

Bladder Pain Syndrome (BPS): A Comprehensive Review of Treatment Strategies and Management Approaches

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Abstract: Bladder pain Syndrome presents a multifaceted challenge in contemporary urological practice, marked by LUTS, negative behavioural, sexual, or emotional experiences, and the potential for sexual dysfunction. We meticulously explored the existing literature of conservative, non-invasive and invasive interventions, aiming to provide clinicians with a nuanced understanding of available options for comprehensive BPS management. We delve into the effectiveness and safety profiles from behavioural approaches through lifestyle changes and physical therapy, to oral or intravesical medications, until the definitive surgical treatment. The best option evaluated is the involvement of a multidisciplinary team, including urologists, urotherapists, gynaecologists, pain specialists, primary care physicians and psychologists, educating those patients regarding the condition and its chronic course and tailoring the perfect treatment for each person. Despite this, BPS remains a challenge for urologists. Indeed, our objective is to contribute to the evolving landscape of BPS management, fostering informed decision-making and personalized care for individuals grappling with this challenging condition.

Keywords: bladder pain syndrome, interstitial cystitis, lower urinary tract symptoms, females, continence, therapy, conservative treatment

Introduction

Bladder pain syndrome (BPS) is a chronic and debilitating condition with unknown aetiology that can be difficult to treat due to its frequent links to negative behavioural, sexual, or emotional experiences, as well as symptoms related to lower urinary tract (LUTS) and sexual dysfunction.¹ Exact epidemiological data is challenging to define, considering that in population based studies, disease assessment is done by symptom-based questionnaires. However, estimates from the USA data suggest a prevalence of 100–300 per 100,000 women, with a male prevalence of 10–20% of the female estimate.²

Regarding the terminology, definition, and diagnostic criteria for BPS, there has been considerable debate in the urological landscape. The International Continence Society's 2002 standardization report referred to it as “painful bladder syndrome/interstitial cystitis”, describing it as suprapubic pain associated with bladder filling, alongside increased day-time and night-time frequency, in the absence of identifiable urinary infection or other clear pathology.³ In contrast, the European Society for the Study of Interstitial Cystitis (ESSIC) refers to it as “bladder pain syndrome” characterized by chronic pelvic pain, pressure, or discomfort thought to be linked to the bladder, accompanied by at least one LUTS such as a persistent urge to void or urinary frequency.⁴

To date, there is no consensus on the best approach from conservative to surgical treatments or combination of more therapies, highlighting the need for further research to evaluate the effectiveness and safety of these procedures. This

review aims to assess and explore the evidence of the existing literature on treatment options or recommendations and pragmatic frameworks for management of BPS in terms of efficacy and safety.

Diagnosis

The diagnosis of BPS is primarily one of exclusion, and various criteria have been proposed. Firstly, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) introduced initial criteria in 1987 based on clinical symptoms and pathological findings from bladder biopsies,⁵ refined further in 1988. However, only about 40% of clinically diagnosed BPS patients meet these criteria, which are thus primarily used in research.⁶ The ESSIC criteria focus more on symptom-based diagnosis, where cystoscopic evaluation is not mandatory but can help with further classification. Indeed, the use of validated questionnaires, as Interstitial cystitis symptom index (ICSI), Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS), Pain, Urgency, Frequency (PUF) score, International Consultation on Incontinence Questionnaires (ICIQs) such as Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) and Lower Urinary Tract Symptoms Quality of Life Module (ICIQ-LUTSqol), are beneficial for the characterization of the disease.⁷ In clinical practice (Figure 1), most urologists diagnose the syndrome based on personal history, risk factors and symptoms after excluding other conditions and may use urine tests (urine culture and/or urinary cytology with 3 samples), cystoscopic assessment with bladder mapping and/or hydrodistension under light general anesthesia to evaluate physiological changes.⁸ Additionally, the diagnostic path should include radiological examinations such as ultrasound to exclude urinary dilation or pathological findings, CT scan abdomen and pelvic MRI as second level examinations.⁹ Consequently, the management of BPS has a multifaceted approach from conservative to pharmacological to minimally invasive treatments to definitive surgical treatment, ideally involving a multidisciplinary team, including urologists, specialist nurses (urotherapists), and gynaecologists with an extended network to involve pain specialists, primary care physicians (PCPs), and psychologists,^{10,11} educating those patients regarding the condition and its chronic course.

Conservative Treatments

Nearly half of all patients with Bladder Pain Syndrome (BPS) experience significant symptom improvement or resolution over time, even without consistent follow-up or new treatments. Figure 2 shows subsequent levels of treatment for BPS patients, starting from conservative and behavioral approaches, that should form the cornerstone of BPS management, given their risk-free nature and relatively low cost, making them accessible and sustainable options for long-term management.¹² These strategies include lifestyle modifications such as stress reduction techniques, dietary changes (eg, reducing caffeine, spicy foods, and alcohol), smoking cessation, and physical therapies like timed voiding, bladder training, and pelvic floor.¹³ Studies have shown that these interventions can lead to significant improvements in urinary frequency, voiding intervals, and overall

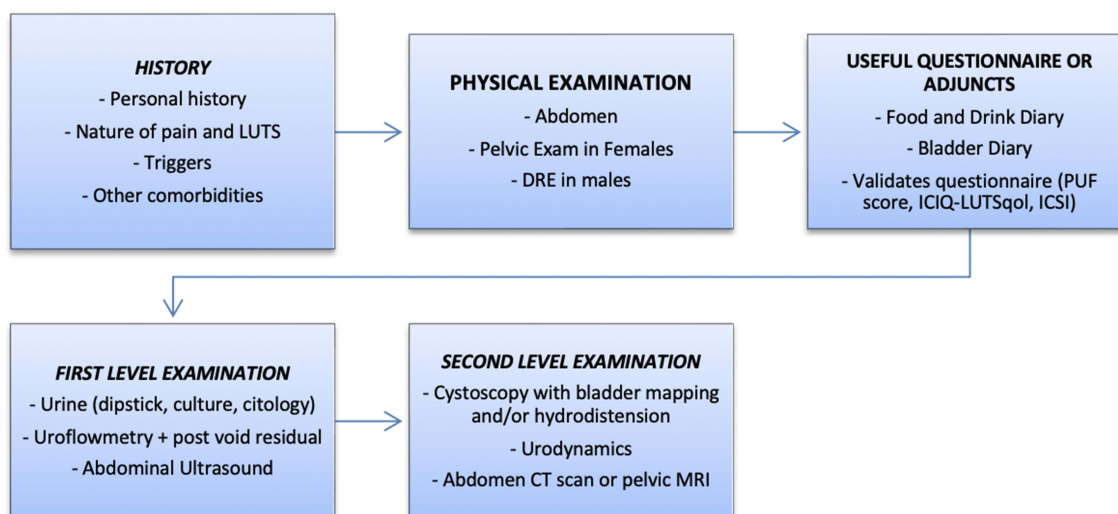


Figure 1 BPS diagnostic flow-chart.

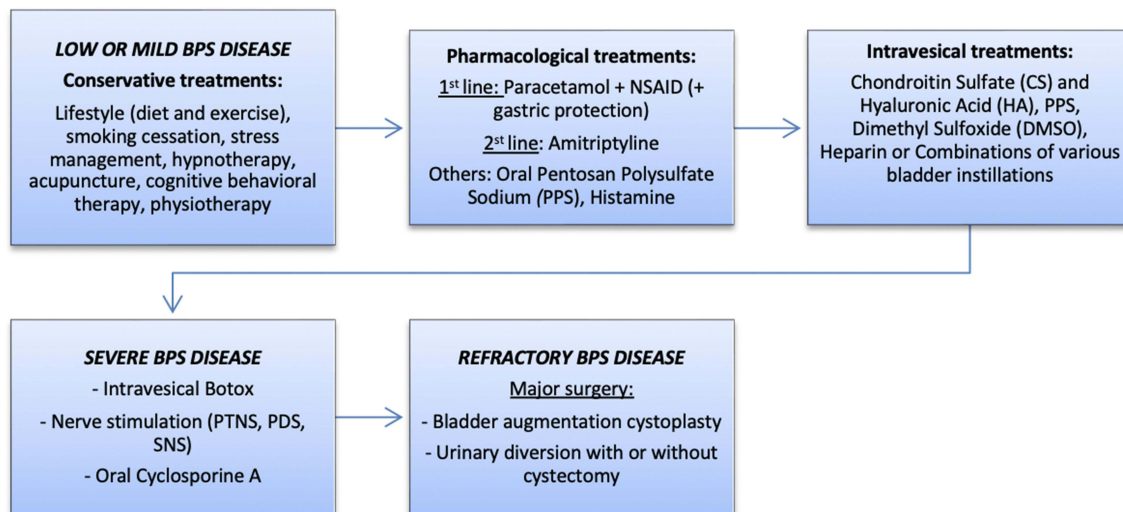


Figure 2 Pathway of treatment from low/mild to severe/refractory BPS disease.

symptom relief, with some reports indicating that up to 88% of patients experience symptom improvement. Furthermore, a 12-week program focusing on controlled fluid intake and pelvic floor exercises significantly increased the time between voids and decreased urinary frequency.¹³

Given the importance of personalized care, the early involvement of a urotherapist is crucial in BPS treatment. This approach allows for a thorough exploration of the patient's history and the establishment of realistic expectations.¹⁴ Physiotherapy, particularly myofascial release therapy for patients with pelvic floor dysfunction or those exhibiting trigger points, has demonstrated up to 94% improvement in symptom scores.¹⁵ Additionally, a randomized trial showed that 59% of women with BPS who received myofascial physical therapy reported significant improvements compared to just 26% of those receiving general therapeutic massage.¹⁶

The role of education and support in managing BPS cannot be overstated. Involving the patient's partner or family during consultations can provide emotional support and enhance the patient's ability to cope with the disease. Given the prevalence of misleading information online, providing clear and accurate educational materials is essential. The EAU Patient Information (EAU PI) working group, supported by EAU guidelines,¹⁷ delivers high-quality video content about various clinical conditions and surgical procedures in patient-friendly language.^{18,19} Support groups also play a valuable role, offering community, understanding, and information on alternative therapies such as acupuncture,²⁰ reflexology, hypnotherapy, or talking therapies like cognitive behavioral therapy (CBT), which can be facilitated by the primary care physician. This comprehensive, multidisciplinary approach to BPS management, grounded in conservative and behavioral strategies, offers a promising path to improving patients' quality of life.

Pharmacological Treatments

When conservative management fails to alleviate symptoms in patients with BPS, the next step typically involves oral pharmacotherapy. Various oral agents have been utilized in BPS treatment, with guidelines offering differing levels of recommendation. While pharmacological therapies are commonly employed, they frequently have variable success rates and are associated with high discontinuation due to minimal long-term efficacy. The choice of treatment often depends on the individual patient's response and tolerance to these medications.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are often the first-line analgesics, reducing pain and inflammation associated with BPS. They are usually combined with paracetamol and regular gastric protection.¹⁷ In clinical practice, combining conservative measures with pharmacotherapy may often serve as the most effective first-line therapy.

Tricyclic Antidepressants (TCAs)

Amitriptyline, a tricyclic antidepressant not officially approved for BPS, is commonly used to manage neuropathic pain, working by blocking the reuptake of serotonin and noradrenaline, which helps alleviate pain and symptoms related to storage LUTS. In randomized trials, it has shown significant symptom improvement in patients compared to placebo, particularly when patients could tolerate doses of 50 mg or higher.²¹ However, side effects like blurred vision, dry mouth, and constipation can limit its use (92% of patients reported at least one side effect), with fewer than half of patients able to tolerate higher doses.²²

Pentosan Polysulphate Sodium (PPS)

PPS is a semi-synthetic drug used both orally and via bladder instillation for BPS. While licensed for BPS, evidence of its efficacy is mixed. Some studies show significant improvements in pain, urgency, and frequency compared to placebo,²³ but recent trials have reported inconsistent results.^{24,25} Long-term use (median 186 months) has been associated with adverse events, particularly pigmentary maculopathy, in up to 16% of patients which may limit its future use.²⁶

Antihistamines

These medications, such as cimetidine and hydroxyzine, are thought to mitigate bladder symptoms by preventing the effects of histamine release from mast cells. Cimetidine, with its action on a similar peptidergic pathway in the bladder, has shown some efficacy in reducing suprapubic pain and nocturia comparing to placebo,²⁷ but evidence for antihistamines overall is limited. Hydroxyzine, especially when combined with PPS than PPS alone, may offer some benefit (40% vs 28%), but more large-scale studies are needed.²⁸

Cyclosporin a (CyA)

An immunosuppressive drug traditionally used in transplant recipients, CyA is emerging as a treatment for refractory BPS. It has shown greater efficacy than PPS in improving symptoms like urinary frequency and pain scores, particularly in patients with Hunner lesions,²⁹ although 94% of patients in the CyA group had high level of adverse events, including nephrotoxicity, hypertension, and immunosuppression.³⁰ For these reasons, it requires administration by specialists with experience in its use and is reserved as a last-line treatment for severe cases.

Intravesical Treatment

A variety of intravesical therapies are employed globally for BPS, including chondroitin sulfate (CS), hyaluronic acid (HA), heparin, lidocaine, pentosan polysulfate sodium (PPS), and dimethyl sulfoxide (DMSO). These therapies generally aim to restore the glycosaminoglycan (GAG) layer in the bladder, which helps protect the bladder lining. The choice of therapy often depends on local regulations and practice guidelines. Overall, while these therapies provide options for managing BPS, the variability in response and side effects underscores the need for ongoing research to optimize treatment strategies and improve patient outcomes.

Chondroitin Sulfate (CS) and Hyaluronic Acid (HA)

CS and HA, Glycosaminoglycan (GAG) Layer Treatments are frequently used in Europe, typically administered once a week for six weeks, followed by monthly maintenance. These treatments can be used individually or combined (iAluRil®). Intravesical HA has demonstrated efficacy rates of 66–87% in observational studies.^{31,32} Similarly, intravesical CS has shown promising efficacy rates of around 60%.³³ Common side effects include pain, irritation, and urinary tract infections (UTIs). Despite their frequent use, there is no definitive evidence favoring one over the other in terms of overall effectiveness.

Pentosan Polysulfate Sodium (PPS)

Pentosan polysulfate sodium (PPS) can be administered either orally or intravesically, showing variable effectiveness. Studies report a moderate efficacy rate of 40–62% for PPS compared to placebo, and combination therapies involving both intravesical and oral PPS appear to be more effective than oral PPS alone.³⁴ Additionally, recent reports indicate that intravesical PPS is a safe and effective option, particularly when considering adverse events like pigmentary maculopathy and visual disturbances, which are more commonly associated with oral administration, which could impact its long-term utility.

Dimethyl Sulfoxide (DMSO)

DMSO is FDA-approved for interstitial cystitis and recommended by the European Association of Urology¹⁷ for BPS. Although its exact mechanism is not fully understood, it is believed to reduce inflammation and relax bladder muscles.³⁵ DMSO is typically administered as a 50% solution once a week for six weeks via a temporary catheter, with additional courses and monthly maintenance if needed. Clinical studies show significant improvements in both subjective symptoms (53% vs 18% in placebo) and objective urodynamic measures (93% vs 35% in placebo).³⁶ However, side effects such as headache and dizziness are common, with 21.8% of patients requiring additional oral medication for symptom management.³⁷

Others Intravesical Treatments or Combinations

Intravesical heparin (40,000 IU) is often combined with anaesthetics like lidocaine (8 mL, 1% or 2%) or sodium bicarbonate (3 mL 8.4%). This combination has shown short-term success rates of 56–73% in cohort studies and provides relief for acute symptoms, though standalone studies are limited.^{38,39} Intravesical lidocaine, especially when combined with sodium bicarbonate, is recommended for short-term relief of acute symptoms.⁴⁰

Intravesical “cocktails”, which combine various agents such as GAG-layer therapies, anaesthetics, and steroids, are used to manage severe symptoms, though evidence for their efficacy mainly comes from small cohort studies.⁴¹ Recent reports combined:

- 8 mL 2% lidocaine, 4 mL 8.4% NaHCO₃, 20000IU heparin⁴²
- 50 mL 0.5% bupivacaine, 50 mL 8.4% NaHCO₃ (8.4%), 100 mg hydrocortisone, 10000IU heparin, 80 mg gentamicin⁴³
- 5 mL 4% lidocaine followed by 5 mL 8.4% NaHCO₃⁴⁰

Minimally Invasive Treatments

Minimally invasive procedures like bladder hydrodistension, intravesical botulinum toxin A injections, platelet rich plasma, neuromodulations etc. are recommended by the EAU guidelines,¹⁷ although the supporting evidence is weak.

Hydrodistension

Hydrodistension is a long-standing technique used both for diagnosis and treatment. More in detail, irrigation was performed under gravity with a pressure of 100 cm until it stopped, and hydrodistension was maintained for 2 minutes. The urologist applied digital pressure against the urethra to prevent irrigant leakage around the cystoscope. After draining the bladder, the hydrodistension was repeated.⁴⁴ A systematic review reported validated rates of 56% in 2–3 months with an acute exacerbation of symptoms in 9% of patients.⁴⁵ Additionally, comparing patients undergoing versus not undergoing hydrodistension, the first group reported most suprapubic pain/pressure, vaginal pain, dyspareunia and ejaculatory pain. Therefore, its efficacy remains under debate due to variability in techniques, complications and study outcomes. When combined with the transurethral destruction or fulguration of Hunner lesions, show high success rates in symptom relief with 40% reporting more than 3 years long-term efficacy.⁴⁶ However, the majority required often multiple interventions for sustained efficacy.⁴⁷

Botulinum Toxin Type a (BTT-A)

The function of BTT-A is related to reducing BPS symptoms through the inhibition of neurotransmitter release in the bladder’s sub-urothelial layer, thereby decreasing sensitivity and modulating detrusor contractility.⁴⁸ It is particularly effective for patients unresponsive to standard intravesical treatments.⁴⁹ Administered typically as a 100-unit dose via cystoscopy, injecting at approximately 10–20 sites, followed by careful monitoring and dose adjustments based on individual responses. Patients must be thoroughly informed about the risks, including the possibility of urinary retention and the potential need for self-catheterization. The effect of BTT-A was explored alone⁵⁰ and against placebo.⁴⁹ While compared with placebo (normal saline), the larger decreases in VAS scores were recorded in patients who received BTT-

A injections in comparison to normal saline (2.6 vs 0.9 $P=0.021$). Moreover, in combination with hydrodistension showed a global response assessment (GRA) of 72% versus 48% in the cisto-hydrodistention alone group ($P<0.05$) at 3 months.⁴⁸ Aforementioned comparative study indicate that BTT-A provides higher success rates and greater improvements in pain scores and bladder capacity compared to hydrodistension alone, with the average length of the effect of BTT-A of 5.4 months.

Platelet Rich Plasma

Transurethral suburothelial injections of PRP deliver growth factors and cytokines that support tissue healing, modulate inflammation, and reduce hypoxia-induced apoptosis in urothelial cells. Studies show multiple injections significantly improved symptoms in 70% of IC/BPS patients, though standardized PRP preparation protocols and a definitive understanding of its therapeutic mechanisms are still lacking. Further research is needed to determine optimal dosages, injection frequencies, and the long-term efficacy of PRP therapy for bladder disorders.^{51,52}

Neuromodulation

Neuromodulation, including different options, such as transcutaneous electrical nerve stimulation (TENS), percutaneous tibial nerve stimulation (PTNS), and sacral nerve stimulation (SNS), offers a conservative yet potentially invasive approach to managing bladder conditions. TENS, a non-invasive method, can be self-administered at home, while more invasive techniques like PTNS, pudendal nerve stimulation (PNS), and SNS are typically considered for advanced treatment stages⁵³ (PMID: 28458478). For patients with refractory bladder pain syndrome (BPS), particularly those with Hunner lesions, sacral neuromodulation (SNM) has shown promising outcomes. This procedure, which involves permanent implantation following a successful test phase, has demonstrated significant long-term efficacy in reducing pelvic pain, frequency, nocturia, and urgency, with success rates up to 80%.^{2,54} In some cases, pudendal nerve stimulation has proven even more effective than sacral nerve stimulation, especially in increasing voided volume and alleviating symptoms (59% vs 44%, $P=0.05$).⁵⁵ Patients must be well-informed about potential adverse effects, such as infections. However, the need for device revision or permanent implants due to poor outcomes is a consideration, with limited evidence.

Surgical Treatments

Patients who have exhausted all other treatment options and continue to experience severe symptoms that significantly affect their quality of life, surgery may be considered as a last resort. However, this decision requires careful patient counselling due to the high risks associated with surgery, including complications such as infection, bowel obstruction, ureteric stricture, and stoma problems, as well as the potential impact on sexual function, body image, and lifestyle. Patients must understand that surgery does not guarantee pain relief and that they may be trading one set of problems for another.⁵⁶ Surgical options include bladder augmentation cystoplasty or urinary diversion with or without cystectomy, and the choice between an ileal conduit or a continent urinary diversion depends on factors like patient preference, previous surgeries or radiotherapy.⁵⁷ There is ongoing debate about whether the bladder should be left in place if a diversion is performed, as some evidence suggests that simply preventing the bladder from storing urine can lead to satisfactory symptom improvement. However, persistent issues like pyocystitis (reported in 3.3% to 67% of cases) may still occur.⁵⁸

Studies show mixed outcomes based on the presence of Hunner lesions. Indeed, research showed as patients with non-Hunner BPS were less likely to benefit from reconstructive procedures, then those with the Hunner subtype of BPS, that were pain-free following surgery in 82% of cases.⁵⁹ A recent systematic review of 448 BPS patients undergoing radical surgery reported that 77% experienced symptomatic improvement, with the better clinical response observed in those who underwent total cystectomy with orthotopic neobladder formation. Despite these results, a significant proportion of patients (23%) did not have improvement, with considerable morbidity (26.5%) and mortality (1.3%). Given the variable outcomes and high risks, major surgical intervention should be reserved for the most severe cases, particularly in patients with Hunner lesions and small bladder capacity and should be approached with caution. There is a need for prospective randomised studies to answer questions regarding patient selection and optimal surgical approach.⁵⁶

Emerging Treatments

BPS/IC is a complex condition with an unclear aetiology, driving ongoing research into new treatments. Current efforts focus on understanding the disease's pathology, the microbiome, and identifying biomarkers to better classify and treat patients. These emerging therapies offer hope, but larger, long-term studies are required to validate their efficacy and safety in treating BPS/IC. Several novel therapies are showing promise in early trials:

- Phosphodiesterase-5 Inhibitors (PDE5-i): a low dose Sildenafil (25 mg) at 3 months' follow-up improved symptoms in 63% of patients, with associated improvements in urodynamic bladder capacity and no serious adverse events,⁶⁰ but further studies are needed to confirm these results.
- Monoclonal Antibodies: Adalimumab and tanezumab have shown potential, with tanezumab particularly improving pain scores in a small trial, though adverse effects like paraesthesia and headaches were noted.^{61,62}
- Cannabinoids: Known for their analgesic properties, cannabinoids have shown promising results in case studies,⁶³ but more research is required.
- Enhanced Intravesical Drug Delivery: New methods such as liposomes, reverse thermal gelation hydrogel, and the lidocaine-releasing intravesical system (LiRIS) are being tested to improve drug delivery within the bladder, with early trials showing potential benefits.^{64,65} Chuang and Kuo investigated liposomal formulated botulinum toxin A (lipotoxin) for the treatment of IC/BPS, but the results were negative. Lipotoxin did not demonstrate a positive proof of concept compared to onabotulinumtoxinA or placebo. However, a single intravesical instillation of lipotoxin was associated with a reduction in interstitial cystitis/bladder pain syndrome symptoms compared to baseline in patients with moderate to severe BPS.⁶⁶
- Hyperbaric Oxygen Therapy (HBOT): HBOT has shown promise in small studies, especially for patients who have not responded to other treatments, by increasing oxygen delivery to hypoxic urothelial tissues of the bladder, thereby stimulating healthy granulation and angiogenesis.⁶⁷
- Extracorporeal Shock-Wave Therapy (ESWT): ESWT reduced pain and inflammation in early trials. In detail, it was administered weekly for 4 weeks, reported success rates of 57% vs 19% in favour of ESWT.⁶⁸ However further research is necessary to confirm its effectiveness.

The Role of Urologists

Given the comprehensive approach advised for managing BPS, urologists are often in a prime position to spearhead the coordination of multidisciplinary efforts and build a local network of health professionals with specialized knowledge. This process is further streamlined when departments create a treatment protocol tailored to their available services. Appointing a lead urologist to drive and oversee these initiatives can be particularly effective. In cases where local treatment options, such as urinary diversion or nerve stimulation, are unavailable, establishing a referral pathway to a specialized centre is advisable. Maintaining strong communication with primary care providers is also crucial for updating referral guidelines, supporting patient care, and organizing educational programs.

Conclusions

BPS is a complex condition that poses significant challenges for clinicians. The absence of high-quality research, along with variability in study inclusion criteria and outcome measures, complicates the ability to draw definitive conclusions about treatment options. Effective management of BPS requires a multimodal approach tailored to each patient, emphasizing the symptoms that most impact their quality of life. Continued research into the underlying causes of BPS is essential for the development of more effective treatments, and several promising oral and intravesical therapies are currently emerging.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

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