Published in final edited form as:

Pain Manag. 2013 September ; 3(5): 387–394. doi:10.2217/pmt.13.40.

New directions in the treatment of pelvic pain

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SUMMARY

The treatment of chronic pelvic pain in both females and males is a challenge for pain clinicians. Standard therapies are multimodal in nature with use of behavioral, medical and procedural therapeutics. In recent years, our understanding of the neuro biology of this disorder has improved and novel approaches have focused on neuro modulatory options, novel pharmacology and complementary/alternative medicine options. This review briefly examines newly employed therapeutic options, while restating currently utilized options. The current state-of-the-art treatment includes focal therapies for identified pathologies and empiric trials of other options for care when precise sources of the chronic pelvic pain are ill defined.

Overview of disease process

Chronic pelvic pain (CPP) is most commonly defined as continuous or intermittent pain that occurs in the lower abdomen or pelvic area that is cyclical or noncyclical in nature, and causes functional limitation in activities of daily living or reduced quality of life [1]. CPP is more prevalent in females, with an estimated worldwide prevalence of 2.1–24%. The annual cost to the USA's health system has been reported to be greater than US\$800 million. Up to two-thirds of patients with CPP do not carry a definitive diagnosis [1,2]. The emotional toll on the patient, family and healthcare providers is immeasurable, as all parties involved become frustrated by the lack of progress that is common in the management of this disorder. The signs and symptoms of CPP vary from patient to patient with regards to location and intensity, as well as presence or absence of associated urinary symptoms and sexual dysfunction. To further confound the issue, innervation of the pelvis is complex, making diagnosis of pain originating in this region of the body very difficult [1]. In addition to a thorough history and physical examination, careful utilization of laboratory and imaging studies should be used to help make the appropriate diagnosis.

The etiology of CPP is multifactorial and its pathophysiology is complex and incompletely understood [1]. CPP can arise from a multitude of causes in various organ systems, including gastrointestinal (e.g., inflammatory bowel disease and irritable bowel syndrome), neurologic (nerve entrapment and disc herniation), gynecologic (e.g., endometriosis and pelvic inflammatory disease), urologic (e.g., bladder pain syndrome and prostatitis) and musculoskeletal (e.g., sacroiliac joint dysfunction and symphysis pubis dysfunction) (**Table 1**) [2]. Coexisting painful disorders may be present and serve to enhance the overall pain symptoms through mechanisms of cross-organ sensitization resulting in viscerovisceral or viscerosomatic hyper-algesia [3]. Treatment of defined disorders follows typical treatment

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Financial & competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

pathways with the use of anti-inflammatory therapies (focal or systemic) when inflammation is identified and the use of neuropathic pain medications when clear pathology is identified within local neurological structures. In many cases, the precise pathology is not identified. In these instances, pathophysiologic theories suggest that CPP may be a result of abnormal CNS responses that maintain the perception of pain in the absence of acute injury [4], taking the features of a subtype of complex regional pain syndrome [5], or more simply as 'central sensitization' of the CNS with a decrease in pain thresholds and increase in normal pain intensities [6]. Since CPP often has mixed elements of neuropathic pain, inflammation and complex regional pain syndrome, patients may respond favorably to central acting medications, as well as stimulation of the CNS and peripheral nervous system.

New knowledge related to the neurobiology of pelvic pain

To meet the challenges posed by inadequately controlled pelvic pain, basic science studies have sought to define the mechanisms whereby this pain is generated and to define potential novel targets for therapeutics. There have been significant new findings related to genetic and epigenetic mechanisms associated with the development of abdominal/pelvic pains. Polymorphisms related to catechol-*O*-methyl transferase and μ -opioid receptors have been associated with differing rates of postoperative pain in patients undergoing radical prostatectomy or hysterectomy by abdominal approaches [7]. By identifying a genetic basis to the variability of pain and response to therapies it may be possible to identify therapies that are as unique as different individuals. A patient's underlying genetics are modified by epigenetic mechanisms that turn different genes on or off within an individual's DNA and the past few years have observed a huge expansion in our understanding of how such gene modulation may alter pain sensitivity or responses to therapies. Drugs that alter epigenetic mechanisms, such as histone deacetylase inhibitors, have been demonstrated to reduce hyperalgesia associated with experimental endometriosis [8] and prostatitis [9]. miRNAs have been implicated as sources of pain associated with cystitis and endometriosis, further modifying gene expression [10,11].

The neurophysiology of pelvic organ sensation has become progressively more defined and has recently been demonstrated to extend beyond neurons alone to include epithelial cells in the periphery and glial cells in the CNS [12]. In general, it has been demonstrated that the transduction interactions between epithelium and primary afferents produce specificity of sensory processing for individual pelvic organs. However, CNS processing of this specific information then contributes to nonspecificity by allowing for a convergence of sensory inputs on common sensory structures in the dorsal horn of the spinal cord. Notably, these neurons appear to follow a common set of modulatory mechanisms with little difference noted between inputs from different visceral structures.

There is logic to having specificity associated with primary afferent nerves innervating visceral structures due to the differences each organ may have in their local environment. The simplest comparison is between the bladder (which holds sterile urine) and the colon (which contains a sewer of bacteria). Activation of TLR-4 mucosal surface receptors by gram negative bacteria in the bladder results in an innate immune response with induction of an inflammatory cascade which then produces changes in the transduction mechanism of primary afferent neurons and resultant pain and urgency. Such mechanisms are absent in the colon which is full of Gram-negative bacteria. There are sub-populations of primary afferents that have been demonstrated to have different receptor expression and transduction properties that differ in prevalence dependent upon the organ of study [13,14]. Additionally, a small number of afferents with branches to more than one pelvic organ have been identified [15].

As noted above, in contrast to the specific patterns of activity noted in primary afferent neurons, second order neuronal responses to visceral stimuli have been demonstrated to have great similarity in responses independent of the organ being stimulated. Recent studies have observed modulation of dorsal horn responses by presentation of environmental stressors, such as footshock [16] or intravesical TRPV1 channel activation [17]. A comparison of dorsal horn neuron studies related to bladder distension and those related to distension of the colon/rectum fails to make any distinction between the two different neuronal populations, with parallel studies demonstrating similar convergence with somatic structures, modulation by centrally acting drugs and other CNS mechanisms. Future studies utilizing subtler modulations may tease apart differences in existent second order neuron populations.

Multiple models of pain associated with pelvic structures are continually being developed, including those associated with ovarian pain, cystitis, prostatitis, endometriosis and colitis (for a review of endometriosis models, see [18]). A particularly notable new model utilizes uropathogenic *Escherichia coli* to produce persistent pelvic mechanical sensitivity to probing following urinary tract infection even after treatment of the infection [19]. ‘Cross-talk’ between pelvic organ structures has been demonstrated by multiple studies with inflammation of one organ, such as the colon, producing alterations in the sensitivity of other organs, such as the bladder. Such ‘cross-talk’ has been treated effectively in animal models with the analgesic tramadol [20]. An interesting study by Malykhina *et al.* demonstrated that TRPV1 mechanisms were associated with this cross-talk, but unfortunately also demonstrated that treatments related to TRPV1 mechanisms, such as intravesical resiniferatoxin, may not be effective because those treatments while decreasing cross-talk mechanisms, increase sensitivity to somatic stimulation [17].

Multiple novel targets for therapy have been identified by preclinical trials, which include sodium channel blocking agents, drugs that modulate CD4⁺ T cells, receptors such as CXCR3/CCL2/CCL3, vascular endothelial growth factor receptors, glutamate transporters, calcium/calmodulin-dependent protein kinase II, macrophage migration inhibitory factor receptors, serotonin 1A receptors, cannabinoid receptors and melatonin receptors [21]. The targets that prove to be useful will depend on further refinement of their actions and toxicities.

Current management options

Since evidence-based management options for CPP with and without defined pathology are limited, as few therapeutics have ‘proven’ clinical efficacy, a multidisciplinary approach to the treatment of these patients is essential (**Table 2**). Frequently, the diagnosis assigned to a painful condition is dependent on the initial specialist who evaluated the patient: urologists assign urological diagnoses; gynecologists assign gynecological diagnoses. A prudent approach for any pain clinician is to take a fresh look at existent evaluations and to assess the multiple etiologies that are possible, but not considered. A phenotypic approach championed by Nickel *et al.* and Shoakes *et al.* is the UPOINT system, which has six domains: urinary, psychosocial, organ-specific, infection, neurologic/systemic and muscle tenderness [22,23]. These domains define potential lines of diagnostic investigation and suggest treatment options in relation to urogenital pain, thereby giving some structure to their clinical approach. The UPOINT approach has been extended and modified by some international organizations to the broader category of pelvic pain [24] and appears to be a valid initial approach to a patient's pain complaints. If the underlying cause of the pain is defined, then subsequent treatment is centered on that particular etiology, otherwise a more global ‘empiric’ approach must be taken. Diagnostic laparoscopy, lysis of adhesions and exploratory laparotomy are the most common procedures performed in this population of patients. Medication management also plays a vital role. Opiates, muscle relaxants,

antidepressants and anticonvulsants have all been used with varying efficacy. In recent years, interventional techniques have moved to the forefront as management has shifted away from invasive surgical exploration to minimally invasive and percutaneous procedures. Focal local anesthetic and depot steroid injections at neuraxial and peripheral sites have been commonly employed. The successful use of neuromodulation (including spinal cord and posterior tibial nerve stimulators) and radio frequency thermocoagulation has been well documented in published literature [25,26]. Adjuvant techniques, including biofeedback, acupuncture and massage, are used as part of a true multimodal treatment approach.

New trends in clinical management with neuromodulation

Neuromodulation/nerve stimulation are now central to the management of refractory CPP. Neuromodulation typically targets the S2–S4 nerve roots even though the pelvis is innervated by peripheral sympathetic (T12–L2) and somatic (S2–4), as well as parasympathetic (S2–4) nerve structures. Therefore, lead placement at the sacral level may appear to cover the appropriate painful area for the patient, but may not lead to satisfactory improvement in clinical symptoms. At this time, pain providers have yet to reach a consensus with regards to optimal lead placement. Percutaneous posterior tibial nerve and sacral lead placement continue to be the most common approach, but with only limited support when using evidence-based medical evaluations [27]. There is new evidence that altering lead location can increase success rates in complex patients. Hunter *et al.* have described lead placement as high as T6/7 and as low as the conus with positive results [28]. The success of high lead placement is attributed to the non dermatomal distribution of visceral pain fibers and the assumption that at higher levels, a greater percentage of visceral fiber coverage is achieved [28]. Placement of leads in the sub-cutaneous tissue of the lower abdomen, as well as pudendal nerve neuromodulation, has also been described in difficult to treat patients with encouraging results [29,30].

Vagal nerve stimulation is used in the management of intractable seizure disorders, but has known antinociceptive effects. The exact mechanism of this analgesic effect is unknown, but is thought to be mediated by afferent input to the nucleus tractus solitarius and higher centers [31]. Noninvasive approaches to vagal nerve stimulation (transcutaneous vagus nerve stimulation) involve stimulation of its auricular branch in the ear. Respiratory gated auricular vagal afferent nerve stimulation (RAVANS) synchronizes vagal stimulation with respiration. In patients with CPP due to endometriosis, RAVANS revealed a trend towards reduction of evoked deep pain intensity and temporal summation of mechanical pain [32].

The use of primary motor cortex stimulation for CPP necessitates implantation of an electrode in the extradural space to stimulate the motor cortex corresponding to the appropriate painful area as identified by repeated transcranial magnetic stimulation. A case report by Louppe *et al.* described the use of this technique in two patients with chronic intractable perineal pain. After electrode and stimulator implantation, both patients experienced significant reduction of their pain symptoms, which was sustained at the end of a follow-up period of approximately 1.5 years [32]. Transcutaneous electrical stimulation is associated with a moderate degree of success in this population [33]. Intravaginal electrical stimulation is a more invasive type of transcutaneous electrical stimulation. Its efficacy was tested with a randomized, double-blind crossover trial of 26 women with CPP. The authors assessed pain severity at the end of 20 weeks of twice-weekly 30-min therapy sessions, reporting that it was associated with greater pain relief than placebo [34].

New trends in medical management

Despite the aforementioned advances in therapy, medications continue to be central to the management of CPP. Tricyclic antidepressants, α -adrenergic blockers, gabapentin and pregabalin all show promise in the treatment of this disorder (**Table 2**). However, in randomized clinical trials, they have not been proven to be clearly superior to placebo and are sometimes associated with severe, dose-limiting side effects. Topical formulations (i.e., amitriptyline–ketamine cream) have been reported to be an effective alternative for patients who may be intolerant of higher doses of some oral medications [35]. COX inhibitors help manage the inflammatory component of pain caused by CPP owing to its ability to decrease prostaglandin production. It may also inhibit central processes that can propagate chronic pain [36]. There is some thought that autoimmune mechanisms play a role in CPP prompting clinicians to trial systemic corticosteroid therapy. The reported advantages of systemic steroid use include better pain and quality-of-life scores. Notably, there have not been any double-blind randomized controlled trials completed to confirm or refute the validity of these results [36]. Given the life-altering adverse effects associated with chronic steroid use, practitioners must carefully weigh the risk–benefit ratio on a patient-by-patient basis prior to choosing this course of therapy.

N-methyl-D-aspartate glutamate receptor antagonists have analgesic effects secondary to their ability to reduce excitatory neurotransmission in the CNS. Memantine is an *N*-methyl-D-aspartate receptor that has demonstrated some early successes in managing the symptoms of CPP [36]. Changes in NGF levels expressed from the prostatic fluid of males suffering from CPP have been implicated in disease severity [37]. NGF has also been implicated in the pathogenesis of CPP. A monoclonal antibody directed against NGF (tanezumab) is currently being investigated for use in this pain syndrome [36,38]. TNF- α is a proinflammatory cytokine that promotes the production of IL-1 and IL-6. There is a relatively large body of evidence in the form of case reports and series supporting its use in the management of patients with severe endometriosis. In a recent Cochrane review, only one randomized clinical trial evaluating the efficacy of anti-TNF- α medications was found in the literature prompting the authors to conclude that there was insufficient evidence for or against the use of this class of medications in the management of pelvic pain due to endometriosis [39]. Aromatase inhibitors (anastrozole and letrozole) are emerging as viable options in the management of women with CPP induced by endometriosis. While there are no randomized clinical trials in the literature to support its use, multiple nonrandomized studies and case series support their efficacy in reducing the pain and burden of endometriomas with minimal side effects [40]. In animal models, thiazolidinediones can reduce endometriosis lesions without affecting their fertility. In a preliminary study designed to evaluate the efficacy of thiazolidinediones as a treatment for endometriosis-related CPP, the authors noted both a decrease in opiate consumption and a decrease in pain as measured by the McGill pain questionnaire in two out of three patients [41]. It must be noted that this class of medication carries a black box warning from the US FDA due to increased risk of myocardial events in patients with risk factors, limiting its overall utility [41]. *N*-palmitoylethanolamine and transpodyatin are two anti-inflammatory and antinociceptive agents that may provide benefits for the CPP patient. Giugliano *et al.* conducted a prospective study of 47 patients with endometriosis and CPP who received these two medications. Their results suggested that intensity of endometriotic pain decreased over time with the use of *N*-palmitoylethanolamine and transpodyatin [42].

New trends in complementary & alternative medicine

Physical therapy, dietary therapy and complementary and alternative medicines are useful adjuvants to traditional therapies. Physical therapy utilizing myofascial release techniques

and pelvic floor muscle exercises is regularly used in multimodal treatment plans. Fitzgerald *et al.* determined the feasibility of performing a randomized clinical trial comparing two types of physical therapy for patients with urologic CPP. Their results were notable for a better response in patients managed with myofascial physical therapy as opposed to global therapeutic massage [43].

In 2011, a randomized clinical trial evaluated the efficacy of yoga in relieving the pain of patients with known primary dysmenorrhea. Its results indicated that the performance of yoga poses during menses (cobra, cat and fish poses) were associated with significant decrease in pain duration and intensity compared with the control [44]. If these results are borne out, a similar technique could be applied to the treatment of patients with CPP. Acupuncture has grown in popularity and is now used to manage a variety of pain disorders, as well as postoperative nausea and vomiting. Regarding acupuncture and CPP, reports about the successful use of acupuncture or acupuncture with electrical stimulation pepper the literature and in general they have been positive, with significant decreases in pain scores over placebo noted in a majority of the studies [33,45,46].

Dietary therapy is based on evidence that a higher intake of fresh fruit and vegetables containing high amounts of antioxidants is associated with increased immune function and decreased free radical/oxidative stress to the body. This therapy recommends increasing the patient's intake of natural inhibitors of COX function (vitamins and n-3 fatty acids). These serve to boost the body's natural ability to fight free radicals and reduce pain via a reduction in prostaglandin and inflammatory cytokine production [47]. It should be noted that work in this arena has been largely experimental. Twice-daily use of quercetin (a red wine/green tea extract) was shown to improve male CPP in double-blind, placebo-controlled trials [48]. In murine models, there is ongoing research to evaluate epigallocatechin-3-gallate, a component of green tea that is thought to be responsible for its antiangiogenic, antioxidant and anti proliferative effects; and resveratrol, found on grape skin, responsible for antioxidant and anti-inflammatory effects of red wine. The authors tested these agents by transplanting endometriosis-like lesions into mice and randomized the animals to receive resveratrol or epigallocatechin-3-gallate. Their results showed significant suppression of the development of endometriosis lesions in treated mice in both groups, but the epigallocatechin-3-gallate group showed a greater degree of suppression of these lesions compared with the resveratrol group [49].

Conclusion & future perspective

CPP is a complex disorder whose prevalence in the general population is comparable to asthma, chronic back pain or migraine headaches [50]. With poorly understood etiology and pathophysiology, management of this disorder mandates the use of a multidisciplinary approach. There are a variety of interventional, surgical, and medical and alternative approaches available to treat this disorder; however, none of them have been proven to be consistently effective and so novel therapies such as those presented in this report have been employed. The current state-of-the-art treatment for CPP often involves a trial and error approach in order to attain the best results for any individual patient. Research on this disorder is extensive and ongoing. The use of neuromodulatory/neurostimulatory methods presents significant potential for interventions related to pain that is unresponsive to more traditional medical and behavioral therapies. Hopefully, within the next 5–10 years, sufficient well-controlled randomized clinical trials will have been performed that clinical practice can be evidence-based, rather than anecdote-based. Given the significant emotional, physical and healthcare costs associated with CPP, there is a vital need for these trials to be performed.

Acknowledgments

TJ Ness receives support from NIH DK51413 for studies of pelvic pain.

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Practice Points

- Chronic pelvic pain can have gastroenterological, urogenital, musculoskeletal and neurological origins.
- Therapeutics are initially driven by any identified pathologies within these organ systems.
- Identification of the inflammatory processes indicates the use of focal or systemic anti-inflammatory therapies.
- Neuropathic processes indicate the use of neuromodulatory therapeutics and neuropathic pain-related medications, including the use of antidepressants, anticonvulsants and other agents.
- When generators of pain are poorly defined, systematic empiric trials of agents may be appropriate; initial trials assume a potential for neuropathic causes.
- Behavioral interventions are always appropriate when pain involves body areas associated with private functions, including defecation, urination and sexual function.
- Complementary and alternative medicine therapeutics have a highly appropriate place in the treatment of a disorder not treated well by traditional medicine.

Table 1

Causes of chronic pelvic pain.

Type of pain	Cause
Neurologic	Nerve entrapment, nerve irritation, shingles, disc herniation, abdominal epilepsy, abdominal migraine, Tarlov cysts
Gynecologic	Endometriosis, pelvic inflammatory disease, adnexal pathology (e.g., ovarian cysts), pelvic congestion syndrome, pelvic floor hypertonia, vulvodynia, tumors (e.g., fibroids), ovarian remnant syndrome
Urologic	Bladder pain syndrome/interstitial cystitis, urethral pain syndrome, chronic prostatitis, prostate pain syndrome, penile pain syndrome
Gastrointestinal	Irritable bowel syndrome, Crohn's disease, diverticular disease, ulcerative colitis, chronic appendicitis, cancer, adhesions (after abdominal surgery)
Musculoskeletal	Sacroiliac joint dysfunction, symphysis pubis dysfunction, pelvic ring hypermobility, coccygeal pain, myofascial pain, piriformis syndrome, fibromyalgia

Table 2

Current management of pelvic pain.

Management type	Method
Surgical	Diagnostic laparoscopy, exploratory laparotomy, lysis of adhesions, presacral neurectomy, paracervical denervation, uterovaginal ganglion excision
Medication	Tricyclic antidepressants, anticonvulsants, opiates, muscle relaxants, antibiotics, α -blockers, pentosan polysulfate
Interventional procedures	Radiofrequency thermocoagulation (pulsed, cooled and so on), sympathetic nerve blocks, neurolysis (cryo or chemical), neuromodulation (spinal cord or peripheral nerve stimulators), botulinum toxin injections
Physical therapy	TENS unit, massage, ultrasound, pelvic floor training, myofascial release
Other/complementary and alternative medicine	Acupuncture, psychological counseling, behavioral modification, guided imagery, biofeedback, phytotherapy, ultrasound

TENS: Transcutaneous electrical nerve stimulation.