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Review

Contemporary Non-Operative Management of Bladder Pain Syndrome: A Narrative Review for General Urologists

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Abstract

Background: Bladder pain syndrome (BPS) is a chronic, debilitating condition defined by the International Continence Society as bladder-related pelvic pain accompanied by urinary symptoms in the absence of identifiable pathology. Its heterogeneous presentation, unclear pathophysiology, and variable treatment response make management challenging for general urologists. This review aims to provide a practical narrative review of current understanding of BPS, with particular emphasis on diagnosis, phenotyping, and non-operative management strategies relevant to the general urologist. Methods: A narrative literature review was undertaken using PubMed/MEDLINE, Embase, Google Scholar, and major international guideline documents to identify evidence relating to the diagnosis and non-operative management of BPS. Publications from January 2015 to December 2025 were reviewed, with selected landmark earlier studies included, where clinically relevant. Priority was given to guidelines, systematic reviews, randomised trials, and cohort studies. Owing to heterogeneity in study design, patient phenotypes, and reported outcomes, findings were synthesized narratively. Results: BPS represents a heterogeneous spectrum, including Hunner-lesion and non-Hunner phenotypes, with proposed mechanisms involving urothelial dysfunction, chronic inflammation, immune dysregulation, and central sensitisation. Diagnosis remains one of exclusion, relying on careful history, examination, symptom scoring, and selective investigations. Non-operative management is stepwise and multidisciplinary, combining lifestyle modification, pelvic floor therapy, oral agents and intravesical therapy. Available evidence suggests that symptom improvement is often modest but clinically meaningful in selected patients, supporting an individualized, phenotype-informed approach to care with realistic patient counselling. Conclusions: Bladder pain syndrome remains a chronic, multifaceted disorder with profound impact on quality of life, requiring clinicians to approach patients with empathy while recognising the physical, psychological, and social burden of the condition. Effective management requires early recognition, thoughtful phenotyping, exclusion of confusable conditions, and realistic expectation-setting within a multidisciplinary framework. For the general urologist, a structured and compassionate non-operative approach can improve symptom control, support shared decision-making, and help guide timely escalation when required.

Keywords: bladder pain syndrome; interstitial cystitis; chronic pelvic pain; phenotyping; diagnosis; conservative management; oral therapy; intravesical therapy; multidisciplinary care

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1. Introduction

Bladder pain syndrome (BPS), also known as bladder pain syndrome/interstitial cystitis (BPS/IC), defined by the International Continence Society (ICS) as chronic pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder, accompanied by at least one additional urinary symptom, such as persistent urgency or frequency, in the absence of identifiable confusable disease [1]. The diagnosis is clinical and requires exclusion of alternative causes of bladder pain, particularly urinary tract infection, malignancy, and other relevant pelvic pathology.

The epidemiology of BPS remains difficult to define because of heterogeneity in diagnostic criteria, symptom-based case definitions, and sampling methodology. In the United States, population-based estimates suggest that 2.7–6.5% of adult women may have symptoms consistent with BPS [2]. In the United Kingdom, prevalence has been estimated at 0.3–0.6% of the adult population based on cross-sectional and epidemiological data, although under-recognition and under-reporting are likely [3].

BPS is a chronic and often debilitating condition associated with substantial impairment in quality of life. Management is challenging because its pathophysiology remains incompletely understood, clinical phenotypes are heterogeneous, and treatment frequently requires a multimodal, individualized, and long-term approach. Symptom control may take months, and in some patients remains difficult despite sequential therapy.

This narrative review aims to provide a practical framework for the diagnosis and non-operative management of BPS in general urology practice, while also outlining the clinical circumstances in which referral to a specialist service should be considered.

2. Materials and Methods

This article was conducted as a narrative review of the contemporary literature on the diagnosis and non-operative management of bladder pain syndrome (BPS).

2.1. Search Strategy

A structured literature search was conducted in PubMed/MEDLINE, Embase, and Google Scholar to identify relevant English-language publications from January 2015 to December 2025. Selected landmark studies published before this period were also included where they were considered important to the current understanding of BPS/IC. Search terms included “bladder pain syndrome”, “painful bladder syndrome”, “interstitial cystitis”, “pathophysiology”, “diagnosis”, “conservative management”, “pharmacotherapy”, and “intravesical therapy”, combined using Boolean operators (AND/OR) as appropriate.

2.2. Inclusion and Exclusion Criteria

Included publications comprised randomized controlled trials, prospective and retrospective cohort studies, systematic reviews, and relevant clinical guidelines relating to the aetiology, diagnosis, phenotyping, and non-operative management of BPS. Exclusion criteria were case reports, conference abstracts without full-text availability, editorials without substantial clinical content, and non-English-language publications. Studies focused primarily on operative interventions were excluded.

2.3. Study Selection and Synthesis

Titles and abstracts identified through the literature search were screened for relevance by the first and second authors. Full-text articles were then reviewed where they appeared to address the pathophysiology, diagnosis, phenotyping, or non-operative management of bladder pain syndrome/interstitial cystitis. Given the heterogeneity of study design, patient populations, diagnostic definitions, and outcome reporting, the evidence was synthesized

narratively. Hence, formal independent dual screening, risk-of-bias assessment, and meta-analysis were not undertaken. Instead, study selection was performed collaboratively, with discussion between the first and second authors to determine clinical relevance and suitability for inclusion. Where uncertainty arose regarding the interpretation or inclusion of specific studies, this was resolved through discussion with the senior author.

The reviewed literature was grouped into three broad domains: pathophysiology, clinical evaluation and diagnosis, and non-operative management. Management strategies were further considered under conservative measures, oral pharmacotherapy, and intravesical therapies, with emphasis on their applicability to general urology practice.

3. Pathophysiology

The pathophysiology of bladder pain syndrome remains incompletely understood, and several interacting mechanisms have been proposed. Contemporary understanding increasingly recognises that BPS is not a single disease entity but a heterogeneous clinical syndrome comprising different phenotypes. A key distinction is between Hunner lesion BPS, which shows visible inflammatory lesions and is usually more bladder-centric, and non-Hunner BPS, which has less obvious inflammation and a more variable symptom profile [4,5].

Patients may also be phenotyped according to symptom distribution, bladder capacity, pelvic floor dysfunction, severity of pelvic pain, and the presence of extra-vesical pain syndromes. In practice, these phenotypes frequently overlap. Recognizing such heterogeneity is clinically important, as it may help explain variation in symptom burden, treatment response, and the need for multidisciplinary management [6].

Several mechanistic pathways have been implicated in the development and persistence of BPS, including urothelial barrier dysfunction, immune dysregulation, chronic inflammation, neural sensitization, pelvic floor dysfunction, and possible genetic or hormonal influences [7]. These mechanisms are unlikely to be mutually exclusive and probably interact in a complex manner to drive symptom generation and chronicity (Figure 1).

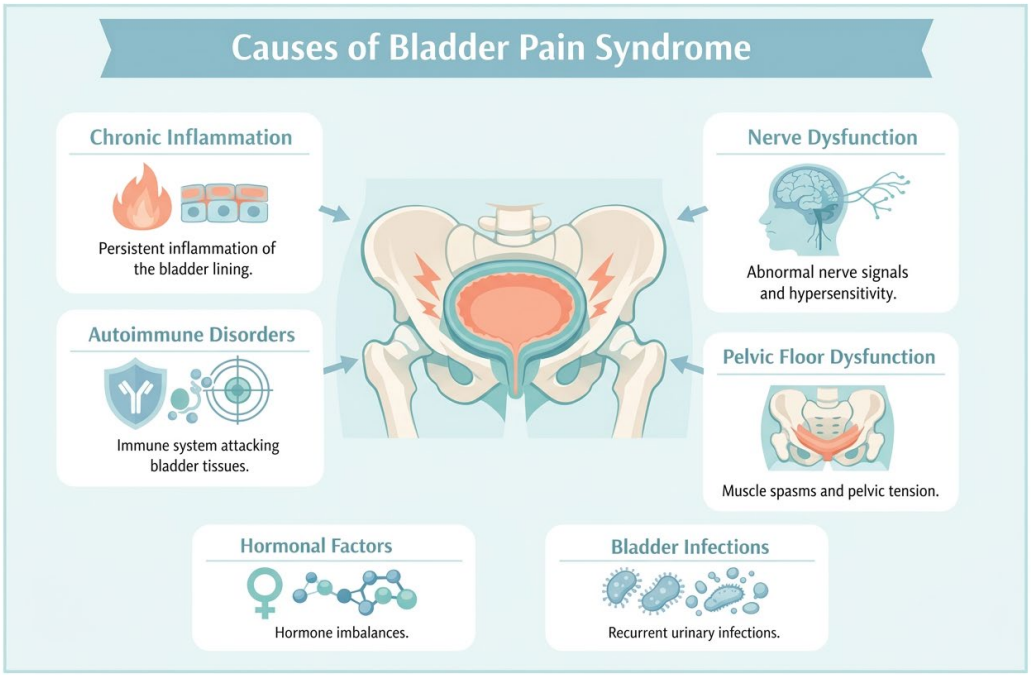


Figure 1. Causes of bladder pain syndrome.

3.1. Urothelial Dysfunction

Urothelial barrier dysfunction is one of the most widely proposed mechanisms in BPS. The urothelium normally provides a protective barrier between urinary solutes and the underlying bladder tissues, in part through the glycosaminoglycan (GAG) layer and associated mucosal defenses [7,8]. Disruption of this barrier may increase epithelial permeability, allowing urinary constituents, particularly potassium ions, to penetrate the bladder wall and trigger sensory irritation, inflammation, and pain [8,9]. This theory has also provided the rationale for intravesical and oral therapies aimed at restoring or protecting the bladder surface.

3.2. Immune Dysregulation

Immune-mediated mechanisms have also been implicated in BPS. Experimental and translational studies suggest that immune activation may contribute to urothelial injury and symptom persistence through upregulation of inflammatory pathways and infiltration of immune cells within the bladder wall [10]. Increased expression of pro-inflammatory mediators, including interleukin-1, interleukin-6, and tumour necrosis factor, has been reported in some studies, supporting the concept of an exaggerated local immune response [10–12]. Although the precise role of these pathways remains uncertain, they may represent potential targets for future phenotype-directed therapy.

3.3. Chronic Inflammation and Oxidative Stress

Chronic inflammation is likely to play an important role in at least a subset of patients with BPS. Histological studies have demonstrated inflammatory cell infiltration, including eosinophils, macrophages, and mast cells, within the bladder wall [13]. Oxidative stress may further contribute to tissue injury through the production of reactive oxygen species, which can impair normal urothelial repair, promote mast cell activation, and sustain inflammatory signaling [14]. These inflammatory and oxidative mechanisms may contribute both to ongoing pain and to progressive dysfunction of the bladder lining.

3.4. Neurological Mechanisms and Central Sensitisation

Neural sensitization is increasingly recognized as a key contributor to chronic pain in BPS. Persistent bladder inflammation or irritation may stimulate afferent C-fibres and promote the release of neuropeptides such as substance P and nerve growth factor, leading to vasodilation, mast cell activation, and amplification of local inflammatory responses [15–17]. Over time, repeated afferent stimulation may lower the threshold for pain signaling at both peripheral and central levels, resulting in exaggerated pain perception during bladder filling and contributing to symptom persistence even when overt bladder pathology is limited. This may partly explain why some patients develop widespread pain and respond poorly to purely bladder-directed treatments.

3.5. Genetic Predisposition

Although environmental and acquired factors are likely to be important in BPS/IC, some evidence suggests a possible genetic contribution. Familial clustering and twin studies have raised the possibility of heritable susceptibility, although this remains incompletely defined and is unlikely to account for disease expression in isolation [18].

3.6. Pelvic Floor Dysfunction

Pelvic floor dysfunction is increasingly recognized as an important contributor to symptom generation in BPS. Hypertonicity, myofascial trigger points, and altered neuromuscular control of the pelvic floor may contribute to pelvic pain, dyspareunia, urinary urgency, and voiding dysfunction [19,20]. Comparative studies have demonstrated higher

resting pelvic floor electromyographic activity and a greater burden of trigger points in patients with BPS than in controls [21]. In some patients, pelvic floor dysfunction may represent a secondary response to chronic pain, anxiety, and guarding behaviour; however, it may also become an independent driver of persistent symptoms through viscero-somatic convergence and central sensitization [20,22,23].

3.7. Hormonal Factors

Hormonal influences may contribute to symptom fluctuation in some patients. Variations in oestrogen and progesterone levels have been proposed to affect bladder sensitivity, autonomic regulation, and pain perception. Observational evidence suggests an association between dysmenorrhoea, chronic pelvic pain syndromes, and increased bladder sensitivity, raising the possibility of shared mechanisms of central sensitisation. In clinical practice, cyclical symptom exacerbation should also prompt consideration of coexisting gynaecological conditions such as endometriosis or adenomyosis, which may contribute to the overall pain phenotype [20,24].

Taken together, these mechanisms support the concept of BPS as a heterogeneous pain syndrome and help explain why successful management often depends on phenotyping, multimodal treatment, and selective multidisciplinary input.

4. Clinical Evaluation

4.1. History and Symptom Assessment

Clinical evaluation of suspected BPS should be comprehensive at the initial outpatient assessment, with the aim of characterising symptoms, identifying potential phenotypes, and excluding confusable pathology (Figure 2).

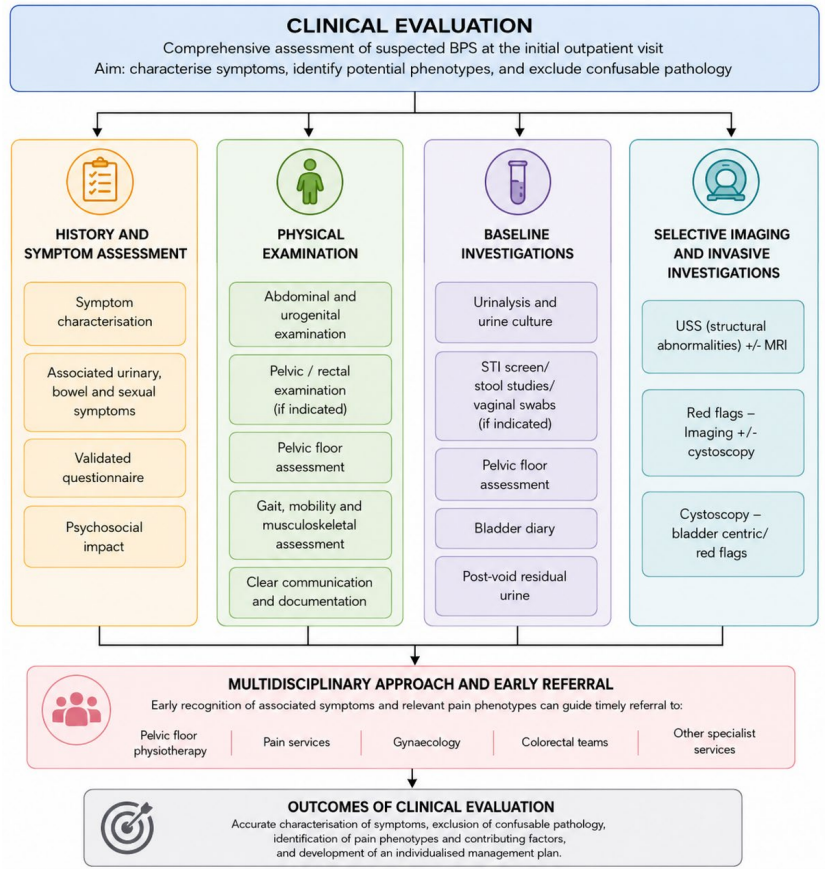


Figure 2. Clinical Evaluation in Bladder Pain Syndrome.

A detailed history should document the duration, location, character, and severity of pain, as well as associated lower urinary tract symptoms such as frequency, urgency, and the relationship of pain to bladder filling and emptying. It is also important to assess bowel symptoms, neuropathic features such as burning pain, hypersensitivity or paraesthesia, and, where relevant, menstrual history, dyspareunia in women, and ejaculatory pain in men.

Symptom questionnaires may be useful both at baseline and during follow-up to quantify symptom burden and monitor response to treatment. Commonly used instruments include the O'Leary–Sant Interstitial Cystitis Symptom and Problem Index, the Pelvic Pain and Urgency/Frequency (PUF) scale, and the Wisconsin Interstitial Cystitis Scale [25–27].

An often under-recognised aspect of assessment is the psychosocial impact of symptoms. Anxiety, low mood, sleep disturbance, sexual dysfunction, reduced mobility, and impaired daily functioning may all influence symptom perception and treatment response. Although several validated tools are available to assess these domains, at a minimum, the evaluating urologist should seek a general understanding of psychological distress and functional impairment [28,29].

4.2. Physical Examination

Physical examination should be undertaken with clear explanation, informed consent, and awareness that it may exacerbate pain. Abdominal and focused urogenital examination are essential. Depending on the clinical context, pelvic examination, rectal examination, and assessment for pelvic floor tenderness, myofascial trigger points, and relevant neurological features may be indicated. Examination should also consider gait, mobility, and evidence of musculoskeletal or neuropathic contributors to pain. The European Association of Urology (EAU) guidance emphasises the importance of clear communication, empathy, and documentation of any patient concerns related to the examination process [29].

4.3. Baseline Investigations

As BPS remains a diagnosis of exclusion, the initial clinical evaluation should also consider alternative causes of pelvic or bladder pain, including urinary tract infection, malignancy, ketamine-associated cystitis, anatomical abnormalities, gynaecological pathology, colorectal disease, and neurological conditions.

Baseline investigations typically include urinalysis and urine culture to exclude infection and haematuria-associated pathology. Even where dipstick testing is negative, urine culture may still be helpful in selected patients to identify low-level bacteriuria that may be clinically relevant. Additional tests such as vaginal swabs, sexually transmitted infection screening, or stool studies may be appropriate when suggested by associated symptoms. Measurement of post-void residual urine can also be useful where incomplete bladder emptying or voiding dysfunction is suspected. A bladder diary is also useful in understanding functional capacity and symptom patterns.

Assessing nerve root involvement and location of triggers may be quite challenging, and this is where a multi-disciplinary approach with a referral to the pain team and pelvic floor physiotherapist can give a deeper insight.

4.4. Selective Imaging and Invasive Investigations

Imaging has a selective rather than routine role. Ultrasonography is often normal in BPS, but may be useful to exclude structural abnormalities or other pathology. Magnetic resonance imaging is not routinely required but may be considered in carefully selected cases where the history or examination raises concern for alternative gynaecological, neurological, or neoplastic causes of pain [30]. Features such as visible haematuria, recurrent culture-positive infection, significant voiding dysfunction, unexplained weight loss, or new-onset severe symptoms should prompt careful evaluation for alternative pathology.

Cystoscopy, with or without bladder biopsy, should be considered selectively, particularly in patients with bladder-centric symptoms, haematuria, atypical features, or where Hunner lesions, carcinoma in situ, tuberculosis, or other bladder pathology are suspected [29,31]. In some cases, cystoscopy may also help assess functional bladder capacity under anaesthesia.

Additional specialist investigations, such as diagnostic laparoscopy or lower gastrointestinal endoscopy, may be warranted when the symptom profile suggests gynaecological or colorectal pathology. Early recognition of associated symptoms and relevant pain phenotypes can help guide timely referral to pelvic floor physiotherapy, pain services, gynaecology, colorectal teams, or other specialist services as appropriate.

5. Principles of Management

Management of BPS requires a holistic, patient-centred, and phenotype-informed approach, with active patient involvement throughout the course of care. Practical phenotyping in the clinic helps the general urologist move beyond a one-size-fits-all approach and tailor first-line treatment to the dominant pain pattern. For instance, bladder-centric pain that changes with filling of the bladder would benefit from an early cystoscopy. A reduced functional bladder capacity supports a more bladder-focused phenotype, while pelvic floor tenderness points toward myofascial dysfunction, making pelvic floor physiotherapy and manual therapy more appropriate. Pelvic pain that is not exactly related to stretching of the bladder suggests a broader chronic pain syndrome, so central pain modulation, analgesic review, and multidisciplinary support become more important. Table 1 summarizes the various non-operative interventions and the phenotypes that they may be most useful in, while recognizing that most patients require multimodal and ongoing management.

Table 1. Summary of Phenotype-directed Non-Operative Management of BPS.

Intervention	Best Phenotype	Expected Benefit Magnitude	Key Adverse Effects	Typical Trial Duration Before Stopping
Trigger avoidance, education, bladder training	All phenotypes, especially central sensitisation and mixed pain	Low to modest, but often clinically useful as a foundation	Minimal; may worsen anxiety if over-restrictive	Long term
Pelvic floor physiotherapy/ myofascial release	Pelvic floor predominant, dyspareunia, trigger points	Moderate in selected patients with pelvic floor tenderness	Temporary soreness, symptom flare if too aggressive	Long term
Amitriptyline/nortriptyline	Central sensitisation, sleep disturbance, widespread pain	Moderate; one of the more consistently helpful oral agents	Sedation, dry mouth, constipation	8–12 weeks at tolerated dose
Hydroxyzine/cimetidine	Mast-cell/allergic features, some non-Hunner disease	Low to modest; benefit inconsistent	Sedation, anticholinergic effects	6–8 weeks
Pentosan polysulfate sodium	Hunner, bladder-centric symptoms, suspected GAG defect	Modest; may help pain/urgency in a subset	GI upset, rare pigmentary maculopathy	3–6 months
Gabapentinoids/duloxetine/ cyclobenzaprine	Central sensitisation, neuropathic pain, mixed pain phenotypes	Low to modest; mostly phenotype-directed off-label use	Drowsiness, dizziness, weight gain, drug interactions	4–8 weeks
Intravesical lidocaine ± heparin	Bladder-centric pain, flare management	Short-term high benefit for pain relief; often rapid	Catheter discomfort, transient dysuria, UTI risk	1–4 instillations or 2–6 weeks
Hyaluronic acid/chondroitin sulfate	bladder-centric symptoms	Low to modest; may improve pain, urgency, capacity	Catheter discomfort, UTI risk	6–12 weeks, often monthly maintenance
DMSO alone and in combination	Bladder-predominant	Moderate in selected patients; one of the better-supported instillations	Garlic odour, irritation, catheter discomfort	6–8 weekly instillations

Table 1. *Cont.*

Intervention	Best Phenotype	Expected Benefit Magnitude	Key Adverse Effects	Typical Trial Duration Before Stopping
Botulinum toxin A	Refractory bladder-centric, reduced capacity, often non-Hunner	Moderate; useful in selected refractory cases	Urinary retention, increased PVR, need for catheterisation	Stop after 1 treatment cycle if no benefit by 4–12 weeks
PRP, EMDA, shock-wave therapy, hyperbaric oxygen	Investigational; usually refractory, mixed phenotypes	Uncertain; promising but evidence remains limited	Protocol-dependent; often catheter or procedure burden	Trial only in specialist setting; stop after short protocol if no early response

Establishing realistic expectations at an early stage and defining individualized treatment goals are central to effective management. Figure 3 summarises the key management principles and the range of outcomes that should be discussed during the initial consultation.

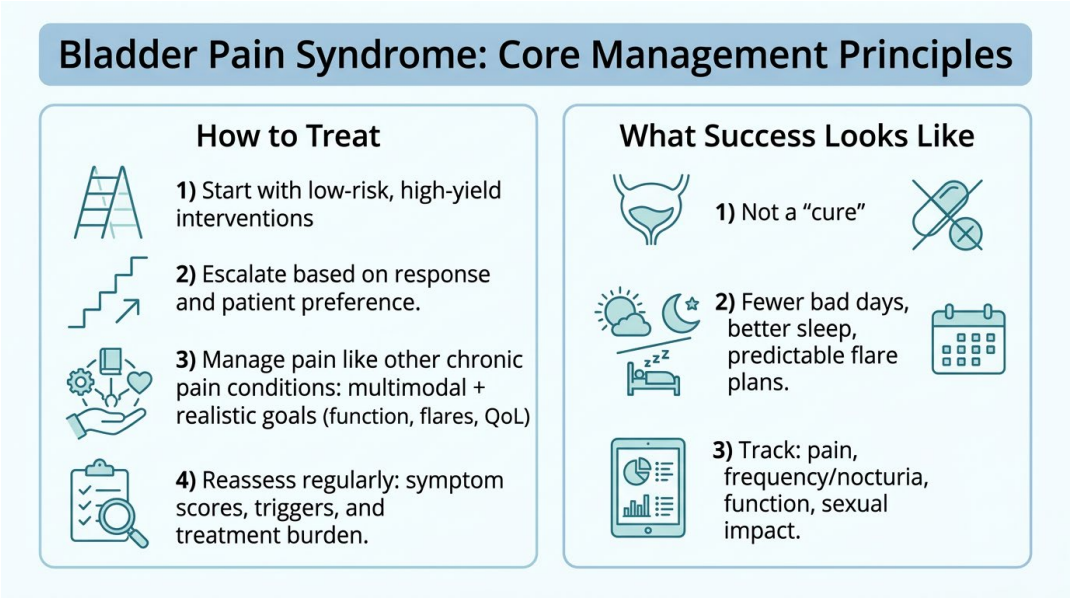


Figure 3. Core principles of management of bladder pain syndrome.

Given the heterogeneity of BPS/IC, multidisciplinary care is frequently required. Depending on symptom profile and associated comorbidities, input may be needed from urology, gynaecology, colorectal or functional gastroenterology services, pelvic floor physiotherapy, pain medicine, and psychology. Although this review focuses primarily on the role of the urologist in non-operative management, early collaboration with other specialties is often essential to support a coordinated and individualized treatment pathway (Figure 4).

5.1. Recognising Triggers

Initial management of BPS should focus on conservative, non-invasive strategies aimed at minimising symptom exacerbation. A key component of this approach is the identification and avoidance of individualised triggers. Careful clinical history-taking can help identify precipitating factors, which commonly include dietary bladder irritants such as caffeine, alcohol, citrus fruits, artificial sweeteners, and spicy foods. These may aggravate symptoms by further irritating a vulnerable urothelium [32].

Additional triggers may include urinary tract infection, concentrated urine related to inadequate fluid intake, prolonged sitting, tight-fitting clothing, sexual intercourse, and constipation. As BPS often coexists with other chronic pain and central sensitisation

syndromes, psychosocial stressors, anxiety, and other mental health factors should also be considered, as they may amplify pain perception and symptom burden. Education and support are therefore essential in helping patients identify relevant triggers and develop practical strategies for symptom self-management.

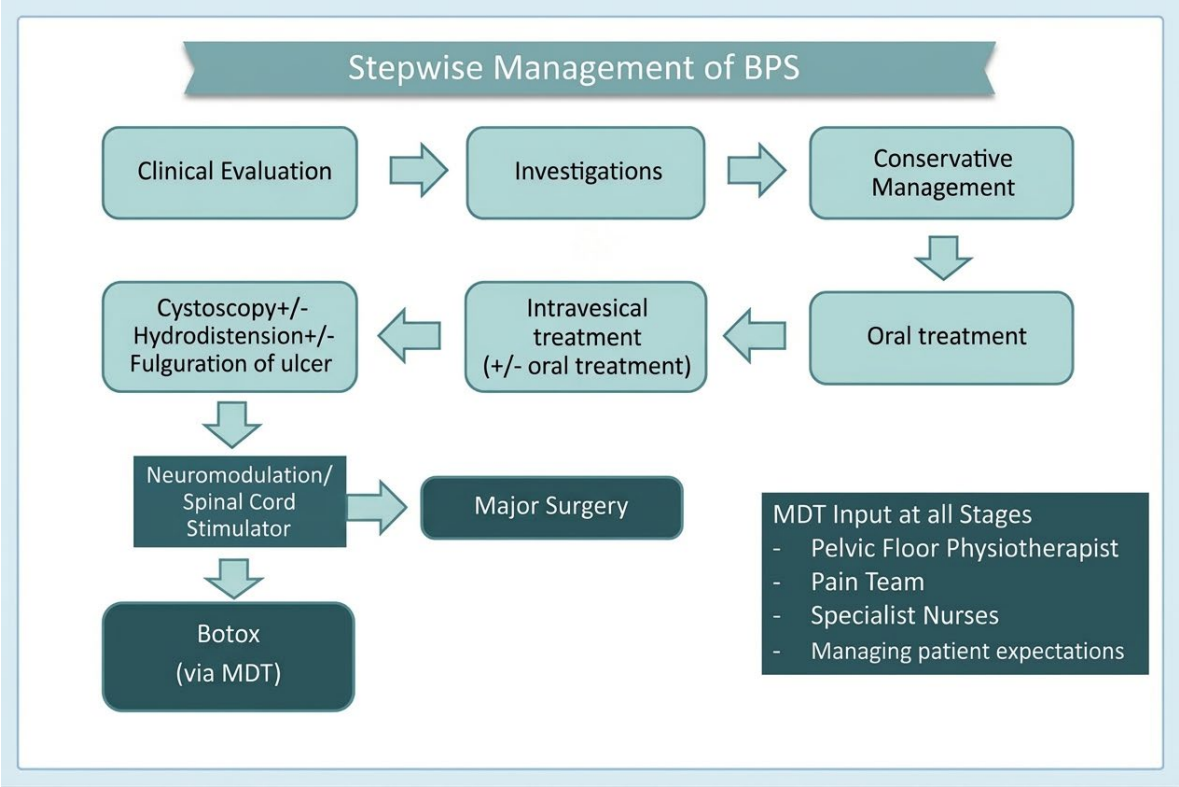


Figure 4. Flow diagram for stepwise management of bladder pain syndrome.

5.2. Physical Therapy

Pelvic floor muscle relaxation and specialized manual physical therapy are important components of non-operative management in BPS, particularly in patients with coexisting pelvic floor dysfunction. In contrast to conventional pelvic floor rehabilitation aimed at strengthening, the therapeutic focus in this setting is on down-training, muscle relaxation, and reduction in myofascial pain. Strengthening exercises such as Kegel exercises may worsen pelvic floor overactivity and exacerbate pain in selected patients. Manual therapy may include internal and external myofascial release targeting trigger points within the levator ani, obturator internus, and related abdominal and hip musculature [33,34].

Biofeedback may provide additional benefit by helping patients recognize and modify maladaptive pelvic floor tension. Through electromyographic (EMG) or similar feedback techniques, patients may learn to reduce resting muscle tone and improve voluntary relaxation of chronically guarded muscles [35].

Supportive adjuncts such as local heat or cold application, bladder training with urge suppression techniques, and stress management strategies may also be incorporated within an individualized multidisciplinary treatment plan [29].

5.3. Oral Pharmacotherapy

5.3.1. Analgesics

Simple analgesics, including non-steroidal anti-inflammatory drugs (NSAIDs), may have a limited role in the management of acute symptom flares and can provide short-term relief of suprapubic pain. However, they do not address the underlying pathophysio-

logical mechanisms of BPS, and their long-term benefit is limited. Current national and international guidance generally discourages the use of chronic opioid therapy in BPS because of the risks of dependence, opioid-induced hyperalgesia, worsening central sensitisation, and gastrointestinal adverse effects, including constipation, which may itself exacerbate symptoms [36,37]. Where pain remains severe and refractory, opioid use should be considered only in carefully selected cases within a specialist multidisciplinary pain management setting.

5.3.2. Tricyclic Antidepressants

Amitriptyline is among the most commonly used oral agents in BPS and has shown benefit in several randomised trials and meta-analyses, particularly for pain, urgency, and symptom burden reduction. Its therapeutic effects are likely to be multifactorial, including modulation of central pain sensitization, antihistaminic effects, and anticholinergic activity [38,39]. Long-term follow-up data from Van Ophoven et al. suggested sustained symptom improvement in a proportion of patients at a mean follow-up of 19 months [39].

In clinical practice, amitriptyline is often limited by adverse effects, including sedation, dry mouth, and constipation. As constipation itself may trigger symptom exacerbation, anticipatory management of bowel symptoms is important when prescribing tricyclic antidepressants. In selected patients, nortriptyline may be better tolerated because of a more favourable side-effect profile.

5.3.3. Antihistamines

Antihistamines have been used in BPS on the basis of the proposed role of mast cell activation and histamine-mediated inflammation in symptom generation. By blocking H1 receptors, these agents may reduce the release of inflammatory mediators that contribute to bladder afferent sensitization. Hydroxyzine has been evaluated in comparative studies, including a large multicentre trial by Sant et al., although evidence for consistent clinical benefit remains limited and not all studies have demonstrated statistically significant improvement over comparator therapies [40]. As such, antihistamines may be considered in selected patients, particularly where there is a suspected allergic or mast cell-mediated component, but their role remains less well established than that of amitriptyline.

5.3.4. Pentosan Polysulphate Sodium

Pentosan polysulfate sodium (PPS) is the only FDA-approved oral therapy for BPS that is directed at the proposed urothelial barrier defect. Its mechanism is thought to involve restoration or protection of the glycosaminoglycan (GAG) layer of the bladder urothelium, thereby reducing permeability to urinary irritants, although the precise mechanism remains incompletely defined. Evidence from systematic reviews suggests that PPS may provide modest improvement in self-reported pain, urgency, and global symptom scores in some patients compared with placebo, although results across studies have been variable and superiority over other treatment options has not been consistently demonstrated [41].

Interpretation of the evidence is complicated by heterogeneity in study design, treatment duration, patient phenotype, and outcome measures, and further high-quality trials would be valuable in clarifying its role [40–42]. The recommended dose is 100 mg orally three times daily. It is generally well tolerated, but increasing recognition of pigmentary maculopathy as a rare though potentially irreversible long-term adverse effect has important implications for counselling and follow-up, particularly in patients receiving prolonged treatment over several years. This would involve a baseline retinal examination and ophthalmology review for patients with underlying visual conditions before commencing PPS, with a further review at 6 months and annual review. In patients with no ophthalmological co-morbidities, the first ophthalmological review would be at 6 months after commencing

PPS if the patient continues to see benefit from the drug, and review at 5 years with safety netting advice to immediately stop the medication if they experience any symptoms [42,43].

5.3.5. Other Oral Agents

Other off-label oral agents include gabapentinoids, duloxetine, cimetidine, and muscle relaxants such as cyclobenzaprine, especially in patients with neuropathic pain, central sensitization, or pelvic floor dysfunction [29]. Their use is generally tailored to individual symptom phenotype and associated comorbidity, as robust evidence specific to BPS remains limited.

Anticholinergic agents and β3-adrenoceptor agonists may also have a role in patients with prominent storage lower urinary tract symptoms, such as urgency, daytime frequency, and nocturia. While these therapies do not target the underlying pain mechanisms of BPS, they may improve urinary symptoms in some patients.

It is important to assess the response of the medications and continue only if there is a meaningful symptomatic response. This is to avoid the risk of polypharmacy and cumulative anticholinergic burden [44].

5.4. Intravesical Therapy

Intravesical therapy involves the direct instillation of pharmacological agents into the bladder via a catheter. This approach allows high local drug concentrations to be delivered directly to the urothelium while minimising systemic adverse effects. Intravesical treatments are particularly relevant in patients with bladder-centric symptoms or where oral therapies have provided insufficient benefit. However, repeated catheterization may be uncomfortable in this patient group, and treatment burden, access, and the risk of urinary tract infection may limit acceptability for some patients.

5.4.1. Lidocaine

Lidocaine is a local anaesthetic used intravesically to reduce pain by blocking sensory nerve activity within the dysfunctional bladder urothelium and sub-urothelial tissues. It is commonly alkalinised with sodium bicarbonate to increase the non-ionised fraction and enhance urothelial penetration [45]. In addition to its local anaesthetic effect, lidocaine may also exert anti-inflammatory actions, including mast cell stabilization and reduced leukocyte activation, which may help explain symptom benefit beyond its short half-life.

Lidocaine is often administered in combination with heparin. In a randomized controlled trial, Parsons et al. reported rapid symptom relief with intravesical lidocaine and heparin, with greater immediate benefit observed at higher lidocaine doses (94% immediate relief with 160 mg vs. 75% at 80 mg) [46]. In practice, it is most often used for short-term symptomatic relief, particularly during exacerbations.

5.4.2. Heparin

Heparin is a polysaccharide that has been used intravesically as a glycosaminoglycan (GAG) replenishment therapy. It is thought to support restoration of the urothelial barrier, reduce inflammation, and limit diffusion of urinary solutes such as potassium, which may otherwise contribute to afferent nerve sensitization. Typical regimens range from 10,000 to 40,000 IU in 40–50 mL of sterile water or saline, administered weekly over several weeks to months, with a dwell time of approximately 15–60 min.

Evidence supporting heparin monotherapy remains limited, and greater benefit has generally been reported when it is used in combination with lidocaine rather than as a single agent [46,47].

5.4.3. Glycosaminoglycan Substitutes

Intravesical glycosaminoglycan substitutes such as hyaluronic acid (HA) and chondroitin sulphate (CS) are used with the aim of restoring the defective urothelial barrier, reducing inflammation, and modulating mast cell activity. Commercial preparations combining both agents are available, including formulations such as hyaluronic acid 50 mg with chondroitin sulphate 800 mg.

Porru et al. reported symptomatic improvement in urgency and pain, together with increased bladder capacity, following a 6-month course of intravesical HA/CS therapy in a small cohort of patients with BPS [48]. Long-term data remain limited, although Cervigni et al. described sustained improvement in bladder function and quality of life over 3 years in a small group of patients with refractory symptoms [49]. Overall, these agents appear promising, but the evidence base remains limited by small study size and heterogeneity, and the benefits are phenotype-dependent.

5.4.4. Dimethyl Sulfoxide (DMSO)

Dimethyl sulfoxide (DMSO) is an intravesical agent with proposed anti-inflammatory, analgesic, and muscle-relaxant properties. It is typically administered weekly and has been used in selected patients with bladder-predominant symptoms. A Japanese phase 3 randomised controlled trial published in 2019 reported significant improvement in pain and voiding symptoms with DMSO compared with placebo [50].

More recently, DMSO has been studied in combination regimens. In a 2023 randomised trial, Moss et al. reported greater symptom improvement with DMSO plus triamcinolone than with a comparator regimen containing bupivacaine, triamcinolone, and heparin (63% vs. 43%) [51]. Despite its potential efficacy, one practical limitation to wider use is its characteristic garlic-like odour, which some patients find unpleasant and which may affect tolerability.

Overall, intravesical therapies may be most useful in selected patients with bladder-centric symptoms, particularly where conservative measures and oral pharmacotherapy have provided insufficient benefit.

5.5. Emerging Novel Therapies

Emerging therapies for bladder pain syndrome include intravesical platelet-rich plasma, liposomal or sustained-release drug systems, EMDA, hyperbaric oxygen, and extracorporeal shock-wave therapy. These therapies are promising but remain investigational, with uncertain durability, heterogeneous protocols, limited comparative data, and subjective short-term outcomes, so they should be considered experimental rather than standard care [29,52].

5.6. When to Refer for Specialist Management

Referral to a specialist functional urologist or multidisciplinary pelvic pain service should be considered in patients with persistent or severe symptoms despite appropriately delivered conservative treatment, pelvic floor physical therapy, oral pharmacotherapy, and intravesical therapy. Specialist referral may also be appropriate earlier in the course of care where there is Hunner lesion disease, marked bladder-centred pain with reduced capacity, significant voiding dysfunction, diagnostic uncertainty, complex comorbid pelvic pain syndromes, or substantial psychological distress.

At this stage, further management may include specialist consideration of additional procedural or minimally invasive therapies, including bladder-directed injections, neuromodulation, or other escalation strategies, within a multidisciplinary framework. Major

reconstructive or ablative surgical interventions should be reserved for carefully selected patients with severe refractory disease and are beyond the scope of this review.

6. What This Review Adds to Current Practice

This review highlights a practical shift in the contemporary management of BPS, from a purely bladder-centred and exclusion-based model toward a phenotype-informed, multidisciplinary approach that is more relevant to general urology practice. It emphasises the importance of identifying pelvic floor dysfunction, psychosocial burden, and features of central sensitisation alongside bladder symptoms, as these factors may significantly influence treatment response and referral needs. While emerging work on biomarkers, advanced imaging, and artificial intelligence may improve phenotyping and diagnostic precision in the future, these approaches are not yet part of routine general urology practice. At present, careful clinical assessment and individualised non-operative management remain the cornerstone of care.

7. Limitations of This Review

This review is limited by its narrative design and reliance on studies with heterogeneous diagnostic criteria, phenotypes, and outcome measures, which makes direct comparison difficult. Much of the available evidence is based on small, short-term studies, and high-quality randomized data are lacking for several interventions. In addition, most included studies used subjective symptom scores, so measurement bias and placebo effects may influence the findings. As no formal risk-of-bias assessment was performed, the conclusions should be interpreted as a clinically oriented synthesis rather than a systematic evaluation of treatment efficacy.

8. Conclusions

Bladder pain syndrome is a complex, chronic, and heterogeneous condition characterised by pelvic pain and urinary symptoms that can have a substantial impact on quality of life. Effective care begins with an empathetic and validating clinical approach that acknowledges the physical, psychological, and social burden of the condition. Careful history-taking and focused clinical evaluation help identify relevant phenotypes and exclude alternative diagnoses. Management relies on realistic expectation-setting, multidisciplinary input, and active patient engagement throughout the treatment pathway. For the general urologist, a structured, compassionate, and phenotype-informed non-operative approach provides the best foundation for symptom control, shared decision-making, and timely referral when specialist input is required.

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