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Professional Paper

CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME: TREATMENT OPTIONS WITH NEUROMODULATORY PHARMACOTHERAPY AND ACUPUNCTURE

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SUMMARY – Chronic prostatitis (CP)/chronic pelvic pain syndrome (CPPS) is a prevalent condition with complex pathogenesis, and the most effective treatment is still unknown. The negative impact of CP/CPPS on patient quality of life (QoL) is significant and represents a challenge for many clinicians. Additionally, studies have indicated a potential association between prostatitis and prostate cancer. Many pharmacologic and nonpharmacologic therapies have been utilized in everyday clinical practice, but the majority have demonstrated limited effectiveness in reducing symptoms. Current "first-line" pharmacology treatment options include antibiotics, anti-inflammatory, alpha-blockers, and 5-alpha reductase inhibitors as monoterapy or their combination, despite the fact that systematic reviews and meta-analyses show that many treatments for CP/CPPS are largely ineffective. Thus far, no highly effective therapy has been identified, and treatment strategies have focused on symptomatic relief. Evidence indicates that CP/CPPS may involve neuropathic pain to varying degrees, and neuromodulatory pharmacotherapy and acupuncture could therefore be considered as potential treatments for cases that are refractory to standard therapies.

Key words: *chronic prostatitis; chronic pelvic pain syndrome; neuromodulatory pharmacotherapy; acupuncture*

Introduction

Prostatitis is a common urological disease with broad spectrum of etiologies and clinical presentation. Approximately 35-50% of men reported prostatitis at some point in their lifetime that notably affected their quality of life (QoL). Prostatitis has a high prevalence rate of 2.2-9.7% (mean prevalence 8.2%), comparable to rates of ischemic heart disease and diabetes mellitus[1].

Inflammation is present in approximately 17% of all cancer cases[2]. Previous biological and epidemiological studies indicate that the inflammatory mediators could promote the prostatic carcinogenesis via multiple signaling pathways[2]. Prevalence of prostatitis could contribute to prostate carcinogenesis, which is the second most common cause of cancer-related death in men. Meta-analyses have indicated an association

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between prostatitis and prostate cancer[2]. Some authors have argued that prostatitis symptoms may increase risk for prostate cancer in men.

According to the National Institutes of Health (NIH), prostatitis is classified into four categories, with category III being the most prevalent (**Table 1**)[1]. This category includes chronic prostatitis (CP) and chronic pelvic pain syndrome (CPPS), accounting for approximately 90-95% cases[3]. CP/CPPS can manifest with various symptoms, but the most commonly reported are urogenital pain, lower urinary tract symptoms (LUTS), sexual dysfunction and a wide range of psychological (cognitive, behavioral, or emotional) issues.

CP/CPPS is a form of chronic pain disease that affects about 2-16% of the adult male population worldwide, with men aged 36-50 being the most impacted group[4-6].

The diagnosis of CP/CPPS can be established after excluding identifiable urogenital pathology (infection, cancer, anatomic abnormalities, etc.). CP/CPPS can be diagnosed if the symptoms persist for at least three months out of the previous six months[4].

Despite numerous studies in this field and different proposed mechanisms of pathogenesis, the exact etiology of CP/CPPS is still unclear. These mechanisms include infection, and genetic, anatomical, physiological, neurological, and immunological factors[7]. Currently, leading experts think that there is no single all-encompassing etiological mechanism for CP/CPPS. It is more likely that different patients with CP/CPPS have different etiological mechanisms and likely also progression pathways. Thus, some patients may have multiple etiological factors[7]. Nickel and Shoskes have proposed etiological pathways for CP/CPPS that are divided into four phases, which include the initiation, induction, maintenance, and progression phases (**Figure 1**)[7]. Various etiological mechanisms eventually lead to a systemic pain syndrome in the progression phase, which includes neuropathic pain and voiding as well as muscular and psychosocial dysfunction[7].

CP/CPPS is still a diagnosis of exclusion because physical examination is non-specific and no standardized diagnostic test has been developed so far[3]. NIH has developed a valid tool – the Chronic Prostatitis Symptom Index (NIH-CPSI), which can be used to asses CP/CPPS. It is based on a 13-item questionnaire which measures the three most significant groups of symptoms: pain, voiding symptoms, and repercussions of the symptoms on the patient's QoL. This questionnaire is currently the most effective tool for measuring symptom severity and evaluating efficacy of treatments. However, it should be noted that this questionnaire is not a diagnostic tool for CP/CPPS[7]. Despite its prevalence, CP/CPPS is still poorly understood and underdiagnosed.

Traditionally "first-line" pharmacotherapy for CP/CPPS

CP/CPPS is particularly difficult to treat and still represents a challenge for many clinicians. Thus far, no

Table 1. NIH Classification system for the prostatitis syndromes

Classification	Description
Category I Acute bacterial prostatitis	Acute infection of the prostate gland
Category II Chronic bacterial prostatitis	Chronic infection of the prostate characterized by recurrent UTIs
Category III – CP/CPPS	Symptoms of discomfort or pain in the pelvic region for ≥3 months in the absence of uropathogenic bacteria cultured by standard techniques.
Category IIIA – inflammatory CPPS	Significant number of leukocytes in EPS, VB3, or semen (ejaculate).
Category IIIB – non-inflammatory CPPS	No evidence of significant leukocytes are found in EPS, VB3, or semen.
Category IV Asymptomatic inflammatory prostatitis	Leukocytes in EPS, VB3, semen, or prostate tissue during evaluation for other disorders in men without symptoms of prostatitis.
PS, expressed prostatic secretion; VB3, voided bladder 3	

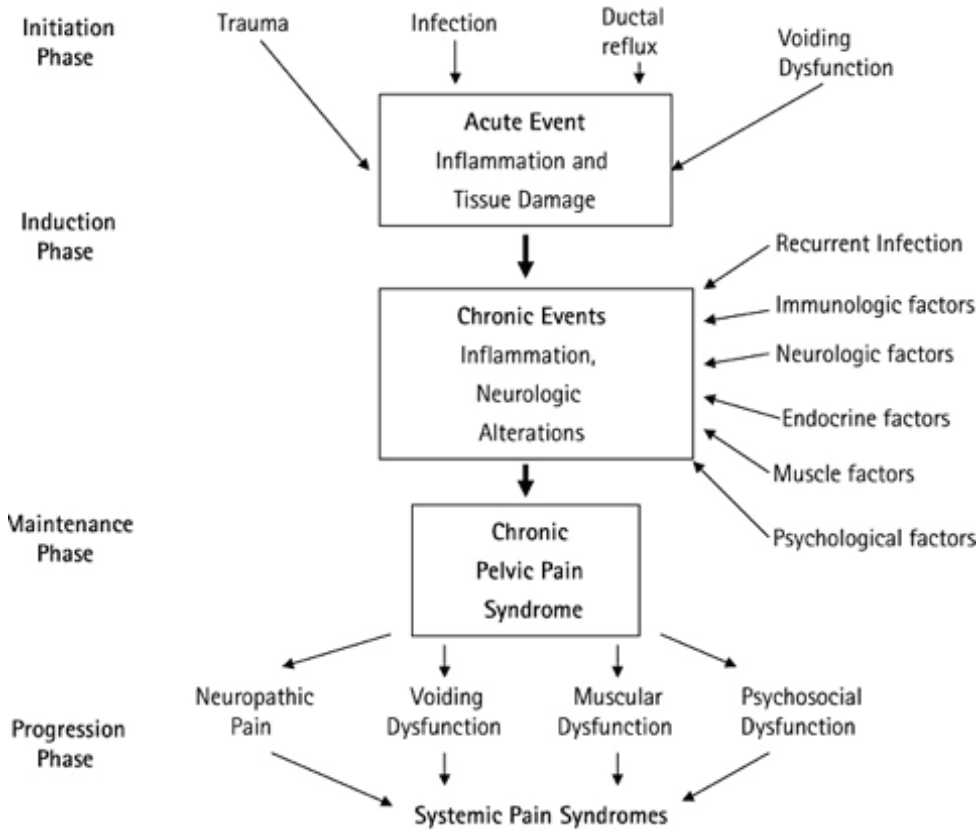

Figure 1. Proposed etiological pathways that lead to CP/CPPS.9

highly effective therapy has been identified and treatment strategies have focused on symptomatic relief. There is no single approach that would be effective for all patients, and there is consequently no "golden standard" therapy[8-10].

There are currently many approaches for the management of CP/CPPS, using both pharmacological and non-pharmacological therapies. Pharmacological treatments are used empirically[5]. Trial evidence is conflicting, and efficacy of various treatments is controversial[3], as various treatments have shown some degree of usefulness in managing CP/CPPS[11].

Traditionally first-line pharmacological therapy includes antibiotics, alpha-adrenergic antagonists, and anti-inflammatory drugs[9,12]. Current treatment options also include 5-alpha-reductase inhibitors and phosphodiesterase type 5 inhibitors as a first-line therapy[9].

Historically, long-term application of antibiotics was the primary treatment for CP/CPPS, but current evidence suggests that their effectiveness is limited[12]. Despite the fact that less than 10% of symptomatic patients have culturable bacteria in the urinary tract, antibiotic therapy has been effective in treating many patients without confirmed infection[11]. It is unclear why antibiotic therapy is beneficial, but it could be due to the anti-inflammatory, anti-neuropathic, or placebo effects of antibiotics. A possible reason is the elimination of microorganisms that cannot be cultured in the laboratory[11].

Cyclooxygenase inhibitors (COX) are able to reduce the production of prostaglandins and the consequently inhibition of COX-2 in the central nervous system (CNS) can prevent the pathophysiological mechanisms responsible for chronic pain, such as central sensitization. Nonsteroidal anti-inflammatory drugs (NSAIDs) are often used to provide quick symptom relief in CP/CPPS, but their effectiveness is limited to short-term use (2-4 weeks)[9]. This means they are primarily used during the acute phase of the disease and cannot be administered for long periods. Autoimmune mechanisms have been associated with

CP/CPPS, indicating that corticosteroid therapy could be a viable option[11].

Alpha-blockers and 5-alpha reductase inhibitors are frequently prescribed to alleviate the symptoms of benign prostatic hyperplasia. These medications are also used to treat CP/CPPS because of the similarity of symptoms and potential overlapping pathogenesis between these two conditions[9,11]. Additionally, phosphodiesterase-5 inhibitor (PDE5-I) have been found to effectively reduce LUTS, erectile dysfunction, and symptoms of CP/CPPS[9]. Anothaisintawee et al. conducted the first network meta-analysis (NMA) in 2011 and reported that alpha-blockers, antibiotics, and their combination exhibited the most significant improvement in clinical symptoms scores compared with placebo[3]. In contrast, Qin et al. recently conducted a NMA to compare and rank the efficacy and safety of medication used to treat CP/CPPS. They concluded that there is limited evidence supporting the efficacy of pharmacological treatments for this condition[5].

Clinicians have become aware that patients with CP/CPPS should be viewed as individuals with varying etiologies and response to therapy. Shoskes et al. have recently developed the novel UPOINT phenotypic classification system. The aim of this approach is to categorize patients into specific phenotypes based on their symptoms. It includes six domains[8]. By classifying patients based on their clinical presentation, subjective description, and psychosocial status into one or more of six domains (U, P, O, I, N, T), it recognizes the role of each domain in contributing to the severity of symptoms. It enables a symptom-oriented diagnosis and treatment approach that targets the main complaints, thus improving patient outcomes[7-9].

Neuromodulatory pharmacotherapy

As per the definition provided by the International Association for the Study of Pain (IASP), neuropathic pain (NP) is a type of pain that arises as a direct consequence of a lesion or disease that affects the somatosensory system[13]. This type of pain is typically chronic and may either persist continuously or manifest as recurrent painful episodes[14]. Despite the wide variety of etiologies, it is now recognized as a distinct clinical entity[15].

NP is often described as burning, pins, and needles (paresthesia), tingling, numbness, electric shocks/shooting, crawling (formication), itching, and intolerance to temperature[16]. It is also associated with objective signs of a sensory disorder, such as allodynia, hypoalgesia, or hyperalgesia. These signs suggest central sensitization and indicate a more severe form of the disease[17]. NP can have a profound effect on various aspects of a patient's life[16]. The pathophysiology of NP is extremely complex, thus justifying the absence of optimal therapy. Consequently, NP is often severe, and effective treatment is lacking for many patients. The efficacy of the treatments is often variable, leading to a continuous introduction of drugs of even more uncertain efficacy[18].

The pharmacotherapy of NP is challenging. Over the past 15-20 years, different clinical practice guidelines/recommendations have been published to help clinicians choose appropriate drugs for the management of NP[19]. The medications recommended as initial treatment options for NP often do not provide adequate relief for a significant number of patients. In addition, treatment options for NP are limited, and dose escalation is often not feasible due to the occurrence of side effects that can compromise patient compliance to therapy[17]. Epidemiological surveys have shown that many patients with neuropathic pain do not receive appropriate treatment[15]. Although the effectiveness of gabapentinoids in treating neuropathic pain (NP) has been inconsistent, they are still considered a first-line treatment option[15-19].

Studies suggest that patients with CP/CPPS may develop NP[12]. An inciting agent may cause inflammation or neurological damage in or around the prostate. This is associated with local and central neuropathic mechanisms involving areas outside the prostate or pelvic area and leads to NP[20,21]. Previous studies have connected neurological disease and pain to CP/CPPS.

According to Pontari et al., previous history of other neurological diseases was almost five times higher in CPPS than in controls[22]. Studies have also shown a correlation between an increased degree of proinflammatory biomarkers (such as nerve growth factor, monocyte chemoattractant protein-1 (MCP), and macrophage inflammatory protein-1α (MIP)) and pain in CP/CPPS[23-25]. Yang et al. found that individuals with CPPS had different heat sensation and pain sensitivity in the perineal region when compared with healthy controls[26].

There is evidence suggesting that CP/CPPS shares similarities with other chronic pain syndromes[22-27]. The similarities between CP/CPPS and other chronic pain syndromes may explain the difficulty in treatment and

the resistance to standard treatment approaches. Gabapentinoids (pregabalin or gabapentin), tricyclic antidepressants (amitriptyline, nortriptyline, or trimipramine), or selective serotonin noradrenaline reuptake inhibitors (SNRIs; such as duloxetine) are possible pharmacological options for treating NP in patients with CP/CPPS. Published evidence regarding the use of pharmacotherapy for NP in patients with CP/CPPS is currently limited.

In a previous study, it was found that pregabalin showed some improvement in pain symptoms when administered at increasing dosages (from 150 mg to 600 mg daily) over a 6-week treatment period[28]. These results suggest that the refractory pain in patients with CP/CPPS may be neuropathic[27]. Available data from several trials suggest that many patients did have a favorable clinical response (mean CPSI score, pain score, subjective responder rate) on neuromodulatory therapy despite primary negative outcomes (CPSI responders). Gabapentinoids were initially used on a case-by-case basis for patients with CP/CPPS, despite being more commonly used for other neuropathic pain conditions. Gabapentin, which is both an antiepileptic and analgesic medication, is known for its effectiveness in treating NP in individuals with diabetes[29]. Pregabalin, on the other hand, has analgesic, antiepileptic, anxiolytic, and sleep-modulating properties[30]. Opioids should be avoided for pain management in patients with early-stage CP/CPPS due to the risk of dependence.

The contemporary approach to treating CP/CPPS should include neuromodulatory therapy in patients who do not respond well to conventional therapy, particularly when refractory NP is present. This implies a multidisciplinary (MDT) approach which include a pain specialist[12]. **Table 2** lists possible pharmacotherapy options for NP in CP/CPPS[12].

Acupuncture

Acupuncture as a form of alternative medicine is a non-pharmacological therapy commonly used to manage chronic pain and other conditions that are not responsive to traditional treatments. It is considered to have immunomodulation, anti-inflammatory, and neuromodulation properties[31,32]. Western medicine suggests that local needling during acupuncture may also promote tissue healing and pain relief by affecting pain reflex arcs and releasing neuropeptides and local endorphins[33]. Different methods of acupuncture have been developed, including traditional, non-insertion acupuncture, electrical stimulation, and heat therapy.

Until 2008, data from uncontrolled series have indicated that acupuncture may provide a benefit for chronic pain, thus also suggesting efficacy for CP/CPPS[34].

Lee et al. reported that the group receiving acupuncture had a 73% positive response rate in

Table 2. Pharmacotherapy options for NP in CP/CPPS[14]

Analgesic class	Drug name	Starting dose	Maintenance dose	Common adverse effects	Practical points
Gabapentinoids	**Gabapentin**	100-300 mg at night	600 mg three times daily	Dizziness, sedation, dyspepsia, dry mouth, ataxia, peripheral oedema, weight gain	Few drug interactions. Safe in overdose. Gut transport mechanism can become saturated, limiting absorption from gastrointestinal tract
	Pregabalin	50-75 mg at night	300 mg twice daily	Dizziness, sedation, dyspepsia, dry mouth, ataxia, peripheral oedema, weight gain	Linear pharmacokinetics
Tricyclic antidepressants/ serotonin-norepinephrine reuptake inhibitors	**Amitriptyline**	10 mg in evening	50-75 mg in evening	Sedation, dry mouth, blurred vision, urinary retention, constipation, postural hypotension, weight gain	Many patients obtain pain relief at a lower dose
	Duloxetine	30 mg in evening (or in morning, if insomnia)	60-120 mg once daily	Nausea, sedation, insomnia, headache, dizziness, dry mouth, constipation	Less sedating. May cause insomnia in some patients

NIH-CPSI scores, while the sham group had a 47% positive response rate. Adverse effects were minor and resolved quickly[35]. Modifications such as needle manipulation or addition of acupoints may improve the effectiveness of acupuncture in an actual treatment setting[35]. The Cochrane review by Franco et al. from 2018 showed that acupuncture may lead to a reduction in prostatitis symptoms compared with a sham procedure, without a significant increase in adverse events, based on three randomized controlled trials involving 204 participants with short-term follow-up. However, no significant improvement in sexual dysfunction was observed compared with a sham procedure. The review suggested that acupuncture could result in clinically significant improvements in prostatitis symptoms when compared with standard medical treatment. Nonetheless, the impact of acupuncture on quality of life, depression, or anxiety was not assessed[36].

A recent overview of acupuncture for CP/CPPS by Khattak et al. showed that it is effective in managing pain based on a mean difference in NIH-CPSI scores. Short-term follow-up studies also suggest an improvement in NIH-CPSI scores with acupuncture, but there is no significant difference in benefits compared with a sham procedure[31].

The pain-relieving effects of acupuncture for CP/CPPS may be due to its impact on various levels of the nervous system, including the tissue, spinal cord, and higher brain centers. This may involve activation of the body's natural pain relief systems, such as the endogenous opioid system, gate control theory, and the purinergic signaling system. Acupuncture has been suggested to have an analgesic effect on CP/CPPS by increasing the levels of certain neurotransmitters such as endomorphin-1, beta-endorphin, encephalin, and serotonin, leading to pain reduction[37]. Apart from that, acupuncture may also help improve CP/CPPS symptoms by modulating the activity of immune cells and their secreted molecules[38].

Although there some encouraging outcomes have been reported, the therapeutic impact of acupuncture on CP/CPPS is currently restricted by the inadequate number of well-designed, high-quality RCTs. Nevertheless, according to the current evidence, acupuncture can be regarded as an effective intervention for patients with CP/CPPS, with minimal adverse effects. Hematoma and local pain are the primary adverse events associated with acupuncture, which can be quickly relieved, giving it an advantage over other therapeutic interventions.

Conclusion

Managing CP/CPPS remains challenging, with many trials demonstrating only modest improvements in symptoms. The multifactorial nature of the condition, with a diverse range of underlying causes and mechanisms, means that no single drug or combination of drugs is likely to be effective for all patients. The traditional approach to managing CP/CPPS works for some patients. A newer approach to CP/CPPS management acknowledges that patients with this condition are not a uniform group, and identifying specific phenotypes within the disease spectrum may assist in tailoring treatment plans. In certain patients, traditional pain management strategies for CP/CPPS may be ineffective, necessitating a change in therapeutic approach.

In severe, refractory cases of CP/CPPS, we should try second-line therapies such as neuromodulatory therapy and acupuncture. If NP is suspected after failure to respond to traditional/initial treatment, the patient should be referral to the MDT team that should include a pain specialist.

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Sažetak

KRONIČNI PROSTATITIS/SINDROM KRONIČNE BOLI U ZDJELICI: TERAPIJSKE MOGUĆNOSTI SA NEUROMODULATORNOM FARMAKOTERAPIJOM I AKUPUNKTUROM

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Kronični prostatitis (KP)/sindrom kronične boli u zdjelici (SKBZ) je česti poremećaj čija kompleksna etiologija, patogeneza i učinkovita terapija još uvijek nepoznata.

KP/KPZ ima značajan negativan utjecaj na pacijentovu kvalitetu života te predstavlja dijagnostički i terapijski izazov za mnoge kliničare. Studije ukazuju na povezanost prostatitisa i karcinoma prostate.

U svakodnevnoj kliničkoj praksi koristi se široki spektar farmakološke i nefarmakološke terapije ali većina ima ograničeni učinak na smanjenje simptoma.

Trenutna "prva-linija" farmakološke terapije uključuje antibiotike, antiinflamatorne lijekove, alfa-blokatore, inhibitore 5-alfa reduktaze kao monoterapiju ili njihove kombinacije unatoč činjenici da pregledni radovi i meta-analize ukazuju da je većina terapija velikim dijelom neučinkovita. Do sada visoko djetotvoran terapijski pristup nije nađen, strategija se bazira na ublažavanju simptoma.

Podaci ukazuju da KP/SKBZ može karakterizirati različiti stupanj neuropatske boli te se neuromodulatorna terapija treba razmotriti kao potencijalni tretman za refrakterne slučajeve KP/SKBZ.

Ključne riječi: *kronični prostatitis, sindrom kronične boli u zdjelici, neuromodulatorna farmakoterpija, akupunktura*