Published in final edited form as:
Nat Rev Urol. 2010 March ; 7(3): 127–135. doi:10.1038/nrurol.2010.4.

New treatments for chronic prostatitis/chronic pelvic pain syndrome

Adam C. Strauss and **Jordan D. Dimitrakov**
Harvard Medical School, Children's Hospital Boston, Enders Research Building, Room 1061, 300 Longwood Avenue, Boston, MA 02115, USA

Abstract

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common condition among men of a wide age range, with detrimental effects on quality of life. The etiology, pathogenesis, and optimal treatment of CP/CPPS remain unknown, although progress has been made in these domains in recent years. A wide variety of pharmacologic and nonpharmacologic therapies have been studied in clinical trials, but most have shown limited efficacy in symptom alleviation. CP/CPPS is increasingly viewed as a condition that involves variable degrees of neuropathic pain. Medications such as gabapentin, pregabalin, memantine, and tricyclic antidepressants are often used in other neuropathic pain conditions and, therefore, are considered potential treatments for CP/CPPS. Few studies of these agents in patients with CP/CPPS have been reported, but future clinical trials should help to determine their utility and to characterize the pathogenetic mechanisms of pain in CP/CPPS. Combining treatment trials with biomarker, genomic, and imaging studies, in addition to epidemiologic and symptom-based assessments, will maximize the ability to probe disease etiology and pathogenesis, as well as identify effective treatment.

Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a highly prevalent condition affecting men of a wide age range. Estimates of CP/CPPS prevalence range from 2% to 10%, with overall lifetime prevalence estimated to be 9-16%.[1] CP/CPPS has detrimental effects on quality of life, comparable to myocardial infarction, angina, Crohn's disease, and diabetes mellitus.[2,3] Symptoms include pelvic pain (localized to the prostate, perineum, or urethra), inflammation of the prostate, and a variable degree of voiding and sexual dysfunction. In particular, pain intensity, urinary frequency and depressive symptoms can impact patient quality of life most significantly[4-6] The etiology of CP/CPPS is currently unknown, and there are no established treatments that consistently relieve patients of their symptoms. The past decade, however, has seen considerable progress in CP/CPPS research, and an improved understanding of the etiology, pathogenesis and optimal treatment is a reasonable prospect in the next few years.

Despite its prevalence and impact on patients, CP/CPPS was long misunderstood and remains enigmatic. The NIH International Collaborative Prostatitis Network developed a prostatitis classification system in 1995, which termed CP/CPPS as ‘Category III prostatitis’ defined by its abacterial nature and occurrence with or without prostatic inflammation (Box 1).[7,8] CP/CPPS comprises the vast majority of prostatitis cases, despite the historical view of prostatitis as primarily a bacterial disease. For this reason, we are exiting an era in which men with CP/

Correspondence to: J. D. Dimitrakov jordan.dimitrakov@childrens.harvard.edu.

Competing interests: The authors declare no competing interests.

CPPS generally received long-term antibiotic treatment. Physicians currently prescribe a wide variety of medications, including many that have not yet been studied in randomized controlled trials (RCTs). However, no therapies have emerged that consistently show high efficacy in RCTs, nor are there sensitive and specific biomarkers for the diagnosis of CP/CPPS.[9,10] Instead, the NIH Chronic Prostatitis Symptom Index (NIH-CPSI) has become the gold standard for the diagnosis of CP/CPPS.

The lack of therapeutic options and objective tests is related to the unknown etiology of CP/CPPS. However, the past decade has seen improvements in our understanding of the disease, and current research endeavors show promise in achieving a better understanding of its etiology and treatment. Increasing use of the NIH-CPSI for the diagnosis and study of CP/CPPS has led to a more consistent definition of the disease in observational cohort studies and therapeutic clinical trials. The NIH Chronic Prostatitis Collaborative Research Network, established in 1997 and more recently merged with the NIH/National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Multidisciplinary Approach to Pelvic Pain network, has helped centralize efforts to study CP/CPPS by facilitating observational cohort studies and large-scale clinical trials. These have included studies of psychosocial variables,[11] common risk factors,[12] quality of life indicators,[5] and trials with anti-inflammatory drugs, alpha-blockers, and antibiotics.[13,14]

Although the general view of CP/CPPS has moved away from a prostate-centric origin,[15] current etiologic hypotheses vary widely. These include the presence of antibiotic-resistant nonculturable microorganisms, urethral obstruction, reflux of urine in the prostatic ducts, autoimmune attack, genetic abnormalities, pudendal nerve entrapment, myofascial pain or dysregulation of pelvic floor muscles, and neuropathic pain. Possible pathogenetic mechanisms include abnormal local or systemic inflammation, immune dysregulation, autonomic nervous system imbalance, endocrine or other metabolic abnormalities, and genetic predisposition. Patients with CP/CPPS are likely to comprise a spectrum of interconnected etiologies, and understanding the pathogenetic mechanisms underlying each patient's symptoms will be crucial for choosing effective therapy.[16]

Key points

- CP/CPPS is a prevalent condition with severe effects on quality of life
- The etiology, pathogenesis, and optimal treatment of CP/CPPS are poorly understood
- Randomized controlled trials have been conducted for a number of therapies, most of which have shown only limited ability to reduce symptoms
- Neuropathic pain might play an important role in CP/CPPS and therefore be a therapeutic target
- Improved clinical trial design in conjunction with research studies has the potential to improve understanding of the etiology and pathogenesis of CP/CPPS as well as discovering effective treatment approaches

Box 1

NIH classification of prostatitis syndromes

Type I: acute bacterial prostatitis

Severe symptoms of prostatitis, symptoms of systemic infection and acute bacterial urinary tract infection, with bacteriuria and pyuria

Type II: chronic bacterial prostatitis

Chronic bacterial infection of the prostate gland with or without symptoms of prostatitis, usually with recurrent UTIs caused by the same bacteria

Type IIIA: CP/CPPS (inflammatory subtype)

Characterized by chronic pelvic pain and possibly voiding symptoms with no bacterial infection; leukocytes present in expressed prostatic secretion or semen

Type IIIB: CP/CPPS (noninflammatory subtype)

Characterized by chronic pelvic pain and possibly voiding symptoms with no bacterial infection; no evidence of inflammation

Type IV: asymptomatic inflammatory prostatitis

Evidence of inflammation without symptoms of prostatitis or UTI

The information in this box was gathered from a number of articles.[7,8] Abbreviations: CP/PPS, chronic prostatitis/chronic pelvic pain syndrome; UTI, urinary tract infection.

The difficulty in pinpointing etiologic mechanisms and obtaining efficacious therapies is probably due to the heterogeneity of factors that contribute to CP/CPPS. Despite this complexity, most experts agree that pain is the defining feature of the condition. Pain is generally divided into three or four categories, based on mechanism: nociceptive pain, inflammatory pain, neuropathic pain, and sometimes 'dysfunctional' pain (Box 2).[17] For the purpose of this Review we assume that dysfunctional pain is a subtype of neuropathic pain and use the term 'neuropathic pain' to encompass both definitions. The pain mechanisms in CP/CPPS are poorly understood, but experts consider neuropathic pain to play an important role. However, few of the agents that have been studied in clinical trials target pain pathways directly, particularly those in the central nervous system (CNS). It has been suggested that medications used to treat other neuropathic pain conditions could be used to treat CP/CPPS. Clinical trials with these drugs are an important goal in CP/CPPS research, and appropriate study design will be crucial in order to map the pathways involved and optimize therapy for individual patients. This Review will provide an overview of current and past therapies for patients with CP/CPPS and discuss emerging treatments that have not yet been studied using the RCT design. We will explore the implications of these treatments with respect to unraveling pain mechanisms and disease etiology and discuss the future of CP/CPPS research, in terms of how best to achieve symptom alleviation through choice of successful therapeutic options.

Overview of existing data

A number of pharmacologic and nonpharmacologic therapies for CP/CPPS have been studied in clinical trials. Most of these correspond to particular etiologic hypotheses (Box 3),[18,19] and many have shown at least some degree of utility in treatment. However, these therapies are all classified as Grade I (indeterminate) evidence, according to the US Preventive Services Task Force system, which is defined as 'current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined'.[18]

Antibiotics

Long-term antibiotics were the mainstay of CP/CPPS treatment until recently. Although it is generally accepted that less than 10% of symptomatic patients have culturable bacteria in the urinary tract, 57% of patients in a 2001 study of ofloxacin treatment perceived moderate to marked improvement in their symptoms.[20] In culture-negative patients, these benefits could

result from the anti-inflammatory properties of antibiotics, the elimination of nonculturable microorganisms, or the placebo effect.[1] However, RCTs in recent years have failed to show significant beneficial effects of antibiotics compared to placebo in patients who have already failed antibiotic treatment.[21,22] Initial treatment with antibiotics is considered to be a prudent clinical decision by some experts,[1] but long-term treatment is not well supported by the data in patients for whom initial treatment was unsuccessful.

Anti-inflammatories

Patients with localized inflammation of the prostate are obvious potential beneficiaries of anti-inflammatory therapy. Cyclooxygenase (COX) inhibitors are known to decrease prostaglandin production, and inhibition of COX2 in the CNS can inhibit the processes, such as central sensitization, that underlie chronic pain. In an RCT of the COX2 inhibitor rofecoxib, the NIH-CPSI total and pain scores showed improvement in the rofecoxib group, but the difference between rofecoxib and placebo was not statistically significant.[22] However, patient global assessment showed a statistically significant improvement in the rofecoxib group compared to placebo, as did the percentage of patients on 50 mg of rofecoxib daily with a 6 point or greater improvement in total NIH-CPSI score. The results of a trial comparing two doses of celecoxib in patients with prostatic inflammation (using the NIH definition for type IIIA prostatitis) demonstrated decreased NIH-CPSI scores and fewer white blood cells in expressed prostatic secretion at the higher dose.[23] A phase II trial examining CC-10004, a small molecule anti-inflammatory drug, is currently underway (Table 1).

Autoimmune mechanisms have been implicated in CP/CPPS, which suggests corticosteroid therapy might be an attractive option.[24] A recent RCT involving combination prednisone and levofloxacin treatment for 2 or 4 weeks showed statistically significant improvement in the treatment group compared to controls in several outcomes, including NIH-CPSI and quality of life scores.[25] In another study, three of four patients with CP/CPPS treated with corticosteroids showed improvement of symptoms.[26] No rigorous large-scale clinical trials have demonstrated statistically significant symptomatic improvement in CP/CPPS patients, suggesting these drugs might be useful in less severe cases or in combination with other drugs. Corticosteroid benefits must obviously be weighed against their significant adverse effects. Mechanistic approaches to assigning therapy and synergistic therapeutic combinations could aid effective utilization of anti-inflammatory therapies in the future.

Agents aimed at relieving obstruction

Alpha-blockers and 5-alpha reductase inhibitors are both commonly used to treat patients with benign prostatic hyperplasia. The rationale for their use in CP/CPPS is based on the overlapping symptoms of these conditions, such as voiding dysfunction, and the potentially overlapping pathogenesis, such as sympathetic overactivation and endocrine imbalances. Alpha-blockers have traditionally been postulated to inhibit overactivation of bladder neck smooth muscle and thus increase urine flow, and more recently have been implicated in blocking proliferation and inducing prostatic apoptosis.[27,28] A metaanalysis of four alpha-blocker trials for CP/CPPS revealed overall benefit with modest efficacy,[29] but a recent large-scale trial did not show statistically significant improvement with alfuzosin compared to placebo.[14] Clinical trials are currently registered for the alpha-blockers tamsulosin (ClinicalTrials.gov identifier: NCT00913315) and silodosin (ClinicalTrials.gov identifier: NCT00740779), and local Botox injection, which is hypothesized to inhibit bladder neck smooth muscle contraction (Table 1).

5-Alpha reductase inhibitors are thought to prevent dihydrotestosterone-induced prostate growth through inhibition of type II (prostatic) 5-alpha reductase. An RCT revealed modest improvement in patients treated with finasteride, but failed to reach statistical significance.[30] A trial comparing finasteride, which selectively inhibits type II 5-alpha reductase, to saw

palmetto, a herbal preparation containing a nonspecific 5-alpha reductase inhibitor, demonstrated modest but statistically significant improvement of the NIH-CPSI total score in the finasteride group.[31] Voiding symptoms did not improve significantly in this group, which raises some interesting mechanistic questions.

Box 2

Types of pain

Nociceptive pain

The activation of nociceptive primary afferent neurons, including C fibers and Aδ fibers, results in nociceptive pain. These neurons are activated by chemical, thermal, and high-threshold mechanical signals that indicate danger or damage.

Inflammatory pain

Inflammatory pain is the result of interaction between the nervous system and inflammatory mediators. This can cause peripheral sensitization and central sensitization, leading to symptoms such as hyperalgesia, allodynia, and spontaneous pain (Box 5). Owing to its role in protecting healing tissue, inflammatory pain is considered adaptive, although it can be maladaptive in the context of chronic inflammation.

Neuropathic pain

Pain of neural origin is known as neuropathic pain. The term can be used to refer specifically to pain resulting from a peripheral nerve injury, or can be used more broadly, to encompass what is described below as dysfunctional pain. Through numerous peripheral and central mechanisms, nerve injury results in increased transmission of pain signals to the brain. The pain is often characterized as shooting, stabbing, or electric pain.

Dysfunctional pain

Dysfunctional pain (sometimes referred to as ‘functional’ pain) is considered by some to be a subtype of neuropathic pain. It is pain of neural origin but without a known injury to the nervous system. It is thought to involve remodeling within pain pathways and might involve neuronal damage caused by excitotoxicity. These processes might be involved in unexplained clinical pain syndromes, such as fibromyalgia. This is still a poorly understood area, the concepts are controversial and the terminology is not used consistently across the literature.

Box 3

Previously studied therapies and proposed mechanisms of action

Antibiotics

Eliminate nonculturable bacteria, reduce inflammation

Anti-inflammatories

Reduce systemic or prostatic inflammation, autoimmunity, CNS transmission of pain signals, and central sensitization

Alpha-blockers

Prevent and alleviate symptoms induced by sympathetic overactivation (such as detrusor contraction,* internal urethral sphincter contraction and epithelial-stromal remodeling of the prostate)

5-Alpha reductase inhibitors
Promote prostate size reduction
Phytotherapy (including saw palmetto, bee pollen extract and quercertin)
Wide variety of proposed mechanisms, including hormonal, anti-inflammatory, and antimicrobial effects
Pentosan polysulfate
Replenish the glycosaminoglycan layer of the bladder, stabilize prostatic stromal mast cells
Myofascial trigger point therapy and feedback
Reduce tension of dysregulated pelvic floor muscles
Transurethral microwave thermotherapy
Prostatic tissue ablation
*Although relaxation is the outcome of alpha-adrenergic stimulation in the normal bladder, recent evidence suggests that in pathologic conditions such as detrusor overactivity associated with bladder outlet obstruction, the alpha-adrenergic receptor density can increase to such an extent that stimulation by norepinephrine results in contraction.[18] Abbreviation: CNS, central nervous system.

Mepartricin, an antifungal and antiprotozoal agent, is postulated to decrease prostate size via a reduction in plasma estrogen levels. The results of an RCT for CP/CPPS symptoms showed substantial decrease in pain, quality of life, and total NIH-CPSI scores in patients treated with mepartricin, although the reduction in voiding symptoms was not statistically significant.[32] Further evidence is needed to assess the utility of mepartricin, alpha-blockers and 5-alpha reductase inhibitors in CP/CPPS. A potential problem with such studies is that the natural history of the disease is unknown. One CP/CPPS disease model postulates that patients might have peripheral pain to begin with that later develops into centralized chronic pain that persists once the peripheral trigger has subsided. In such a scenario, some patients are likely to present after centralization of the pain has begun, and those patients would not benefit from therapies aimed at peripheral triggers.

Other drugs and therapies

Many other pharmacologic interventions have been studied in patients with CP/CPPS, with variable results.[29] Pentosan polysulfate is commonly used to treat patients with painful bladder syndrome/interstitial cystitis (PBSIC) to replenish the glycosaminoglycan layer of the bladder. PBS/IC and CP/CPPS are thought to be related conditions, and pentosan polysulfate has been tested in an RCT for CP/CPPS.[33] The results showed some clinical benefit in the treatment arm, but the change in total NIH-CPSI score was not statistically significant.

Several natural therapies have also been used for CP/CPPS, including saw palmetto and its extract, bee pollen extract and quercetin. A review of trials using these products suggests potential for each of them to have a therapeutic role,[34] and a recent multicenter RCT has demonstrated statistically significant symptomatic improvement in patients receiving bee pollen extract.[35]

*Although relaxation is the outcome of alpha-adrenergic stimulation in the normal bladder, recent evidence suggests that in pathologic conditions such as detrusor overactivity associated with bladder outlet obstruction, the alpha-adrenergic receptor density can increase to such an extent that stimulation by norepinephrine results in contraction.[18] Abbreviation: CNS, central nervous system.

Nonpharmacologic therapies aimed at decreasing pelvic floor muscle dysfunction have also been studied. Muscle tenderness or tension has been found in a large percentage of men with CP/CPPS,[36] supporting the notion that CP/CPPS could be related to myofascial pain. Dysfunction of the pelvic floor muscles is considered to be a downstream effect of a breakdown in CNS regulation.[37] A number of uncontrolled studies have reported benefits of physical therapy based on myofascial trigger points for patients with CP/CPPS or other genitourinary conditions.[38–41] A recent study compared myofascial physical therapy to global therapeutic massage in men and women with chronic pelvic pain to assess the feasibility of controlled trials for physical therapy.[42] The study showed a statistically significant improvement of symptoms in the patients receiving myofascial therapy, although the improvement did not reach significance when only men with CP/CPPS were analyzed. Nonetheless, this study demonstrates the feasibility and potential utility of controlled trials for physical therapy techniques. Biofeedback and pelvic floor retraining have also been employed to promote relaxation of the pelvic floor muscles, with some positive results in patients with CP/CPPS.[43–45] Use of RCTs to study these techniques is needed, but current results are promising.

A number of other procedures have been employed to treat men with CP/CPPS, including transurethral microwave thermotherapy, transurethral needle ablation, spinal cord stimulation, pudendal nerve block or decompression, transurethral prostate resection, electromagnetic therapy and acupuncture. Assessment of each of these options is beyond the scope of this Review, but the data on transurethral microwave thermotherapy in particular is encouraging.[1,46,47]

Summary

The last decade has seen substantial improvements in the design of RCTs for CP/CPPS treatments and an increased breadth of the agents being studied. A number of therapies have shown promise but have only modest clinical effects, appear beneficial in only certain patients, or both. Currently, patients' options are limited and far from guaranteed to provide substantial relief from the debilitating symptoms of CP/CPPS. Future studies should focus on targeting appropriate therapies to the appropriate patient populations, developing new therapies, and utilizing synergistic combination therapies.

Emerging therapies

A number of newer drugs have been suggested to offer the possibility of a new era of CP/CPPS treatment. Many of these agents are known to target pain pathways (Box 4). Some have been, or are currently being, tested in clinical trials, and some have anecdotal evidence of success, but few of these emerging therapies are supported by gold standard evidence from RCTs. It is becoming apparent that optimal management of CP/CPPS will involve a multidisciplinary team of urologists, internists, pain specialists, gastroenterologists, rheumatologists, physical therapists, neurologists and primary care physicians.

Gabapentin and pregabalin

Gabapentin and pregabalin are anticonvulsant drugs that have been used anecdotally in patients with CP/CPPS. They are commonly used to treat various other neuropathic pain syndromes, including diabetic neuropathy, postherpetic neuralgia, and fibromyalgia. Results from the NIDDK-sponsored phase III trial of pregabalin in CP/CPPS were reported at the 2009 American Urological Association (AUA) Meeting.[48] The primary end point of this trial was defined as an at least 6 point decrease in total NIH-CPSI score. After 6 weeks of pregabalin therapy, this treatment was not superior to placebo for the alleviation of CP/CPPS symptoms. However, statistically significant improvement was observed in a number of secondary end points. For example, the proportion of men who reported marked or moderate improvement

from baseline (according to global response assessment) was 31% and 19% respectively (P = 0.023). In addition, the pregabalin group demonstrated improvement over the placebo group in the McGill pain questionnaire total score (P = 0.006) and for both the sensory (P = 0.03) and affective (P = 0.02) subdomains.

Gabapentin was initially developed as a gamma-aminobutyric acid analog but was not found to activate any of the gamma-aminobutyric acid receptors. It is an antiepileptic and analgesic drug that has gained particular attention for its efficacy in treating diabetes-related neuropathic pain.[49] It is thought to act through antagonism of the α2-δ subunit of voltage-sensitive calcium channels.[50] Pregabalin also acts on the α2-δ subunit of calcium channels, but with greater binding affinity and potency.[51] Pregabalin has analgesic, antiepileptic, anxiolytic, and sleep-modulating activity.[52] The primary known site of analgesic action for both drugs is the dorsal horn of the spinal cord, where they bind to the α2-δ receptor and block the release of glutamate and peptide neurotransmitters, such as substance P and calcitonin-related gene product, thereby decreasing pain signal transmission.[53]

Experimental and human clinical studies of neuropathic pain have demonstrated the antiallodynic and antihyperalgesic effects of pregabalin and gabapentin,[49,54,55] which are probably related to upregulation of the α2-δ receptor during the central sensitization process (Box 5).[53] Pregabalin and gabapentin have relatively favorable adverse effect profiles considering they are centrally acting drugs. Dizziness and drowsiness are the primary common adverse effects of both. Peripheral edema has been reported in up to 16% of patients on pregabalin and 1.7–8.3% of patients on gabapentin.[56–58] Neither drug undergoes hepatic metabolism, reducing the potential for drug interactions.[50,59]

Box 4

Potential analgesics for chronic prostatitis/chronic pelvic pain syndrome

Pregabalin and gabapentin

Antagonism of α2-δ subunit of voltage-sensitive calcium channel

Amitriptyline

Serotonin/norepinephrine reuptake inhibitor

Antagonism of sodium channels, NMDA receptors, alpha-adrenergic receptors, H_1-histaminergic receptors and muscarinic cholinergic receptors

Direct or indirect activation of opioid receptors

Agonism of nerve growth factor receptors TrkA and TrkB

Memantine

Uncompetitive inhibitor of NMDA receptors

Abbreviation: NMDA, N-methyl-D-aspartic acid.

Box 5

Components of heightened pain states

Peripheral sensitization

Increased sensitivity at the level of the peripheral nerve terminal, such as the autonomic somatosensory nerve endings in the prostate of patients with CP/CPPS. Inflammation and tissue damage cause release of substances that activate nociceptors and sensitize them by

reducing the activation threshold, thus rendering them more responsive. Changes in transcription and translation of the receptors, as well as post-translational modifications, play a role in increased sensitivity.

Central sensitization

Occurs via similar mechanisms to peripheral sensitization but at the level of the synapse between the primary afferent neuron and the secondary projecting neuron, in the dorsal horn of the spinal cord. Prompted by strong nociceptive signals, chronic signals, and spontaneous signals from damaged peripheral nerves, central sensitization also involves neuronal remodeling on multiple levels (synapse, spinal cord, pain neurotransmission pathways). Central sensitization is thought to play an important role in chronic pain conditions.

Hyperalgesia, allodynia and spontaneous pain

Symptoms that frequently occur in heightened pain states and chronic pain conditions. Hyperalgesia is increased length or severity of pain perception to a stimulus that is normally painful. Allodynia is a painful response to a stimulus that is not normally painful. Pain in the absence of stimulus is termed spontaneous pain. Processes such as central and peripheral sensitization contribute to these symptoms. Nerve injury, such as in neuropathic pain, can lead to these symptoms through multiple mechanisms. These include loss of mechanoreceptors that normally inhibit pain signals (disinhibition), structural reorganization and phenotype switching of mechanoreceptors allowing them to transmit pain signals to secondary projecting neurons in the CNS, and ectopic signals owing to receptor reorganization in injured nociceptors.

Tricyclic antidepressants

Tricyclic antidepressants (TCAs), such as amitriptyline, have both antidepressant and analgesic effects. The overlap of pathways involved in these processes is unknown.[60] Although TCAs have peripheral actions,[61] their primary analgesic effects are thought to occur in the CNS.[60]

The primary mechanism by which TCAs exert their antidepressant effects is considered to be the inhibition of serotonin and norepinephrine reuptake. However, other serotonin and norepinephrine reuptake inhibitors have shown reduced efficacy compared to TCAs in reducing neuropathic pain, suggesting the importance of other mechanisms in this context.[62] TCAs interact with a number of other receptors, but the exact role of these interactions in analgesia is not well understood. These interactions include antagonism of sodium channels, N-methyl-D-aspartic acid (NMDA) receptors, alpha-adrenergic receptors, H_1-histaminergic receptors, and muscarinic cholinergic receptors, as well as direct or indirect activation of opioid receptors.[62–64] Agonism of TrkA and TrkB nerve growth factor receptors, resulting in a neurotrophic effect, has also been suggested as an important mechanism of TCA analgesic action.[65]

The analgesic efficacy of TCAs has been demonstrated in a number of neuropathic and other chronic pain conditions, including headaches, low back pain, irritable bowel syndrome, and fibromyalgia.[62,66] The evaluation of TCAs for treatment of neuropathic pain, in comparison to anticonvulsants such as gabapentin and pregabalin, has produced inconsistent results, so there is no clear clinical recommendation.[62,67,68] Results of a recent NIH/NIDDK-sponsored trial (ClinicalTrials.gov identifier: NCT00124306) that evaluated the efficacy and safety of amitriptyline in the treatment of patients newly diagnosed with painful bladder syndrome were reported at the 2009 AUA Meeting.[69] After 12 weeks of therapy, the response rate on the global response assessment was not statistically different between the amitriptyline and placebo groups (55% versus 45%). However, significant differences favoring amitriptyline were found in four secondary end points: urinary frequency score, 24 h voiding frequency, O'Leary-Sant

Symptom Index and Interstitial Cystitis Problem Index. A secondary analysis indicated that drug therapy was beneficial for those patients who were able to reach higher doses (more than 25 mg) and stay on them (71% versus 53% in the placebo arm on the secondary end points above). This might reflect an inherent problem associated with intent-to-treat trials—that participants who drop out of the trial owing to intolerance are classified as failures. Although an unbiased method, these trials do not provide the urologist with information regarding the likelihood of success for a patient who can tolerate medication.

TCAs have adverse effects that warrant consideration, including anticholinergic effects, such as dizziness, orthostatic hypotension, sedation, and problems with micturition. Higher doses are associated with an increased risk of sudden death owing to cardiac arrhythmias;[62] a 75 mg daily dose of amitriptyline is generally accepted as 'cardio-safe', but clinical experience shows that cardiac dysrhythmias can occur at daily doses as low as 25 mg. Therefore, in our opinion, the definition of cardiac safety should be based on pharmacogenomic, rather than event-driven, end points. Future genome-wide association studies and pharmacogenomic trials in CP/CPPS will be required to define the 'cardio-safe' amitriptyline dose. Patients on TCAs also have the potential to develop tolerance. These effects are significant enough that other monoaminergic reuptake inhibitors, such as duloxetine and bupropion, are sometimes favored in the treatment of neuropathic pain despite potentially reduced efficacy compared to TCAs.[62]

Memantine

Memantine is an NMDA receptor antagonist currently approved by the FDA for Alzheimer's disease, but its potential uses are diverse, including the treatment of obesity, chronic pain, depression, and schizophrenia.[70] NMDA receptors are glutamate receptors that propagate excitatory signals in the CNS. However, they are also thought to mediate neuronal injury when overactivated, leading to excessive calcium influx (excitotoxicity). Competitive inhibitors of the NMDA receptor block both its physiologic and pathologic actions, causing substantial CNS adverse effects that negate their use in most settings. Memantine was developed as an uncompetitive inhibitor of the NMDA receptor and is thought to selectively inhibit in the setting of excessive activation. It thus shows promise in preventing the pathologic consequences of NMDA overactivation without the unwanted inhibition of normal NMDA activity.[71,72]

Inhibition of NMDA receptors can decrease pain via multiple mechanisms. Excessive excitatory transmission in pain pathways is an important component of neuropathic pain. Neuronal damage and remodeling of neuronal pathways are the most probable consequences of this overactivity that allow for the establishment and maintenance of chronic neuropathic pain.[73] NMDA receptor overactivation might be a critical factor in the development and maintenance of hyperalgesia and allodynia in CP/CPPS (Box 5).[73,74] Furthermore, the decreased expression of opioid receptors observed in neuropathic pain conditions is thought to be mediated by excessive NMDA signaling,[75] and, even in acute pain, antagonism of NMDA signaling can play a role in opioid analgesia.[76] The effective blockade of NMDA receptors, therefore, potentially has multiple roles in decreasing pain. In this regard, results from a recent European study have demonstrated promising efficacy and safety of memantine in alleviating the symptoms of CP/CPPS.[77]

Memantine has a relatively positive safety profile. Adverse effects can include dizziness, drowsiness, constipation, hypertension, and headaches, but these occur in a small proportion of patients and demonstrate no statistical significance in comparison with placebo.[70,78] Risk of drug interactions with memantine is very low.

Opioids

Opioids are generally thought not to be as effective in treating neuropathic pain as the drugs previously discussed. No controlled trials evaluating opioids for the treatment of CP/CPPS have been published, although they are sometimes used in patients with severe treatment-refractory pain. High doses are commonly required to achieve efficacy, and the effect is often limited. This might result from numerous causes, including the downregulation of opioid receptors observed upon overactivation of NMDA receptors. Furthermore, in some patients neuronal damage and remodeling are likely to affect regions of the CNS downstream from the afferent nociceptor synapse in the dorsal horn. Therefore, opioid actions in the dorsal horn might have reduced ability to modulate pain signal transmission in these patients.

The author of a recent review advised physicians of the myriad reasons why opioids might not be the best choice for patients with CP/CPPS.[79] He also highlighted the potential of combining opioid treatment with other analgesics, such as gabapentin, NMDA receptor antagonists, or NSAIDs; one might expect, based on the NMDA-mediated downregulation of opioid receptors, to see a synergistic effect with a combination of an opioid and an NMDA receptor antagonist. In our experience, such combination therapy has produced promising preliminary results. Furthermore, despite the general notion that opioids are not the best agents for neuropathic pain, evidence suggests they are effective against certain symptoms, such as spontaneous pain, and several subtypes of evoked pain.[80,81] Evidence also suggests that certain opioids, such as oxycodone, have greater antiallodynic and antihyperalgesic properties compared to others, such as morphine.[82] As the specific pharmacologic profiles of different opioids are understood better, certain ones are likely to emerge as better suited for treating neuropathic pain. Although opioids are unlikely to revolutionize the treatment of CP/CPPS, careful research into their best usage might prove valuable.

Other drugs

A number of other drugs are either currently under investigation in patients with CP/CPPS or are likely to be studied in the future, as the condition becomes better understood (Table 1). One such agent is tanezumab, a monoclonal antibody directed against nerve growth factor (NGF). Several lines of evidence have implicated NGF in the pathogenesis of CP/CPPS. Postprostatic massage urine and seminal plasma NGF levels have been shown to correlate with pain severity in men with CP/CPPS.[83] Based on this evidence, the efficacy and safety of tanezumab is currently being evaluated in a phase II multicenter, double-blind, placebo-controlled RCT (ClinicalTrials.gov identifier: NCT00826514). Lidocaine is a local anesthetic that has been shown to be effective in the alleviation of prostate-related pain in an animal model of CP/CPPS.[84] The rationale for intraprostatic botulinum toxin A is based on several observations that it can inhibit COX2 expression and suppresses prostatic pain in a capsaicin-induced prostatitis rat model.[85] Other agents targeting pain pathways, such as cannabinoids, could potentially be explored, especially as more is understood about the nature of pain in CP/CPPS.

Future perspectives

Many of the new therapies under consideration for use in CP/CPPS target pain pathways in the CNS. Categorization of the pain in CP/CPPS is difficult given the unknown etiology and pathogenesis, but it is generally thought that all pain types could contribute to different degrees at different times in different patients.[79] Furthermore, it is likely that acute lesions, caused by infection, inflammation, or trauma, could transform from nociceptive pain, inflammatory pain, or neuropathic pain owing to nerve damage, to neuropathic or dysfunctional pain resulting from remodeling of pain pathways and excitotoxic damage in the CNS. CP/CPPS patients would thus exist within a spectrum of different pain types.

The use of agents such as gabapentin, pregabalin, amitriptyline, and memantine suggests at least some degree of neuropathic pain involvement in CP/CPPS, although further studies of these drugs are necessary before the extent of their potential becomes clear. Data concerning new treatments, coupled with improved understanding of more-established therapies, provides hope for the successful treatment of CP/CPPS in the future. In clinical trials of these drugs, it will be important to correlate outcomes with pain characterization measures. Subjective measures, such as pain intensity, are the current standard in pain measurement and characterization, but development of biomarkers, such as proteins, genetic signatures, and imaging parameters, could prove to be of great utility in the future. Profiling the pain of patients through objective and subjective measures and correlating this data with the outcomes of treatment regimens will provide powerful means of probing disease pathogenesis and determining optimal therapeutic options for individual patients. It is likely that subgroups of patients with particular etiologies will report specific objective findings and respond to different therapies. The development of combination therapies with synergistic actions in controlling pain and other symptoms should further elucidate the pathways and networks through which the disease manifests.

The biomarker discovery process in CP/CPPS has already begun. A recent study identified increased levels of two chemokines in the expressed prostatic secretion of patients with either type IIIA or IIIB CP/CPPS.[86] Another study implicated IL-8 as a potential biomarker for type IIIA prostatitis.[87] The possible genetic causes of CP/CPPS are another important area to explore. Substantial evidence exists to support a relationship between PBS/IC and CP/CPPS, and furthermore, a common genetic underpinning of these conditions.[88–90] A study of adrenocortical hormone levels in patients with CP/CPPS demonstrated abnormalities in the CYP21A2 enzyme, potentially resulting from genetic variability.[91] Genome-wide association studies are likely to be an important tool in identifying the single nucleotide polymorphisms, genes, proteins, and processes involved in disease pathogenesis.

The use of imaging and other radiologic techniques in pain syndromes offers great promise in diagnostic capabilities and insight into pathogenesis. Magnetic resonance spectroscopy can be used to measure the concentration of specific chemicals, such as metabolites and neurotransmitters, in specific regions of the brain. A study analyzing the spectral profiles of patients with chronic low back pain, has demonstrated the ability to distinguish between patients and healthy controls with 97–100% accuracy.[92] This technology could lead to objective findings that can sensitively and specifically diagnose particular types of pain, as well as give insight into the locations and mechanisms of dysfunction in CP/CPPS.

Conclusions

Although the treatment of CP/CPPS is still suboptimal, RCTs continually add to a growing body of data that will undoubtedly improve the prognosis for patients with CP/CPPS. Many of the newer therapeutic agents target pain pathways in the CNS, and carefully designed trials with these agents should give us insight into the nature and precise role of pain in CP/CPPS. Because of the apparent complexity and diversity of etiologic and pathogenetic factors in CP/CPPS, one drug is unlikely to work for all patients; a notion supported by many of the RCTs reported in the literature that have only demonstrated modest symptomatic improvements. Studies that help identify disease subtypes, which can be characterized by epidemiologic, objective and subjective measures, and which respond to particular therapies, are likely to play a crucial role in improving CP/CPPS treatment. Discovering biomarkers, genetic markers, and radiologic findings in patients with CP/CPPS and correlating these objective measures with treatment trial outcomes is an important step in moving toward this goal. Over time, such studies should help effect the transition to an era of therapies that rationally target the disease mechanisms of individual patients.

Review criteria

We searched PubMed, CINAHL, Healthstar, Current Contents, ISI Web of Science, Psychlnfo, Science Citation Indexes, Cochrane Collaboration Reviews, EBSCO Academic Search Premier, EMBASE, Scirus, Scopus and Google Scholar for articles published between 1966 and 2009. The expanded search headings “prostatitis”, “chronic nonbacterial prostatitis”, “chronic abacterial prostatitis”, “chronic pelvic pain syndrome” and “prostatodynia” were combined with truncated keywords that described the type of publication, such as “random”, “double-blind”, “random allocation”, “placebo”, “clinical trial” and “comparative study” and was limited to studies in humans. We limited the search to studies in English and full text articles. Additional studies and abstracts were identified through a manual search of the bibliographies of retrieved articles, recent reviews, monographs, Annual Meetings of the AUA abstracts and proceedings from NIH/NIDDK meetings.

Acknowledgments

This work was supported by grants R01 DK065990, R21 DK070672 and R01 DK081647 from the NIH/NIDDK to J. D. Dimitrakov.

References

1. Nickel, JC. Campbell-Walsh Urology. 9th. Wein, AJ.; Kavoussi, LR.; Novick, AC.; Partin, AW.; Peters, CA., editors. Saunders; Philadelphia: 2007. p. 305-329.
2. Wenninger K, Heiman JR, Rothman I, Berghuis JP, Berger RE. Sickness impact of chronic nonbacterial prostatitis and its correlates. J Urol 1996;155:965–968. [PubMed: 8583619]
3. McNaughton Collins M, et al. Quality of life is impaired in men with chronic prostatitis: the Chronic Prostatitis Collaborative Research Network. J Gen Intern Med 2001;16:656–662. [PubMed: 11679032]
4. Walz J, et al. Impact of chronic prostatitis-like symptoms on the quality of life in a large group of men. BJU Int 2007;100:1307–1311. [PubMed: 17941922]
5. Tripp DA, Curtis Nickel J, Landis JR, Wang YL, Knauss JS. Predictors of quality of life and pain in chronic prostatitis/chronic pelvic pain syndrome: findings from the National Institutes of Health Chronic Prostatitis Cohort Study. BJU Int 2004;94:1279–1282. [PubMed: 15610105]
6. Tripp DA, Nickel JC, Ross S, Mullins C, Stechyson N. Prevalence, symptom impact and predictors of chronic prostatitis-like symptoms in Canadian males aged 16-19 years. BJU Int 2009;103:1080–1084. [PubMed: 19007369]
7. Krieger JN, Nyberg L Jr, Nickel JC. NIH consensus definition and classification of prostatitis. JAMA 1999;282:236–237. [PubMed: 10422990]
8. Schaeffer AJ. Clinical practice. Chronic prostatitis and the chronic pelvic pain syndrome. N Engl J Med 2006;355:1690–1698. [PubMed: 17050893]
9. Alexander RB. Treatment of chronic prostatitis. Nat Clin Pract Urol 2004;1:2–3. [PubMed: 16474440]
10. Alexander RB. Prostatitis: clinical phenotyping of patients with pelvic pain. Nat Rev Urol 2009;6:531–532. [PubMed: 19806172]
11. Nickel JC, et al. Psychosocial variables affect the quality of life of men diagnosed with chronic prostatitis/chronic pelvic pain syndrome. BJU Int 2008;101:59–64. [PubMed: 17924985]
12. Pontari MA, et al. A case-control study of risk factors in men with chronic pelvic pain syndrome. BJU Int 2005;96:559–565. [PubMed: 16104910]
13. Schaeffer AJ. NIDDK-sponsored chronic prostatitis collaborative research network (CPCRN) 5-year data and treatment guidelines for bacterial prostatitis. Int J Antimicrob Agents 2004;24(Suppl 1):S49–S52. [PubMed: 15364307]

14. Nickel JC, et al. Alfuzosin and symptoms of chronic prostatitis-chronic pelvic pain syndrome. N Engl J Med 2008;359:2663–2673. [PubMed: 19092152]
15. Potts JM. Chronic pelvic pain syndrome: a non-prostatocentric perspective. World J Urol 2003;21:54–56. [PubMed: 12819913]
16. Potts J, Payne RE. Prostatitis: infection, neuromuscular disorder, or pain syndrome? Proper patient classification is key. Cleve Clin J Med 2007;74(Suppl 3):S63–S71. [PubMed: 17549825]
17. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 2004;140:441–451. [PubMed: 15023710]
18. US Department of Health and Human Services. US Preventive Services Task Force Grade Definitions. 2009. [online], http://www.ahrq.gov/clinic/uspstf/grades.htm
19. Yoshimura, N.; Chancellor, M. Campbell-Walsh Urology. 9th. Wein, AJ.; Kavoussi, LR.; Novick, AC.; Partin, AW.; Peters, CA., editors. Saunders; Philadelphia: 2007. p. 1922-1972.
20. Nickel JC, Downey J, Johnston B, Clark J. Predictors of patient response to antibiotic therapy for the chronic prostatitis/chronic pelvic pain syndrome: a prospective multicenter clinical trial. J Urol 2001;165:1539–1544. [PubMed: 11342913]
21. Alexander RB, et al. Ciprofloxacin or tamsulosin in men with chronic prostatitis/chronic pelvic pain syndrome: a randomized, double-blind trial. Ann Intern Med 2004;141:581–589. [PubMed: 15492337]
22. Nickel J, et al. Levofloxacin for chronic prostatitis/chronic pelvic pain syndrome in men: a randomized placebo-controlled multicenter trial. Urology 2003;62:614–617. [PubMed: 14550427]
23. Zeng X, et al. Clinical evaluation of celecoxib in treating type IIIA chronic prostatitis [Chinese]. Zhonghua Nan Ke Xue 2004;10:278–281. [PubMed: 15148925]
24. Tomaskovic I, Ruzic B, Trnski D, Kraus O. Chronic prostatitis/chronic pelvic pain syndrome in males may be an autoimmune disease, potentially responsive to corticosteroid therapy. Med Hypotheses 2009;72:261–262. [PubMed: 19095365]
25. Yang MG, et al. Corticoid combined with an antibiotic for chronic nonbacterial prostatitis [Chinese]. Zhonghua Nan Ke Xue 2009;15:237–240. [PubMed: 19452696]
26. Bates S, Talbot M. Short course oral prednisolone therapy in chronic abacterial prostatitis and prostatodynia: case reports of three responders and one non-responder. Sex Transm Infect 2000;76:398–399. [PubMed: 11141861]
27. Yun AJ, Doux JD. Opening the floodgates: benign prostatic hyperplasia may represent another disease in the compendium of ailments caused by the global sympathetic bias that emerges with aging. Med Hypotheses 2006;67:392–394. [PubMed: 16427746]
28. 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. [PubMed: 12496995]
29. Dimitrakov JD, Kaplan SA, Kroenke K, Jackson JL, Freeman MR. Management of chronic prostatitis/chronic pelvic pain syndrome: an evidence-based approach. Urology 2006;67:881–888. [PubMed: 16698346]
30. Nickel JC, Downey J, Pontari MA, Shoskes DA, Zeitlin SI. A randomized placebo-controlled multicentre study to evaluate the safety and efficacy of finasteride for male chronic pelvic pain syndrome (category IIIA chronic nonbacterial prostatitis). BJU Int 2004;93:991–995. [PubMed: 15142149]
31. Kaplan SA, Volpe MA, Te AE. A prospective, 1-year trial using saw palmetto versus finasteride in the treatment of category III prostatitis/chronic pelvic pain syndrome. J Urol 2004;171:284–288. [PubMed: 14665895]
32. De Rose AF, Gallo F, Giglio M, Carmignani G. Role of mepartricin in category III chronic nonbacterial prostatitis/chronic pelvic pain syndrome: a randomized prospective placebo-controlled trial. Urology 2004;63:13–16. [PubMed: 14751338]
33. Nickel JC, et al. Pentosan polysulfate sodium therapy for men with chronic pelvic pain syndrome: a multicenter, randomized, placebo controlled study. J Urol 2005;173:1252–1255. [PubMed: 15758763]

34. Capodice JL, Bemis DL, Buttyan R, Kaplan SA, Katz AE. Complementary and alternative medicine for chronic prostatitis/chronic pelvic pain syndrome. Evid Based Complement Alternat Med 2005;2:495–501. [PubMed: 16322807]
35. Wagenlehner FM, et al. A pollen extract (Cernilton) in patients with inflammatory chronic prostatitis-chronic pelvic pain syndrome: a multicentre, randomised, prospective, double-blind, placebo-controlled phase 3 study. Eur Urol 2009;56:544–551. [PubMed: 19524353]
36. Shoskes DA, et al. Muscle tenderness in men with chronic prostatitis/chronic pelvic pain syndrome: the chronic prostatitis cohort study. J Urol 2008;179:556–560. [PubMed: 18082223]
37. Zermann DH, Ishigooka M, Doggweiler R, Schmidt RA. Neurourological insights into the etiology of genitourinary pain in men. J Urol 1999;161:903–908. [PubMed: 10022711]
38. Anderson RU, Wise D, Sawyer T, Chan C. Integration of myofascial trigger point release and paradoxical relaxation training treatment of chronic pelvic pain in men. J Urol 2005;174:155–160. [PubMed: 15947608]
39. Anderson RU, Wise D, Sawyer T, Chan CA. Sexual dysfunction in men with chronic prostatitis/chronic pelvic pain syndrome: improvement after trigger point release and paradoxical relaxation training. J Urol 2006;176:1534–1539. [PubMed: 16952676]
40. Weiss JM. Pelvic floor myofascial trigger points: manual therapy for interstitial cystitis and the urgency-frequency syndrome. J Urol 2001;166:2226–2231. [PubMed: 11696740]
41. Anderson RU, Sawyer T, Wise D, Morey A, Nathanson BH. Painful myofascial trigger points and pain sites in men with chronic prostatitis/chronic pelvic pain syndrome. J Urol 2009;182:2753–2758. [PubMed: 19837420]
42. FitzGerald MP, et al. Randomized multicenter feasibility trial of myofascial physical therapy for the treatment of urological chronic pelvic pain syndromes. J Urol 2009;182:570–580. [PubMed: 19535099]
43. Clemens JQ, et al. Biofeedback, pelvic floor reeducation, and bladder training for male chronic pelvic pain syndrome. Urology 2000;56:951–955. [PubMed: 11113739]
44. Nadler RB. Bladder training biofeedback and pelvic floor myalgia. Urology 2002;60:42–44. [PubMed: 12521595]
45. Cornel EB, van Haarst EP, Schaarsberg RW, Geels J. The effect of biofeedback physical therapy in men with Chronic Pelvic Pain Syndrome Type III. Eur Urol 2005;47:607–611. [PubMed: 15826751]
46. Leskinen MJ, Kilponen A, Lukkarinen O, Tammela TL. Transurethral needle ablation for the treatment of chronic pelvic pain syndrome (category III prostatitis): a randomized, sham-controlled study. Urology 2002;60:300–304. [PubMed: 12137830]
47. Kastner C, Hochreiter W, Huidobro C, Cabezas J, Miller P. Cooled transurethral microwave thermotherapy for intractable chronic prostatitis-results of a pilot study after 1 year. Urology 2004;64:1149–1154. [PubMed: 15596188]
48. Pontari M, et al. A randomized placebo-controlled multicenter trial of pregabalin for the treatment of men with chronic prostatitis/chronic pelvic pain syndrome [abstract 340]. J Urol 2009;181:123.
49. Bennett MI, Simpson KH. Gabapentin in the treatment of neuropathic pain. Palliat Med 2004;18:5–11. [PubMed: 14982201]
50. Rose MA, Kam PC. Gabapentin: pharmacology and its use in pain management. Anaesthesia 2002;57:451–62. [PubMed: 11966555]
51. Guay DR. Pregabalin in neuropathic pain: a more “pharmaceutically elegant” gabapentin? Am J Geriatr Pharmacother 2005;3:274–287. [PubMed: 16503325]
52. Gajraj NM. Pregabalin: its pharmacology and use in pain management. Anesth Analg 2007;105:1805–1815. [PubMed: 18042886]
53. Chiechio S, et al. Pregabalin in the treatment of chronic pain: an overview. Clin Drug Investig 2009;29:203–213.
54. Chizh BA, et al. Effects of oral pregabalin and aprepitant on pain and central sensitization in the electrical hyperalgesia model in human volunteers. Br J Anaesth 2007;98:246–254. [PubMed: 17251214]
55. Gottrup H, et al. Chronic oral gabapentin reduces elements of central sensitization in human experimental hyperalgesia. Anesthesiology 2004;101:1400–1408. [PubMed: 15564948]

56. Dworkin RH, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol 2003;60:1524–1534. [PubMed: 14623723]
57. Pfizer prescription products. LYRICA® US physician prescribing information. 2010. [online], http://media.pfizer.com/files/products/uspi_lvrica.pdf
58. Pfizer prescription products. Neurontin® US physician prescribing information. 2010. [online], http://media.pfizer.com/files/products/uspi_neurontin.pdf
59. Lyseng-Williamson KA, Siddiqui MA. Pregabalin: a review of its use in fibromyalgia. Drugs 2008;68:2205–2223. [PubMed: 18840008]
60. Micó JA, Ardid D, Berrocoso E, Eschalier A. Antidepressants and pain. Trends Pharmacol Sci 2006;27:348–354. [PubMed: 16762426]
61. Yaron I, et al. Fluoxetine and amitriptyline inhibit nitric oxide, prostaglandin E2, and hyaluronic acid production in human synovial cells and synovial tissue cultures. Arthritis Rheum 1999;42:2561–2568. [PubMed: 10616001]
62. Sindrup SH, Otto M, Finnerup NB, Jensen TS. Antidepressants in the treatment of neuropathic pain. Basic Clin Pharmacol Toxicol 2005;96:399–409. [PubMed: 15910402]
63. Song JH, Ham SS, Shin YK, Lee CS. Amitriptyline modulation of Na(+) channels in rat dorsal root ganglion neurons. Eur J Pharmacol 2000;401:297–305. [PubMed: 10936487]
64. Benbouzid M, et al. Delta-opioid receptors are critical for tricyclic antidepressant treatment of neuropathic allodynia. Biol Psychiatry 2008;63:633–636. [PubMed: 17693391]
65. Jang SW, et al. Amitriptyline is a TrkA and TrkB receptor agonist that promotes TrkA/TrkB heterodimerization and has potent neurotrophic activity. Chem Biol 2009;16:644–656. [PubMed: 19549602]
66. Verdu B, Decosterd I, Buclin T, Stiefel F, Berney A. Antidepressants for the treatment of chronic pain. Drugs 2008;68:2611–2632. [PubMed: 19093703]
67. Sator-Katzenschlager SM, et al. Chronic pelvic pain treated with gabapentin and amitriptyline: a randomized controlled pilot study. Wien Klin Wochenschr 2005;117:761–768. [PubMed: 16416358]
68. Morello CM, Leckband SG, Stoner CP, Moorhouse DF, Sahagian GA. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. Arch Intern Med 1999;159:1931–1937. [PubMed: 10493324]
69. Hanno, P. A new look at the use of amitriptyline for the treatment of interstitial cystitis: results of an NIH clinical trial. Presented at the 2009 Annual Meeting of the American Urological Association;
70. Kavirajan H. Memantine: a comprehensive review of safety and efficacy. Expert Opin Drug Saf 2009;8:89–109. [PubMed: 19236221]
71. Chen HS, Lipton SA. The chemical biology of clinically tolerated NMDA receptor antagonists. J Neurochem 2006;97:1611–1626. [PubMed: 16805772]
72. Lipton SA. Failures and successes of NMDA receptor antagonists: molecular basis for the use of open-channel blockers like memantine in the treatment of acute and chronic neurologic insults. NeuroRx 2004;1:101–110. [PubMed: 15717010]
73. Parsons CG. NMDA receptors as targets for drug action in neuropathic pain. Eur J Pharmacol 2001;429:71–78. [PubMed: 11698028]
74. Mao J, Price DD, Hayes RL, Lu J, Mayer DJ. Differential roles of NMDA and non-NMDA receptor activation in induction and maintenance of thermal hyperalgesia in rats with painful peripheral mononeuropathy. Brain Res 1992;598:271–278. [PubMed: 1362520]
75. Mao J, Price DD, Phillips LL, Lu J, Mayer DJ. Increases in protein kinase C gamma immunoreactivity in the spinal cord dorsal horn of rats with painful mononeuropathy. Neurosci Lett 1995;198:75–78. [PubMed: 8592645]
76. Fischer BD, Carrigan KA, Dykstra LA. Effects of N-methyl-D-aspartate receptor antagonists on acute morphine-induced and I-methadone-induced antinociception in mice. J Pain 2005;6:425–433. [PubMed: 15993820]
77. Dimitrakov JD, Chitalov J, Dechev I. Memantine in the alleviation of symptoms of chronic pelvic pain syndrome: a randomized, double-blind, placebo-controlled trial [abstract 339]. J Urol 2009;181:123.

78. van Marum RJ. Update on the use of memantine in Alzheimer's disease. Neuropsychiatr D/'s Treat 2009;5:237–247.

79. Nickel JC. Opioids for chronic prostatitis and interstitial cystitis: lessons learned from the 11th World Congress on Pain. Urology 2006;68:697–701. [PubMed: 17070334]

80. Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. JAMA 2005;293:3043–3052. [PubMed: 15972567]

81. Eisenberg E, McNicol ED, Carr DB. Efficacy of mu-opioid agonists in the treatment of evoked neuropathic pain: systematic review of randomized controlled trials. Eur J Pain 2006;10:667–676. [PubMed: 16337151]

82. Mizoguchi H, Watanabe C, Yonezawa A, Sakurada S. New therapy for neuropathic pain. Int Rev Neurobiol 2009;85:249–260. [PubMed: 19607975]

83. Miller LJ, et al. Nerve growth factor and chronic prostatitis/chronic pelvic pain syndrome. Urology 2002;59:603–608. [PubMed: 11927336]

84. Rudick CN, Schaeffer AJ, Thumbikat P. Experimental autoimmune prostatitis induces chronic pelvic pain. Am J Physiol Regul Integr Comp Physiol 2008;294:R1268–R1275. [PubMed: 18287220]

85. Chuang YC, et al. Intraprostatic botulinum toxin a injection inhibits cyclooxygenase-2 expression and suppresses prostatic pain on capsaicin nduced prostatitis model in rat. J Urol 2008;180:742–748. [PubMed: 18554636]

86. Desireddi NV, et al. Monocyte chemoattractant protein-1 and macrophage inflammatory protein-1alpha as possible biomarkers for the chronic pelvic pain syndrome. J Urol 2008;179:1857–1862. [PubMed: 18353390]

87. Penna G, et al. Seminal plasma cytokines and chemokines in prostate inflammation: nterleukin 8 as a predictive biomarker in chronic prostatitis/chronic pelvic pain syndrome and benign prostatic hyperplasia. Eur Urol 2007;51:524–533. [PubMed: 16905241]

88. Dimitrakov JD. A case of familial clustering of interstitial cystitis and chronic pelvic pain syndrome. Urology 2001;58:281. [PubMed: 11489726]

89. Dimitrakov J, Guthrie D. Genetics and phenotyping of urological chronic pelvic pain syndrome. J Urol 2009;181:1550–1557. [PubMed: 19230927]

90. Pontari MA. Chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis: are they related? Curr Urol Rep 2006;7:329–334. [PubMed: 16930505]

91. Dimitrakov J, et al. Adrenocortical hormone abnormalities in men with chronic prostatitis/chronic pelvic pain syndrome. Urology 2008;71:261–266. [PubMed: 18308097]

92. Siddall PJ, et al. Magnetic resonance spectroscopy detects biochemical changes in the brain associated with chronic low back pain: a preliminary report. Anesth Analg 2006;102:1164–1168. [PubMed: 16551917]

Table 1

Current chronic prostatitis/chronic pelvic pain syndrome drug treatment trials*

Drug	Class	Placebo-controlled	Route of administration	ClinicalTrials.gov identifier
CC-10004	Anti-inflammatory	No	Oral	NCT00701311
Botulinum toxin A	Anticholinergic	Yes	Intrasphincteric	NCT00464373
Botulinum toxin A Lidocaine	Anticholinergic Anesthetic	No	Intraprostatic	NCT00529386
Pregabalin	Anticonvulsant	Yes	Oral	NCT00371033
Tolterodine Tamsulosin	Antimuscarinic Alpha-blocker	Yes	Oral	NCT00913315
Tanezumab	Anti-nerve growth factor	Yes	Intravenous	NCT00826514

* These drugs are registered in clinical trials that are either active, recruiting, or not yet recruiting.