the effect of drugs on CPPPSm-related symptoms, further RCTs are needed that have clearly defined inclusion and exclusion criteria and well-documented methodology, and in which the outcomes are measured with objectified criteria (for example, NIH-CPSI, IIEF, PHQ-9).

Treatments other than drugs

Compared to placebo, acupuncture probably alleviates CPPPSm symptoms over the short term, with only mild side effects or none (e14, e103-e109). Tibial nerve stimulation may also yield a clinically relevant reduction in symptoms (e14, e110-e112). Perineal extracorporeal shock wave therapy (ESWT) can also help relieve symptoms, especially pain, and may improve sexual dysfunction (e14, e113-e118). A recent systematic review indicates, however, that symptom relief is probably not sustained over the long term (NIH-CPSI six months after ESWT and sham acupuncture: weighted mean difference 2.18; 95% confidence interval [–3.5; 7.86]) (e119). The efficacy of increased physical activity and certain lifestyle modifications (diet modification, sexual and physical activity, perineal protection) remains uncertain, but these treatments should be used because they are easily implemented in everyday life and tend to have beneficial effects in general (e14, e120, e121).

Pain-modulating antidepressants

Pain-modulating antidepressants such as amitriptyline and duloxetine are especially suitable for use in patients with CPPPSm.

Drugs that can be used to treat this syndrome

- alpha-blockers
- antibiotics (fluoroquinolones: beware of side effects)
- 5α-reductase inhibitors
- botulinum toxin A
- traditional Chinese medicine

The treatments just mentioned vary widely in their invasiveness, practicality, and availability, and their risk-benefit profiles must be considered individually (e14). Except for acupuncture and ESWT, the supporting evidence is also generally weak. There is thus a need for further high-quality trials, just as there is regarding drugs for CPPPSm.

Somatic and mental factors in CPPPSm

Interdisciplinary diagnostic evaluation and multimodal pain management

The understanding of chronic pelvic pain syndromes in men within the medical specialty of pain medicine has markedly improved over the past decade (e122). CPPPSm is a chronic visceral pain syndrome characterized by complex neural dysfunction at both peripheral and central levels. There is a mutual hypersensitization of organs served by the visceral pain conduction system (viscero-visceral cross-sensitization), and there is also an amplification of somatic pain that is mediated by systems enabling bidirectional communication between the viscera and the brain (viscerosomatic convergence mediated, e.g., by the autonomic nervous system and the hormonal and immunological axes). Further pathophysiological factors promote pain chronification, including persistent inflammatory changes, vascular mechanisms, and mechanical factors (e123-e125). The combined influence of all these phenomena may lead to the simultaneous presence of visceral pain disorders, myofascial imbalances, and visceral dysfunction, such as urinary urgency and constipation (e124–127). Moreover, central sensitization with lessened pain inhibition may lead to the further spread of pain (e.g., concomitant fibromyalgia syndrome). Numerous studies have documented the psychological, psychiatric, and social components of CPPPSm in addition to its somatic component (e126, e128, e129).

In a German cross-sectional study, urogenital pain in men had a 1-week prevalence of ca. 10% and was associated with depressiveness and reduced quality of life (e130). This clearly implies that treating physicians should give due attention to psychological factors in their patients with CPPPSm.

These findings imply the need for a biopsychosocial model of CPPPSm. If CPPPSm fulfills the criteria for a "chronic pain disorder with somatic and psychological factors" (ICD-10 F45.41) (e131), then it is considered an independent nosological entity requiring interdisciplinary algesiological (i.e., pain-medical) evaluation, in other words, a standardized interdisciplinary diagnostic assessment for patients with chronic pain, code 1–910 according to the German Operations and Procedures Catalog (OPS) (e132, e133). This comprises pain-medical, psychological, and physiotherapeutic assessments aided by standardized questionnaires (German Pain Questionnaire with the module entitled "Visceral and Urogenital Pain for Men" (e134). In a concluding discussion, the team establishes the indication for interdisciplinary multimodal pain therapy (IMPT), which is the most suitable treatment for chronic pain syndromes.

IMST is characterized by an interdisciplinary collaboration in which the content and timing of the various interventions are coordinated. In a team-integrated approach, multimodal physical and psychotherapeutic exercises and training methods are implemented in small groups (e135, e136). Effective interdisciplinary pain management in CPPPSm requires an approach that is both mechanism-based and individually tailored (e17, e137-e139).

Conflict of interest statement

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JF states that she has no conflict of interest.

Non-drug treatment options

- acupuncture
- tibial nerve stimulation
- extracorporeal shock-wave therapy (ESWT)
- lifestyle changes

Overview

Patients with CPPPSm should be managed with a comprehensive differential-diagnostic evaluation and an induvidually tailored treatment strategy.

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► Supplementary material

eReferences, eTable:
www.aerzteblatt-international.de/m2023.0036

Further Information on CME

- Participation in the CME certification program is possible only via the Internet: cme.aerzteblatt.de. The submission deadline is 23 July 2024. Submissions by letter, email, or fax cannot be considered.
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CLINICAL SNAPSHOT

Treatment-Refractory Hypercholesterolemia in a Child

A 9-year-old girl was referred for a diagnostic evaluation of hypercholesterolemia. On physical examination, xanthomas and corneal arcus were striking *(Figure)*. Laboratory tests revealed significantly elevated levels of total cholesterol (471 mg/dL) and LDL cholesterol (414 mg/dL). Statins (pravastatin 20 mg) failed to lower cholesterol levels. Genetic testing for familial hypercholesterolemia was normal. Extended genetic testing revealed the presence of a homozygous mutation in the *ABCG8* gene (*c.2T, p.?*, loss of the translational start codon of ABCG8 mRNA), consistent with sitosterolemia. This is characterized by a massive increase in plant sterols in the blood and increased cholesterol absorption. The patient's sterol determination revealed strongly elevated levels of campesterol (1368 µmol/L, reference <20 µmol/L) and sitosterol (576 µmol/L, reference <9 µmol/L), thereby confirming the diagnosis. Following a treatment switch to the cholesterol absorption inhibitor ezetimibe (10 mg daily) and dietary reduction of plant sterols, phytosterol levels decreased (campesterol 360 µmol/L, sitosterol 227 µmol/L) and LDL cholesterol normalized to 76 mg/dL.

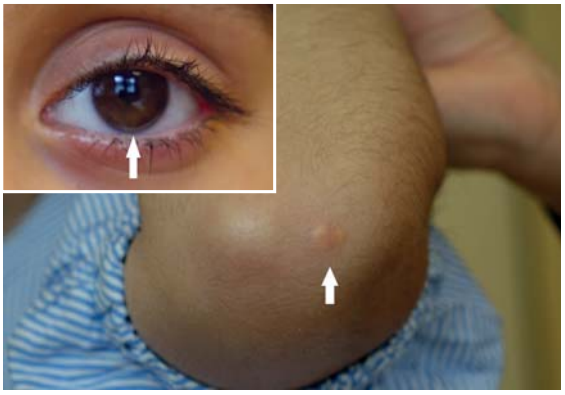

Figure: a) Corneal arcus; b) tendinous xanthomas in the elbow region. The two figures show typical changes caused by lipid deposits that can occur in the context of various lipid metabolism disorders.

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Participation is possible at cme.aerzteblatt.de. The submission deadline is 23 July 2024.

Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

What constellation of symptoms characterizes the chronic primary pelvic pain syndrome in men?

a) perineal pain, restricted range of motion, dysuria, dizziness
b) urogenital pain, micturition symptoms ("lower urinary tract symptoms"), sexual dysfunction, emotional disturbance
c) abdominal pain, erectile dysfunction, restricted mobility, urinary retention
d) anal pruritus, dysuria, emotional disturbance, nocturia
e) lumbar pain, sciatica, restricted mobility, sexual dysfunction

Question 2

The pathophysiology of chronic primary pelvic pain syndrome in men (CPPPSm) has not been fully elucidated. According to currently available evidence, which of the following seem to play a role?

a) hormonal dysregulation, dietary habits, cardiovascular disease
b) mental illness, cancer, bacterial infection
c) inflammatory mediators, psychological aspects, spinal degeneration
d) sexually transmitted diseases, hormonal dysregulation, dietary habits
e) inflammatory mediators, psychological aspects, neural/neurological changes

Question 3

Mr. M., 48 years old, has been suffering from lower abdominal pain for 6 months, urinary frequency and urge sensation, and erection difficulties. No bacterial infection has been found to date. How should you continue with the diagnostic assessment?

a) meticulous history-taking and physical examination, including digital rectal examination
b) urodynamic study and uroflow
c) ultrasonography of kidneys and urinary bladder, with measurement of the prostate gland
d) urine PCA for streptococci
e) blood draw for PSA measurement

Question 4

Which questionnaire is most appropriate for assessing sexual function in patients with CPPPSm?

a) International Prostate Symptom Score (IPSS)
b) International Index of Erectile Function (IIEF)
c) Patient Health Questionnaire 9
d) Clinical Frailty Scale
e) Mini-Mental-Status-Test (MMST)

Question 5

The symptoms of CPPPSm can be assigned to the different domains of the so-called UPOINT(S) system. Which of the following assignments of letters and domains is correct?

a) U – abdominal pain
b) P – pathology
c) I – infection
d) N – nocturnal urination
e) T – trauma

Question 6

What percentage of men suffer from symptoms of prostatitis?

a) 2–10%
b) 4–20%
c) 6–30%
d) 8–40%
e) 10–50%

Question 7

Early in the diagnostic work-up of chronic primary pelvic pain syndrome, the examiner should be alert for potential evidence of a depressive state. What are the core symptoms that should be particularly sought?

a) joylessness, reduced drive, depressed mood
b) apathy, headaches, sleep disturbances
c) aching limbs, sadness, anxiety
d) lethargy, fatigue, pain
e) delusions, daytime sleepiness, hyperactivity

Question 8

What substance class is appropriate for men with lower urinary tract symptoms (LUTS) who mainly suffer from voiding dysfunction?

a) selective serotonin reuptake inhibitors
b) macrolide antibiotics
c) anticonvulsants
d) alpha-blockers
e) vasopressin analogues

Question 9

Mr. F, 54, is under treatment for chronic primary pelvic pain syndrome. To date, he has received only alpha-blockers and physical therapy, but he now complains of new-onset erectile dysfunction. Which of the following therapeutic options should you consider first?

a) aripiprazole
b) acupuncture
c) psychotherapy
d) glucocorticoids
e) prostate massage

Question 10

Which approach is most appropriate for treating chronic pain syndromes such as the chronic primary pelvic pain syndrome?

a) interdisciplinary multimodal pain therapy (IMST)
b) use of low-potency opioids
c) various methods of acupuncture
d) extensive physiotherapy and psychotherapy
e) combination of deep brain stimulation and nonsteroidal anti-inflammatory drugs

► **Participation is only possible online: cme.aerzteblatt.de**

Supplementary material to:

Chronic Primary Pelvic Pain Syndrome in Men

Differential Diagnostic Evaluation and Treatment

by Julia Franz, Kristin Kieselbach, Claas Lahmann, Christian Gratzke, and Arkadiusz Miernik

Dtsch Arztebl Int 2023; 120: 508–18. DOI: 10.3238/arztebl.m2023.0036

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eTABLE

The differential diagnosis of chronic primary pelvic pain syndrome in men (CPPPSm).
This list of selected competing diagnoses is not intended to be complete.

Differential diagnosis	Clinical differentiation from CPPPSm	Diagnostic assessment and confirmation of diagnosis	Treatment options
Urological			
Bacterial prostatitis	**acute:** sudden onset; mainly irritative urinary symptoms; acute/recurrent urinary tract infections, frequent fever	pathological urine test strip findings, documentation of urinary pathogen (**acute:** urine culture, **chronic:** two- or four-glass test, urethral swab)	**acute:** antibiotics **chronic:** antibiotics tailored to resistance pattern, supportive symptomatic treatment
Interstitial cystitis	chronic pollakisuria, suprapubic pain	cytoscopy with hydrodistention test: glomerulation and fissures of the bladder mucosa	multidisciplinary pain therapy
Benign prostatic syndrome	LUTS, more common in old age	ultrasonographic volumetry, IPSS, uroflowmetry, urodynamic testing when indicated	drugs (alpha-blockers, 5α-receptor inhibitors, PDE5 inhibitors), surgery (TURP, SP), interventional procedures
Urethritis	LUTS, urethral pain	IPSS, cystoscopy	pain therapy, conservative (often self-limiting)
Neurological			
Pudendal neuralgia	intermittent severe intestinal and genital pain, esp. while sitting, sometimes with paresthesiae; can be secondary (fractures, surgery, tumor)	history, physical examination, imaging (MRI)	analgesics, co-analgesics, injection of local anesthetics or cortisone, transcutaneous electrical nerve stimulation, physiotherapy
Fibromyalgia	diffuse pain, esp. at muscle and tendon insertions; oversensitive tender points, sleep disturbance, exhaustion, accompanying functional and vegetative symptoms	clinical diagnosis	patient education; when indicated, psychosomatic consultation; pharmacotherapy when indicated for depressive symptoms
Gastroenterological			
Chronic inflammatory bowel disease	stool changes (esp. diarrhea), non-gastrointestinal manifestations (arthritis, skin changes, oral changes, uveitis/episcleritis/iritis)	ileocoloscopy with stepwise biopsies, esophagogastroduodenoscopy when indicated	specific regimens of induction and maintenance therapy (mesalazine, steroids, azathioprine, biologic agents, other)
Irritable bowel syndrome	functional symptoms: stool changes, bloating, diffuse abdominal pain; often worse under emotional stress	clinical and laboratory exclusion of somatic causes, stool investigation for pathogenic organisms; when indicated, ultrasonography, DRE, colonoscopy	patient education; when indicated, autogenic training, probiotics, spasmolytic agents

CPPPSm, chronic primary pelvic pain syndrome in men; DRE, digital rectal examination; IPSS, Internationaler Prostata-Symptomen-Score; LUTS, lower urinary tract symptoms; MRI, magnetic resonance imaging; SP, simple prostatectomy; TURP, transurethral resection of the prostate.