Research Article

Pentosan polysulfate sodium for chronic bladder pain conditions: Real-world experiences from a tertiary care center

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Abstract

Background: Bladder pain syndrome (BPS) is a chronic condition characterized by pelvic pain and lower urinary tract symptoms. Pentosan polysulfate sodium (PPS) is the only oral therapy licensed in the United Kingdom (UK) for BPS; however, evidence on its effectiveness is inconsistent, with limited data for off-label use in ketamine- or radiation-induced cystitis. **Objective:** This study evaluates real-world outcomes of PPS in patients with BPS and other chronic bladder pain at a UK tertiary center. **Methods:** A retrospective review included 42 patients prescribed PPS between 2020 and 2024 for BPS (n = 29), ketamine-induced cystitis (n = 9), or radiation/chemotherapy-induced cystitis (n = 4), excluding Bacillus Calmette–Guérin cystitis. Demographics, comorbidities, prior treatments, symptom severity, and treatment response were recorded. Changes in quality of life (QoL) and Interstitial Cystitis Symptom Index/Interstitial Cystitis Problem Index (ICSI/ICPI) scores were analyzed using the Wilcoxon signed-rank test and one-way analysis of variance. **Results:** The mean age was 49.7 years, and 81% were female, with a median follow-up of 15.3 months. All patients were severely symptomatic at baseline. Among those with follow-up data, 42.5% were asymptomatic, 25% mildly symptomatic, and 32.5% remained severely symptomatic. QoL improved significantly (Wilcoxon $Z = -4.71$, $p<0.001$). Greatest reductions in ICSI and ICPI scores were observed in BPS patients, with modest improvements in off-label groups. Side effects occurred in 14.2% of patients. PPS was associated with significant symptom improvement and acceptable tolerability in a treatment-refractory cohort, particularly in BPS. **Conclusion:** Modest benefits in ketamine- and radiation-induced cystitis suggest potential off-label utility, warranting further investigation. These findings support PPS use in selected cases, while accounting for placebo effects and disease heterogeneity.

Keywords: Pentosan polysulfate sodium, Bladder pain syndrome, Interstitial cystitis, Ketamine-induced cystitis, Radiation cystitis, Overactive bladder, Functional urology, Glycosaminoglycan therapy

1. Introduction

Chronic bladder pain is one of the most recognized causes of chronic pelvic pain syndrome. It can be caused by a spectrum of conditions with different etiologies. These include bladder pain syndrome (BPS) and chronic cystitis secondary to radiation or chemicals such as ketamine and Bacillus Calmette–Guérin (BCG).[1]

The definition of BPS varies between different societies and organizations. The European Association of Urology definition is very comprehensive and detailed. It is defined as the occurrence of persistent or recurrent pain perceived in the urinary bladder region, accompanied by at least one other symptom, such as pain worsening with bladder filling and daytime and/or nighttime urinary frequency in the absence of proven infection or other obvious local pathology. It is often associated with negative cognitive, behavioral, sexual, or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. Other terms that have been used include "interstitial cystitis," "painful bladder syndrome," and "PBS/IC" or "BPS/IC." These terms are no longer recommended.[2]

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Submitted: 10 August 2025; Revision received: 29 October 2025; Accepted: 10 November 2025; Published: 19 December 2025

How to cite this article: Jacob D, Hanna G, Ghonaimy A, *et al*. Pentosan polysulfate sodium for chronic bladder pain conditions: Real-world experiences from a tertiary care center. *Bladder.* 2026;13(1):e21200076. DOI: 10.14440/bladder.0247

The prevalence of the disease is generally underestimated. This is likely due to a lack of specific diagnostic criteria among different studies. According to the Third National Health and Nutrition Examination Survey of the United States of America (USA), the prevalence was 470/100,000 people, with a higher prevalence in women than men.[3] In 2019, the United Kingdom (UK) National Institute for Health and Care Excellence (NICE) projected that BPS impacted roughly 400,000 individuals in the UK.[4]

Although thoroughly investigated, the pathophysiology of BPS is still heterogeneous and incompletely understood. Proposed mechanisms include chronic inflammation, urothelial dysfunction (such as a deficit in the glycosaminoglycan [GAG] layer), autoimmune processes, neurogenic inflammation, and activation by neuropeptides, mast cell activation, and central sensitization. The literature suggests that an initial bladder insult (such as trauma, stress, allergies, toxin exposure, or acute bacterial infection) induces an inflammatory cascade that results in localized and systemic inflammation, leading to the emergence of clinical signs.[5,6]

Despite increasing awareness, the diagnosis and management of BPS remain challenging for clinicians. The overlap in symptomatology with other lower urinary tract and gynecological disorders often results in diagnostic delay, misclassification, and fragmented care. Furthermore, the unpredictable clinical course, fluctuating symptom severity, and psychosocial burden contribute to significant impairment in quality of life (QoL) and high healthcare utilization.

Like all other chronic pain conditions, chronic bladder pain requires a holistic, multimodal approach along with shared decision-making and active involvement of the patient.[2] A realistic discussion of the condition, management options, and the tendency for symptoms to remit is essential before starting any treatment, which aims primarily to improve QoL.[7]

It is generally agreed by all guidelines that management should begin with conservative options, such as dietary modifications, pelvic floor relaxation, biofeedback, and bladder retraining. If these are insufficient, oral pharmacologic therapy is considered, ranging from simple analgesics to oral neuromodulator agents. In cases where oral treatments fail to provide adequate symptom relief, second-line treatments such as oral pentosan polysulfate sodium (PPS) or intravesical instillations of local anesthetics, heparin, dimethyl sulfoxide, mixtures of lidocaine/sodium bicarbonate, or GAG replacement therapy can be offered.[2,7,8]

Cystoscopy with hydrodistension can provide both diagnostic and symptomatic benefit. In selected patients, intra-detrusor Botox, spinal cord stimulation, or fulguration/resection of Hunner's lesions can be offered before considering more invasive options such as urinary diversion (ileal conduit) with or without total cystectomy or substitution cystoplasty.[2]

In recent years, increasing attention has been directed toward the role of bladder surface repair and urothelial barrier restoration in the treatment of BPS. PPS, a synthetic heparin-like macromolecule, is thought to replenish the defective GAG layer of the bladder epithelium and exert anti-inflammatory effects. Although it remains the only oral therapy licensed for BPS in the UK, clinical evidence regarding its real-world effectiveness and safety remains limited and at times inconsistent. Moreover, there is growing interest in its off-label use for related conditions such as ketamine-associated and radiation-induced cystitis, where mucosal injury and inflammation share similar pathophysiological mechanisms.

The efficacy of oral PPS in patients with BPS has been shown in several randomized controlled trials when compared to a placebo. Our study aims to assess the safety and efficacy of this treatment in the management of chronic bladder pain conditions.

2. Materials and methods

2.1. Methods

A retrospective review was conducted in a tertiary care center to evaluate the use of PPS in patients with chronic bladder pain. The study included all urology patients prescribed PPS from the initiation of PPS prescribing at our institution, from January 2020 to December 2024. We included all living patients who were prescribed oral PPS after being diagnosed with chronic bladder pain conditions, including BPS, ketamine-induced cystitis (KIC), and radiation cystitis. None of our patients received the treatment for BCG cystitis. Patients were identified through hospital pharmacy dispensing records. Two patients were excluded due to loss to follow-up. Three of the patients who were started on PPS in our Trust passed away during the study period and were therefore excluded from our cohort. By including all consecutive patients treated at the institution, the study aimed to minimize selection bias and reflect pragmatic prescribing practices.

Data were extracted by two independent reviewers to enhance accuracy, and discrepancies were resolved by consensus. Where documentation was incomplete, patients were contacted through telephone to clarify follow-up status and symptom progression. The study population was intentionally broad to encompass not only classic BPS but also off-label indications such as KIC and radiation-induced cystitis, enabling subgroup comparison and exploratory evaluation of differential responses across etiologies.

The study was registered with the Trust's clinical audit department and did not require ethical approval due to its retrospective nature.

The dosing protocol for PPS followed institutional standards based on NICE guidance, typically 100 mg administered orally three times daily. Treatment duration varied according to clinical response, tolerability, and patient preference, with follow-up assessments conducted every 3–6 months. Adherence was assessed through pharmacy refill data and patient-reported continuation.

Data collection was performed through a detailed review of electronic medical records and outpatient clinic correspondence. The following variables were extracted: age, gender, past medical history, indication for PPS use, results of prior investigations, previous treatments, prior use of intravesical GAG therapy, whether PPS was used concurrently with GAG therapy, documentation of counseling regarding the risk of macular degeneration, ophthalmology referral status, treatment discontinuation, and any reported side effects.

The diagnosis of BPS was based on the European Society for the Study of Interstitial Cystitis criteria. Specifically, inclusion required chronic bladder-related pain with associated urinary symptoms persisting for more than 6 months, after exclusion of infection and other identifiable causes. All patients with BPS underwent cystoscopy to evaluate for Hunner lesions and rule out other pathologies. Urodynamics was not part of the routine diagnostic pathway and was selectively performed to assess detrusor overactivity or poor compliance. The QoL was assessed based on patient-reported outcome measures, including the Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI) questionnaires before and after treatment. A routine ophthalmology referral at 6 months was offered if the patient decided to continue treatment.

2.2. Statistical analysis

Descriptive statistics were used to summarize demographic and clinical data. Frequencies, means, medians, and ranges were reported where appropriate. Changes in patient-reported QoL were analyzed using the Wilcoxon signed-rank test for paired non-parametric data. Differences in symptom scores (ICSI and ICPI) across indications were assessed using one-way analysis of variance (ANOVA). Effect sizes were reported using eta squared (η^2). Statistical analyses were conducted using SPSS (IBM SPSS Statistics, USA), and significance was set at $p<0.05$. The primary outcome measures were patient-reported improvement in QoL and treatment continuation rates. Secondary outcomes included the incidence and nature of reported side effects.

3. Results

3.1. Patient demographics and baseline characteristics

The baseline characteristics are given in Table 1. The cohort was predominantly female (81%, *n*=34), with a mean age of 49.7 years (SD=19.0). The primary indication for treatment was BPS in 69% (*n* = 29) of patients, KIC in 21.4% (*n* = 9) of patients, and radiation-induced cystitis in 9.5% (*n* = 4) of patients (Table 2). Relevant comorbidities included a history of pelvic surgery in 31% (*n* = 13), mental health conditions in 26.2% (*n* = 11), endometriosis in 12% (*n* = 5), and fibromyalgia in 4.8% (*n* = 2). The median follow-up period was 15.3 months (range: 4.5–117.5).

Table 1. Baseline characteristics of the patients

Characteristic	Value
Total patients	42
Mean age (years)	49.7
Age range (years)	20–86
Female, *n* (%)	34 (81)
Male, *n* (%)	8 (19)
History of pelvic surgery, *n* (%)	13 (31)
Mental health conditions, *n* (%)	11 (26.2)
Endometriosis, *n* (%)	5 (12)
Fibromyalgia, *n* (%)	2 (4.8)
Median follow-up (months)	15.3

All patients had previously trialed conservative measures and oral analgesics. These included paracetamol in 100% (*n* = 42), oral opioid-based analgesics (co-codamol and codeine) in 95% (*n* = 40), non-steroidal anti-inflammatory drugs in 90% (*n* = 38), neuromodulatory pain killers (amitriptyline/pregabalin) in 38% (*n* = 16), and antimuscarinic solifenacin in 78% (*n* = 33). Intravesical GAG therapy was used in 40.5% (*n* = 17) of cases, and 26.2% (*n* = 11) underwent bladder hydrodistension. Intra-detrusor botulinum toxin injections were administered in 14.3% (*n* = 6). Radiological investigations were performed in 97.6% (*n* = 41) of patients, with ultrasound (81%) and computed tomography (42.9%) being the most common modalities. Magnetic resonance imaging was utilized in 19.0% of cases. Cystoscopic evaluation was performed in 100% (*n* = 42). In 5 out of the 27 patients (18.5%) with BPS who underwent cystoscopy, Hunner's ulcers were seen. Urodynamic studies were performed for 23.8% (*n* = 10) of patients due to predominant storage lower urinary tract symptoms. The previous investigations and treatments are listed in Table 2.

The median duration of treatment among responders was 10.5 months (inter-quartile range: 7–18), whereas non-responders discontinued therapy earlier (median: 4 months), usually due to perceived lack of benefit. Patients who continued treatment for at least 6 months had a higher likelihood of meaningful QoL improvement, suggesting a time-dependent therapeutic effect.

3.2. Subjective QoL

At baseline, all 42 patients reported themselves as being "severely symptomatic." Following treatment with PPS,

42.5% (n = 17) reported being "not symptomatic," 25% (n = 10) reported being "mildly symptomatic," and 32.5% (n = 13) remained "severely symptomatic." Two patients were lost to follow-up. A Wilcoxon signed-rank test showed a statistically significant improvement in QoL post-treatment ($Z = -4.71$, $p<0.001$), indicating that the treatment had a meaningful effect.

3.3. ICSI/ICPI scores

Symptom severity, as assessed by ICSI and ICPI scores, also demonstrated clinical improvement. Out of the 38 who responded, patients treated for BPS experienced the greatest mean reductions (ICSI: 6.04 ± 7.01; ICPI: 5.26 ± 6.42). Patients with KIC exhibited relatively more improvement (ICSI: 3.25 ± 2.32; ICPI: 2.13 ± 2.30) than those with radiation-induced cystitis (ICSI: 3.00 ± 3.00; ICPI: 1.33 ± 2.31). Two patients did not provide completed post-treatment questionnaires as they stopped the medication due to perceived side effects early in the course of treatment. Figure 1 shows the patients available for analysis. One-way ANOVA did not reveal statistically significant differences in symptom improvement between indication groups; however, the effect sizes (η^2 = 0.046 for ICSI and 0.074 for ICPI) suggest a small-to-moderate association between underlying diagnosis and treatment response (Table 3).

Table 2. Prior investigations and treatments

Investigation/Treatment	*n* (%)
Cystoscopy performed	42 (100)
Imaging performed	41 (97.6)
CT scan	18 (43)
MRI	8 (19)
Ultrasound	34 (81)
Urodynamic studies	10 (23.8)
Prior oral analgesia	42 (100)
Prior intravesical GAG therapy	17 (40.5)
Hydrodistension	11 (26.2)
Intra-detrusor Botox injection	6 (14.3)

Abbreviations: CT: Computed tomography; GAG: Glycosaminoglycan; MRI: Magnetic resonance imaging.

4. Discussion

PPS has been used since the 1940s for interstitial cystitis and in the European Union for preventing blood clots. In 1996, the Food and Drug Administration (FDA) approved pentosan for use as an oral medication for symptoms of BPS to relieve bladder pain and discomfort.[9] It was then approved by NICE for use in BPS patients in 2019.[10]

Pentosan is a heparin-like, sulfated polysaccharide that is thought to be structurally analogous to endogenous GAGs. Following oral administration, a modest fraction is systemically absorbed and subsequently excreted into the urine, allowing the compound to come into direct contact with the bladder urothelium. Within the bladder, PPS is postulated to adhere to the epithelial surface, functioning as a surrogate GAG. This interaction is thought to restore or reinforce the compromised GAG layer, thereby enhancing the bladder's protective barrier and decreasing mucosal permeability. Moreover, *in vitro* studies have demonstrated its anti-inflammatory action by inhibiting bladder mucosal and connective tissue mast cells and suppressing histamine release.[9]

The most common side effects of PPS include hair loss, diarrhea, gastrointestinal upset, and headache. Other side effects, such as thrombocytopenia, amblyopia, and macular degeneration, are serious but rare.[11] The available literature on the efficacy of PPS is inconsistent, with some trials showing no significant benefit over placebo and others demonstrating modest symptom improvement.[12]

The baseline characteristics (Table 1) highlight that most patients represented a treatment-refractory population who had failed multiple prior modalities. The high prevalence of psychiatric comorbidity reflects the psychosomatic burden often observed in chronic bladder pain.[13,14] Notably, the subset of radiation-induced cystitis patients tended to be older (mean: 61.4 years) compared to BPS (mean: 46.3 years) and

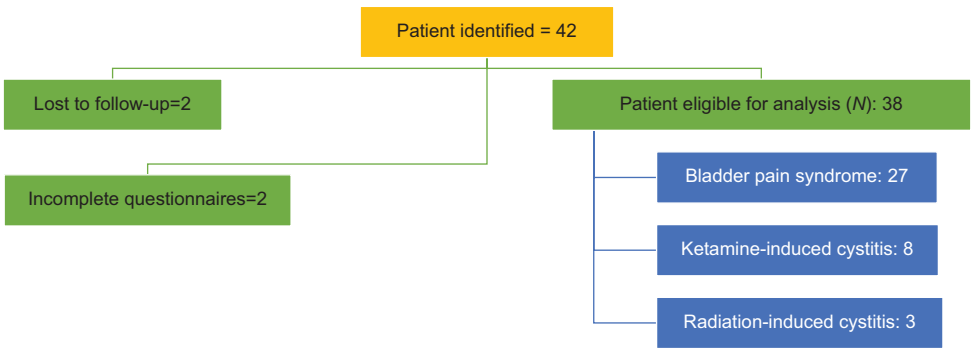

Figure 1. Patients available for analysis

Table 3. ICSI/ICPI scores

Indication	Mean Δ ICSI (SD)	Mean Δ ICPI (SD)	*n*	Effect size (η^2)
BPS	6.04 (±7.01)	5.26 (±6.42)	27	-
Ketamine cystitis	3.25 (±2.32)	2.13 (±2.30)	8	-
Radiation/Chemo cystitis	3.00 (±3.00)	1.33 (±2.31)	3	-
Total	5.21 (±6.15)	4.29 (±5.71)	38	0.046 (ICSI), 0.074 (ICPI)

Abbreviations: BPS: Bladder pain syndrome; ICPI: Interstitial Cystitis Problem Index; ICSI: Interstitial Cystitis Symptom Index.

KIC (mean: 41.7 years), consistent with the epidemiology of these conditions.

The systematic review and meta-analysis by Van Ophoven *et al*.,[15] which included six randomized placebo-controlled trials, reported similar results for symptomatic improvement compared to placebo. More recently, Kasyan *et al*.[16] conducted a randomized, placebo-controlled, double-blind multicenter trial on 90 patients and found statistically significant improvement in ICSI after treatment with PPS (p=0.014). These results align with our findings, which showed a statistically significant improvement in QoL after treatment (p<0.001) and notable symptomatic improvement evidenced by the ICSI and ICPI scores.

Unlike our data, the 2020 Cochrane network meta-analysis,[12] which included 81 randomized controlled trials, found no evidence that PPS improved or cured pain, frequency, or nocturia compared to placebo. The certainty of evidence was rated as low or very low due to small sample sizes and methodological heterogeneity in the included studies.

At our center, we used PPS off-label for treatment-refractory radiation-induced cystitis and KIC, as these conditions share key pathophysiological features with BPS, including urothelial injury, GAG layer disruption, and chronic inflammation. KIC is characterized by denudation of the urothelium, ulceration, and chronic inflammation, with clinical and histopathological features similar to interstitial cystitis/BPS.[1-5] PPS acts as a synthetic GAG analogue, forming a protective barrier over the bladder mucosa, which can mitigate the direct irritant effects of urinary ketamine metabolites and reduce neurogenic and immune-mediated inflammation.[17,18] Unsurprisingly, symptomatic improvement, as demonstrated by ICSI and ICPI, was greater with BPS than with KIC and better compared to radiation cases. Our data are consistent with limited case series suggesting that PPS may have utility in select off-label contexts.[11,19,20]

For KIC, available evidence is limited but suggests that adjunctive use of PPS may provide symptomatic relief in some patients. Both Chen *et al*.[19] and Shahani *et al*.[20] described cases where PPS was used as part of a multimodal approach, with some improvement in suprapubic pain and lower urinary tract symptoms, but outcomes were variable and dependent on disease severity.

The evidence is also limited for radiation cystitis. Sandhu *et al*.[11] reported a case series of 60 patients with hemorrhagic cystitis (mostly post-radiotherapy) treated with PPS, with a substantial proportion experiencing resolution or improvement of hematuria. However, this evidence is limited by the non-randomized nature of the study.

Regarding the safety profile in our patient cohort, we did not report any serious side effects. Although 14.2% (6/42) of cases reported only mild side effects, four patients discontinued treatment as a result. In 2000, Waters *et al*. retrospectively analyzed the safety of PPS in 27 patients and found that hair thinning, neurologic symptoms (paresthesia and visual disturbances), and diarrhea occurred in 11%, 7%, and 15% of patients, respectively.[21]

Grigoryan *et al*.[22] reported no serious side effects in the 13 clinical trials they included in their systematic review in 2022. In 2018, Pearce *et al*.,[23] from two eye centers in the USA, published findings about possible pigmentary maculopathy in six patients who had long-term treatment with PPS. This maculopathy may be due to the cumulative effect of macular degeneration, which is thought to be dose-related and can be suspected in patients who take more than 1,500 g of PPS.[22] Compared to this, in our cohort, although we did not have any serious side effects, gastrointestinal disturbances were seen in two patients, while rash, headache, lethargy, and weight gain were reported in one patient each.

Although macular degeneration was not reported in our patient cohort, we recognize the importance of having specific guidelines for the follow-up of patients on long-term PPS. The recommended surveillance protocol for macular degeneration in patients who have been treated with PPS includes obtaining a detailed ophthalmologic history before starting PPS, performing a comprehensive baseline retinal examination for those with preexisting ophthalmologic conditions, and conducting a retinal examination within 6 months of initiating PPS, followed by periodic retinal exams during ongoing therapy. If pigmentary changes in the retina develop, the risks and benefits of continued PPS should be reassessed, as these changes may be irreversible.[24] Expert consensus and recent cohort studies suggest that all patients initiating PPS should undergo a baseline ophthalmic examination, with repeat screening at 5 years and/or after reaching a cumulative exposure of 500 g, then annually thereafter, especially for those with prolonged or high-dose use.[25,26] Multimodal retinal imaging, including fundus autofluorescence, near-infrared reflectance, and optical coherence tomography, is recommended for early detection and monitoring of PPS-associated maculopathy.[27,28]

The findings of this study also have implications for prescribing practice and service delivery within the National Health Service (NHS), particularly in light of NICE Technology Appraisal TA610,[10] which formally endorsed PPS for BPS in adults with refractory symptoms. Despite this approval, PPS prescribing remains limited across the UK, with variations in local formulary inclusion and clinician familiarity potentially restricting patient access. Given the burden of chronic bladder pain on healthcare resources, earlier and evidence-based PPS use could potentially reduce reliance on more invasive, expensive, or resource-intensive interventions, such as intravesical therapy or cystectomy.

The cost of PPS in the UK for patients with BPS or interstitial cystitis is typically £120–£150 per month for a standard dose of 300 mg/day (100 mg 3 times daily). This price reflects the cost of branded and generic formulations available through the NHS and private pharmacies, and may vary depending on local procurement and dispensing fees. In the USA, the cost is approximately $500–$600 per month for a standard dose of 300 mg/day, based on average wholesale and retail pharmacy prices. This cost can vary depending on insurance coverage, pharmacy, and manufacturer discounts. PPS is the only FDA-approved oral agent for this indication in the USA, as noted by the American Urological Association guidelines.[24,29]

Our study is subject to several limitations inherent to its retrospective design, which restricts the ability to establish causality and introduces potential selection and information bias. The absence of a control group limits our ability to attribute improvements in symptoms solely to PPS, and the potential influence of placebo effects cannot be excluded. Although symptom burden was quantified using the ICSI and ICPI tools, these scores were collected retrospectively via telephone interviews, relying on patient recall of symptoms before and after starting PPS. This introduces a degree of recall bias and may affect the accuracy of symptom reporting. Moreover, it is important to note that PPS was used alongside the patients' other regular medication, raising the potential for confounding factors to influence results. Our sample size was relatively small, particularly within the off-label treatment subgroups, which may limit statistical power and generalizability of findings. The real-world tertiary center setting may also introduce referral bias, as patients with more severe or treatment-refractory disease are more likely to be represented, potentially overestimating or underestimating treatment benefit compared to community populations. However, to the best of our knowledge, this is the first case series reporting PPS outcomes in different subgroups of chronic bladder pain conditions. Finally, follow-up duration varied between patients, and long-term safety outcomes, particularly regarding ocular toxicity, may have been underreported.

Given the heterogeneous and multifactorial nature of chronic bladder pain, PPS should be viewed as part of a multimodal, patient-centered management strategy rather than a stand-alone treatment. In practice, shared decision-making is important when initiating PPS, as patients must be counseled regarding the expected time to onset of benefit, which is often several months, variable efficacy, and the importance of adherence and follow-up. Incorporating routine ophthalmologic monitoring, in line with emerging recommendations regarding maculopathy risk, can enhance patient safety and long-term treatment acceptability.

5. Conclusion

In our study, PPS provides clinically meaningful improvements in symptom severity and QoL in patients with chronic bladder pain conditions, particularly those with BPS. Modest improvements in off-label indications, such as KIC and radiation-induced cystitis, also warrant further investigation. While our results support the potential role of oral PPS as a therapeutic option for refractory bladder pain conditions, given the retrospective nature of the study, the observed associations should be interpreted cautiously. Prospective, randomized studies are required to confirm the therapeutic role of PPS in BPS, KIC, and radiation-induced cystitis.

Acknowledgments

The authors would like to thank Mr Tony Roberts, Clinical Effectiveness Advisor, Health Innovation North East and North Cumbria, for their invaluable assistance with the statistical analyses that contributed to this manuscript.

Funding

None.

Conflict of interest

The authors declare they have no competing interests

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Conceptualization: Dayan Jacob, Mehwash Nadeem, Ahmed Ghonaimy, George Hanna
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Ethics approval and consent to participate

This study was exempted from formal Research Ethics Committee review because it involved analysis of routinely collected clinical data with no intervention, no alteration to standard care, and no identifiable patient information. In accordance with our institutional governance policy, such service-evaluation/audit activities do not require ethics approval but do require registration and oversight within the Trust. The project was prospectively registered with the hospital's Clinical Governance/Audit Department. All data were anonymized before analysis, and no patient-level identifiers were accessible to the investigators at any stage.

Consent for publication

Not applicable.

Data availability statement

Data are available from the corresponding author on reasonable request.

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