Pharmacological Treatment of Bladder Pain Syndrome/Interstitial Cystitis

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Abbreviations

ATP	Adenosine triphosphate
AUA	American Urological Association
BPH	Benign prostatic hyperplasia
BPS	Bladder pain syndrome
CPP	Chronic pelvic pain
EAU	European Association of Urology
FDA	Food and Drug Administration
GERD	Gastroesophageal reflux disease
IC	Interstitial cystitis
IgE	Immunoglobulin E
LUTS	Lower urinary tract symptoms
PDE5-I	Phosphodiesterase 5 inhibitors
UTI	Urinary tract infections

16.1 Introduction

Chronic pelvic pain (CPP) is defined as a non-cyclic pain with a duration of at least 6 months. This form of painful condition may definitely worsen patients' quality of life [1].

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Certain researchers also suggested that CPP syndrome might be a form of bladder pain syndrome/interstitial cystitis (BPS/IC). In fact, in 2007 the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) began to group together BPS/IC and chronic prostatitis/CPP syndrome under a single umbrella term: urologic chronic pelvic pain syndromes. According to this idea, in the last decades the scientific community tried to circumscribe chronic bladder pain and IC in a single entity, thus generating scientific and clinical confusion both from a diagnostic and from a therapeutic point of view.

Recently, to ensure a systematic approach and to provide clearness in the clinical practice, the International Continence Society set out a series of four domains in CPP syndromes, based on the pelvic organs: lower urinary tract domain, female genital domain, male genital domain and gastrointestinal domain. In this attempt of standardization, the lower urinary tract domain includes both bladder and urethra while worldwide the definitions for BPS and IC are not yet completely standardized [1].

Actually, the classic Hunner's disease is a specific and well-defined pathology and fulfils the requirements for the denomination of "interstitial cystitis". Evidences are accumulating on the unique and outstanding features of this clinical entity, as the therapeutic requirements differ significantly between this and other phenotypes of IC [2].

In this chapter, we would examine the pharmacological options in the treatment of BPS/IC, both oral and intravesical, and thus providing a critical analysis of what is currently established by internationally recognized guidelines and by the most significant publications on this issue.

16.2 Oral Therapy

16.2.1 Antidepressants

Antidepressants are often used in the treatment of many forms of chronic pain. Their mechanisms are variable and their action on pain may be independent from antidepressant effect.

16.2.1.1 Amitriptyline

Amitriptyline is a tricyclic antidepressant that inhibits serotonin and noradrenaline reuptake and blocks acetylcholine and histamine (H1) receptors. Anticholinergic effect may alleviate urinary urgency and frequency and reduces inflammatory response; moreover, the inhibition of these neurotransmitters has an analgesic effect [3]. The suggested dose of amitriptyline is 10 mg to 75–100 mg daily and can be used in association with gabapentin [4]. Common side effects include dry mouth, constipation and drowsiness.

(Level of Evidence: 2. Grade of Recommendation: B)

16.2.1.2 Duloxetine

Duloxetine is a serotonin and noradrenaline reuptake inhibitor. This drug can improve stress urinary incontinence and is also used in the treatment of neuropathic pain [5]. The suggested dose is 20–80 mg daily. However, there are insufficient data to demonstrate its efficacy in chronic pelvic pain syndrome [6].

(Level of Evidence: 4. Grade of Recommendation: C)

16.2.2 Pentosan Polysulphate Sodium

In patients with BPS the glycosaminoglycan (GAG) layer of the bladder urothelium can be damaged; a defective GAG layer is hypothesized to be one important mechanism for BPS. Pentosan polysulphate sodium (PPS) is a synthetic sulphated polysaccharide that aims to restore the damaged GAG layer and can inhibit histamine release from mast cells. PPS is available in oral and intravesical formulation and is approved by FDA for BPS [7]. The suggested dose is 300–900 mg daily and it can be administered in association with subcutaneous heparin. Side effects include thrombocytopenia and alopecia. Many studies have demonstrated its efficacy and its ability to improve pain and urinary symptoms [8].

(Level of Evidence: 1. Grade of Recommendation: D)

16.2.3 Antihistamines

In patients with BPS there can be an increased number of mast cells in the bladder wall, suggesting that histamine may be responsible for the development of BPS. Blocking histamine release can lead to reduced inflammatory response, thus improving pain and urinary symptoms.

16.2.3.1 Hydroxyzine

Hydroxyzine is a histamine H1 receptor antagonist and it also has anticholinergic and slight sedative properties. Many patients show improvement from their baseline symptoms [9]. The suggested dose is 25 mg to 50–75 mg daily at bedtime. Common side effects include sedation and drowsiness.

(Level of Evidence: 1. Grade of Recommendation: D)

16.2.3.2 Cimetidine

Cimetidine is a histamine H2 receptor antagonist, mostly used for the treatment of peptic ulcer disease. Cimetidine improves pain and nocturia, though does not lead to histological changes of the bladder mucosa [10]. The suggested dose is 300–400 mg twice a day. Side effects include dizziness and headache.

(Level of Evidence: 3. Grade of Recommendation: C)

16.2.4 Analgesics

Analgesics are one of the most used drugs in the treatment of BPS. They often represent the first-line treatment in people suffering from chronic pain and patients may use these drugs independently. Analgesics include many heterogeneous compounds, such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDS), cyclooxygenase (COX) inhibitors, opioids and corticosteroids.

16.2.4.1 Acetaminophen

Acetaminophen (paracetamol) is an analgesic with antipyretic activity. Though it is well tolerated, its efficacy is limited and should be used in association with other compounds to enhance their effect.

16.2.4.2 NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)

NSAIDs include many compounds that inhibit COX-1 and COX-2 enzymes, while COXIB are highly selective COX-2 inhibitors (such as celecoxib and etoricoxib). The COX-1 enzyme usually regulates gastric mucosal integrity and both renal and platelet function; its block is the typical cause of NSAIDs complications. On the contrary, COX-2 enzyme is inducible and it is generated as a result of tissue damage and it is involved in inflammatory response. Despite this, there is little evidence for a role of NSAIDs in the management of chronic pelvic pain, though they can be used as first-line analgesics [11]. These drugs should be avoided in patients with increased risk of gastric complication or chronic kidney failure; likewise, COX-2 selective drugs should be avoided in patients with known cardiovascular disease.

16.2.4.3 Opioids

Although they are mainly used in the treatment of cancer pain, opioids have a role in the management of chronic pain [12, 13]. Opioid treatment should be prescribed only after other reasonable treatments have been tried and failed. Due to their potentially life-threatening side effects, the decision to instigate long-term opioid therapy should be made by an appropriately trained specialist [11]. The common side effects of opioids include sedation, nausea, constipation and confusion. Respiratory depression is rare if they are used as prescribed. Morphine is the first-line drug, though there is no evidence that one compound is better than another. Other opioids include fentanyl, methadone, oxycodone, hydromorphone, codeine and tramadol.

(Level of Evidence: 4. Grade of Recommendation: C)

16.2.4.4 Corticosteroids

There is insufficient data for the long-term use of corticosteroids and their side effects can be serious. However, intravesical injection of corticosteroids may be considered.

(Level of Evidence: 4. Grade of Recommendation: D)

16.2.5 Immunosuppressant

BPS could have an autoimmune component which leads to an inflammatory response: in fact, cytokines and chemokines are significantly increased in urine and bladder tissues from BPS patients. The modulation of immunological response is a therapeutic option to reduce urinary and pain symptoms.

16.2.5.1 Cyclosporine A (CyA)

Cyclosporine A (CyA) is a widely known immunosuppressive drug, mostly used in transplantation and in autoimmune disease. It inhibits calcineurin and suppresses T cell activity and cytokine release, thus interfering with the production of IL-2 and T cell-related immune response. CyA treatment reduces voiding frequency and mean voided volume [14]. Evidences suggest that CyA is more effective in patients with Hunner's lesion than in those without [15]. Despite it is a recommended therapy by the AUA, it is currently without FDA approval. Oral treatment with CyA should begin with a starting dose of 2.5–5.0 mg/kg/day and a maintenance dose of 1.5–3.0 mg/kg/day. Side effects are common and include hypertension, increased serum creatinine level and alopecia.

(Level of Evidence: 3. Grade of Recommendation: C)

16.2.5.2 Azathioprine

This molecule has shown efficacy in reducing both pain and lower urinary tract symptoms [16]. The suggested dose is 50–100 mg daily and common side effect is nausea.

(Level of Evidence: 4. Grade of Recommendation: D)

16.2.5.3 Methotrexate

Low dose oral methotrexate can improve pain in patients with BPS but does not improve urinary symptoms [17].

(Level of Evidence: 4. Grade of Recommendation: D)

16.2.5.4 Suplatast Tosilate

Suplatast tosilate (IPD-1151T) is an oral immune regulator that suppresses helper T cell-mediated allergic processes, including IgE production and eosinophilic inflammation. This compound may significantly increase bladder capacity while decreasing voiding and pain symptoms [18]. However, there are insufficient data to justify its use, though it is commonly prescribed in Japan for the treatment of BPS.

(Level of Evidence: 1. Grade of Recommendation: D)

16.2.6 Antibiotics

UTIs might play a role in the genesis of LUTS. The exclusion of UTIs is a key step in the management of LUTS but sometimes persistent LUTS may originate from undetected UTIs. It is important to note that most BPS patients have been treated

with empiric antibiotics prior to diagnosis. Antimicrobial therapy (quinolones or tetracyclines) has a moderate effect on total pain, voiding and QoL scores [19]. Patients responding to antibiotics should be maintained on medication for 4–6 weeks as recommended by EAU guidelines.

(Level of Evidence: 4. Grade of Recommendation: D)

16.2.7 Anticonvulsants

Anticonvulsants are widely used in the treatment of neuropathic and chronic pain. They exert their effects in different ways and some compounds have more than one mechanism of action. They can also be used in association with other classes of medication to enhance their effect on pain relief, while reducing doses and consequent side effects. They include gabapentin, pregabalin and carbamazepine.

16.2.7.1 Gabapentin

This anticonvulsant drug induces activation of α2δ subunit of the voltage-gated calcium channels, modulating the release of neurotransmitters involved in nociception. It has favourable action profile, including few side effects and lack of interactions with other medications [20]. The suggested dose is 300–1200 mg/day and side effects include drowsiness and peripheral oedema.

(Level of Evidence: 4. Grade of Recommendation: D)

16.2.7.2 Pregabalin

It has similar structure as gabapentin and has similar mechanism of action. Although it is commonly used in neuropathic pain disorders, pregabalin is not effective for the treatment of BPS.

16.2.7.3 Carbamazepine

Carbamazepine is a sodium channel blocker mainly used in the treatment of epilepsy and neuropathic pain. It is no longer a first choice drug due to its side effects.

16.2.8 New Emerging Compounds

16.2.8.1 Rosiptor (AQX-1125)

This compound activates SH2-containing inositol-5′-phosphatase (SHIP1), which modulates the PI3K pathway involved in chronic inflammation. SHIP1 has anti-inflammatory effect by downregulating the PI3K pathway. This is a promising medication, currently under evaluation in a phase III study. Women taking AQX-1125 at the dose of 200 mg daily reported significant reduction in their subjective bladder pain and an improvement in urinary symptoms. The most reported side effects were dyspepsia, GERD and sinusitis. No serious adverse events have been reported so far [21, 22].

16.2.8.2 Gefapixant (AF-219)

Bladder distension releases ATP from the urothelium and ATP activates purinergic receptors such as P2X2 and P2X3. P2X3 purinoceptors are thought to play a role in sensitization of bladder afferent neurons in response to ATP, so that upregulation of ATP stimulation and P2X3 expression in the urothelium of patients with BPS may contribute to chronic symptoms. Gefapixant is a P2X3 receptor antagonist that has been investigated in a placebo-controlled, randomized phase II study (NCT01569438). The suggested dose is 50 mg BID–300 mg and common side effects are dysgeusia or hypogeusia. It improves urinary urgency and pain, but further investigations are needed [23].

16.2.8.3 Tanezumab

Tanezumab is a humanized antibody that blocks nerve growth factor (NGF) binding with high selectivity and specificity. It prevents NGF from interacting with its receptors on nociceptive receptors. In a phase II randomized double-blinded placebo-controlled trial, tanezumab showed a significant decrease in pain and urgency. The suggested dose was 200 μg/kg intravenous or 20 mg IV or 20 mg subcutaneous. Side effects included paraesthesia and headache [24]. It was also found that tanezumab improved pain in patients who had pelvic pain and a concomitant somatic syndrome, but not in patients with pelvic symptoms only [25]. This suggests that tanezumab may be helpful in patients with appropriate phenotypes.

16.2.8.4 Adalimumab

Adalimumab is a monoclonal antibody against TNFα, which is a proinflammatory cytokines release by immune cells. In a phase III randomized double placebo-controlled study, patients who received 80 mg subcutaneous loading dose followed by 40 mg every 2 weeks showed improvement in outcomes measures but no statistically significant difference between treatment and placebo group. Currently, adalimumab is not considered as a treatment option, but it might still have a role in ulcerative subtypes BPS [26].

16.2.9 Other Compounds

16.2.9.1 Quercetin

It is a bioflavonoid with a wide range of biological effects, including anti-inflammatory activity. The suggested dose is 500 mg BID. Further studies are needed to assess its efficacy [27].

(Level of Evidence: 4. Grade of Recommendation: D)

16.2.9.2 Misoprostol

It is an oral prostaglandin analogue that is hypothesized to have cytoprotective effect on bladder. The suggested dose is 600 μg daily, but side effects are common and include abdominal cramping and diarrhoea [28].

(Level of Evidence: 4. Grade of Recommendation: D)

16.2.9.3 L-Arginine

It is a semi-essential amino acid, precursor of nitric oxide (NO). NO may have immunoregulating properties and, taken systematically, L-arginine increases the production of NO. Current data does not support the use of L-arginine for BPS [29].

(Level of Evidence: 1. Grade of Recommendation: A)

16.2.9.4 Montelukast

It is a leukotriene receptor antagonist. Leukotrienes are produced by mast cells and may promote inflammation. In patients with BPS, montelukast at the dose of 10 mg daily can reduce frequency, nocturia and pain but the data supporting its use in BPS in not strong [30].

(Level of Evidence: 4. Grade of Recommendation: D)

16.2.9.5 Muscle Relaxants

There are insufficient data on the effectiveness of muscle relaxants in BPS.

16.2.9.6 Alpha-Blockers

Alpha-blockers are largely used in the treatment of BPH. They have moderate effect on total pain, voiding and QoL scores in BPS and their use may be considered in patients with a recently onset BPS [31, 32].

16.2.9.7 5-Aplha Reductase Inhibitors

As alpha-blockers, 5-α-reductase inhibitors are mostly used in the treatment of BPH due to their action on prostate volume. 5-α-Reductase inhibitors cannot be recommended for use in BPS in general, but symptom scores may be reduced in a restricted group of older men with an elevated PSA serum concentration [33].

16.2.9.8 Sildenafil

Sildenafil is a PDE-5 inhibitor mainly used for erectile dysfunction in men. Its mechanism of action is still unclear, but some hypothesis suggest that it can lower bladder smooth cells contraction sensibility, hence reducing potassium ions penetrating the submucosa and mast cell degeneration. Even though there is limited published data on its use, it seems that in patients with BPS sildenafil can improve objective and subjective parameters [34]. The suggested dose is 25 mg daily and most common side effects are flushing and headache.

16.2.9.9 Phytotherapy

Patients treated with phytotherapy have significantly lower pain scores. In particular, it seems that pollen extract administration significantly improves BPS patients' symptoms, while phytotherapy in general shows an overall favourable treatment response in BPS, especially on pain [35, 36].

16.3 Intravesical Therapies

Intravesical therapies can be used alone or in association with oral therapies and are indicated when first-line therapy fails. Its rationale is to replenish the deficient GAG layer or to modify the process of inflammation or hypersensitivity. These treatments have the main advantage to localize therapy into the bladder, thus reducing systemic absorption. Intravesical drugs can be used alone or in combination ("*bladder cocktails*").

16.3.1 Dimethyl-Sulphoxide

Dimethyl-sulphoxide (DMSO) is an organosulphur non-toxic solvent whose mechanism of action has not been clarified. However, it is thought to exert its clinical effect through several mechanism: it reduces inflammation and pain and facilitates detrusor relaxation [37, 38]. The instillation method has not been standardized, although generally 50 cc of a solution of medical grade 50% DMSO is instilled into the bladder. It can be given as a single-agent instillation or as part of bladder cocktail (see further). Side effects include temporary garlic-like odour and irritative symptoms. DMSO is listed in the AUA guidelines as a second-line treatment option; however the EAU guidelines state that there is insufficient data to recommend its use. Moreover, DMSO is the only intravesical agent approved for the treatment of BPS/IC by the FDA.

(Level of Evidence: 2. Grade of Recommendation: B)

16.3.2 Heparin

Heparin is a sulphonated GAG with the theoretical action of replenishing the urothelial GAG layer. It also has anti-inflammatory effects and inhibits fibroblast proliferations [39]. The suggested dose is 10′000–40′000 units and can be used alone or in association with other compounds, such as alkalinized lidocaine. Single-agent heparin studies have shown modest benefit in patients with BPS [40]. Side effects are not significant but may include local haemorrhage.

(Level of Evidence: 3. Grade of Recommendation: C)

16.3.3 Pentosan Polysulphate Sodium

Pentosan polysulphate sodium (PPS) in an oral heparinoid that likely exerts its effect by restoring the GAG layer; it also inhibits histamine release by mast cells and reduces the intracellular calcium ion level in the bladder [41]. At present, PPS is the

only oral agent approved by the FDA for the treatment of BPS. When taken orally, it achieves slow urine concentration resulting in a lag time before clinical improvement is observed. Intravesical therapy has the theoretical advantage of quickly achieving a response to PPS treatment. Intravesical PPS can be used in association with oral PPS resulting in a higher response rate than intravesical PPS alone [42].

(Level of Evidence: 4. Grade of Recommendation: D)

16.3.4 Lidocaine

Lidocaine is a local anaesthetic with rapid onset of action, more commonly used in combination with other agents. Alkalinisation helps the lidocaine to better penetrate the urothelium [43]. Lidocaine provides immediate response and no significant side effects are reported.

(Level of Evidence: 1. Grade of Recommendation: C)

16.3.5 Chondroitin Sulphate

Chondroitin sulphate (CS) is a component of the GAG layer which is deficient in patients with BPS. CS inhibits the recruitment of inflammatory cells to the deep layers of the bladder wall [44]. The suggested dose is 2% in buffered saline and no significant side effects were reported. CS is mostly used in association with hyaluronic acid (HA).CS is commercially available as Gepan® or Uracyst®.

(Level of Evidence: 1. Grade of Recommendation: C)

16.3.6 Hyaluronic Acid

Hyaluronic acid (HA) is another component of the urothelial GAG layer that has anti-inflammatory effects. HA is commercially available as Cystistat® that comes as a 40 mg dose in a 50 mL solution. HA-CS has been shown to reduce the production of pro-inflammatory cytokines, reduce urothelial permeability and facilitate the repair of the GAG layer [45]. HA-CS is commercially available as Ialuril®, a 50 mL preparation containing 1.6% HA and 2% CS with calcium chloride in water.

(Level of Evidence: 1. Grade of Recommendation: C)

16.3.7 Other Compounds

16.3.7.1 Oxybutynin

Oxybutynin is an anti-cholinergic drug mostly used in overactive bladder syndrome. When combined with bladder training, it provides significant urodynamics improvement but no effects on pain were reported [46].

(Level of Evidence: 4. Grade of Recommendation: D)

16.3.7.2 Triamcinolone

Triamcinolone is a corticosteroid that can be used as an intravesical instillation or administered via submucosal injection through cystoscopy. Low dose triamcinolone injection seems to be more effective in patients with Hunner's lesions [47]. More often, triamcinolone is used in combination with other compounds.

16.3.7.3 Bacillus Calmette-Guérin (BCG)

Bacillus Calmette-Guérin (BCG) is mostly used for vaccination against tuberculosis and in bladder cancer immunotherapy. There are insufficient data to recommend its use.

(Level of Evidence: 1. Grade of Recommendation: -A)

16.3.7.4 Vanilloids

Capsaicin and resiniferatoxin (RTX) are neurotoxins that specifically bind to the transient receptor potential vanilloid type 1 (TRPV1) which is involved in the development of bladder pain [48]. Despite their theoretical ability to alleviate bladder symptoms, vanilloids are currently not recommended [49].

(Level of Evidence: 1. Grade of Recommendation: -A)

16.3.7.5 Liposomal Sphingomyelin

Sphingomyelin is a phospholipid found in cell membranes. It is thought that its use in BPS could restore the GAG layer and decrease the cell permeability [50, 51].

16.3.7.6 Botulinum Toxin A (BTX-A)

Botulinum Toxin A (BTX-A) inhibits the release of acetylcholine and other neurotransmitters from both afferent and efferent nerve-terminals as well as ATP from urothelium [52]. Intradetrusor BTX-A injections provides reduction in pain and urgency compared to placebo [53, 54].

16.3.8 Bladder Cocktails

The intravesical intillation of a combination of more than one substance or drug is defined "bladder cockatail". Various cocktails have been described in the literature and most often they include anesthetics and/or coricosteroids in the preparation. These treatments can be administered at home in selected case. Below, we report some of the most used "bladder cocktails".

- 20 mL 0.5% bupivacaine, 20 mL 2% lidocaine jelly, 40 mg triamcinolone, 10–20,000 IU heparin, 80 mg gentamicin [55]
- 8 mL 2% lidocaine, 4 mL 8.4% $NaHCO_3$, 20,000 IU heparin [56]
- 50 mL 0.5% bupivacaine, 50 mL 8.4% $NaHCO_3$, 100 mg hydrocortisone, 10,000 IU heparin, 80 mg gentamicin [57]
- 50 mL DMSO, 44 mEq $NaHCO_3$ (1 ampule), 10 mg triamcinolone, 20,000 IU heparin [58]
- 300 mg PPS, 10 mL 2% lidocaine, 10 mL 4.2% $NaHCO_3$ [59]

– 40,000 IU heparin, 8 mL 1% (80 mg) or 2% lidocaine (160 mg), 3 mL 8.4% $NaHCO_3$ [60]
– 5 mL 4% lidocaine followed by 5 mL 8.4% $NaHCO_3$ [43].

16.4 Conclusion

The pharmacological therapy of BPS/IC is complex and requires a multidisciplinary approach. Although numerous studies on the use of several drugs in BPS are present in the literature, only few of them are appropriate and with adequate levels of evidence to provide them grades of recommendation. We believe that, as on one side we will learn more on the aetiological and pathophysiological mechanisms that lead to chronic bladder pain and IC, on the other side we will certainly develop more therapeutic opportunities for these painful conditions.

Currently, drugs in chronic bladder pain can be administered both orally and intravesically. We definitely believe that further efforts should be made to standardize the intravesical treatments, through several safe and efficacy experiences. Thus, in future, we might even be able to develop study protocols based on the patient's phenotype.

As BPS/IC population is heterogeneous and multiform, further studies are mandatory to better define the best therapeutic options in this setting, which should certainly be as patient's tailored as possible.

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