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PHARMACOTHERAPIES AND DRUG DEVELOPMENT/AGENTS (ES ROVNER, SECTION EDITOR)

Pharmacotherapy for Interstitial Cystitis/Bladder Pain Syndrome

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Abstract

Purpose of Review Current literature regarding pharmacotherapy treatment strategies available for the management of interstitial cystitis/bladder pain syndrome (IC/BPS) will be addressed including oral, transdermal, and intravesical therapies. Pharmacotherapies with emerging data will be addressed, but the focus is on those treatments described by the AUA guidelines for IC/BPS.

Recent Findings While multiple pharmacotherapy options for the management of IC/BPS exist, the evidence for most medical therapies is not strong and frequently yields mixed results. It has been over two decades since a new medication has gained FDA approval for the treatment of IC/BPS. This has prompted clinicians to reassess the approach to evaluating patients with IC/BPS, leading to the advent of phenotype-directed multimodal therapy.

Summary Though national and international guidelines recommend a step-wise treatment algorithm beginning with the most conservative treatment options, the evidence for most therapies is mixed. Furthermore, recent randomized controlled trials of promising treatment options have yielded negative results, highlighting the importance of phenotype-directed classification to aid in the current management of IC/BPS and to allow for better research trial designs.

Keywords Interstitial cystitis · Bladder pain syndrome · Pentosan polysulfate · Pharmacotherapy

Introduction

Much of the difficulty surrounding treatment of interstitial cystitis or bladder pain syndrome (IC/BPS) centers on the difficulty in defining and diagnosing this clinical syndrome both for clinical and research purposes. Most recently, in 2009, the Society for Urodynamics and Female Urology (SUFU) defined interstitial cystitis/bladder pain syndrome (IC/BPS) as "an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms for more than six weeks duration, in the absence of infection or other identifiable causes." [1] This is the definition used by the American Urological Association (AUA), and as such, is the definition used in the scope of this review.

Treatment goals center around improving quality of life by improving symptoms and avoiding adverse events as there is no cure for IC/BPS. Regardless of the guideline referenced, there is consensus that treatment strategies should proceed in a stepwise fashion with more conservative therapies being utilized first. When first-line treatments including patient education, behavioral modifications, stress management, and physical therapy are insufficient, escalation to pharmacotherapy or procedural treatment options is appropriate [2••, 3, 4••, 5•]. Herein, we will describe the pharmacotherapeutic options available for the treatment of IC/BPS including oral therapy, intravesical therapy, and transdermal therapy and will discuss the treatment strategy of clinically characterizing patients based on symptoms to aid in phenotype-directed therapy. Our focus will be those medications highlighted in the AUA guidelines and will mention other medications discussed in other international guidelines. Table 1 provides a summary of each of the treatment options

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Table 1 Summary of pharmacotherapies for IC/BPS with guideline recommendation grade

Treatment	Suggested dose	AUA	ICI	CAU	EAU
Oral					
Pentosan polysulfate	100 mg TID	Option (B)	D	Option (D)	A
Amitriptyline	titrate to 25–100 mg QHS as tolerated	Option (B)	B	Option (B)	A
Cimetidine	300–400 mg BID	Option (B)	C	Option (B)	–
Hydroxyzine	10–75 mg QHS	Option (C)	D	Option (B)	A
Cyclosporine A	2–3 mg/kg divided BID	Option (C)	C	Option (C)	A
Gabapentin	100–400 mg TID	–	C	Option (C)	–
Phenazopyridine	100–200 mg TID PRN	–	–	–	
Intravesical					
DMSO	50 mL of 50% DMSO	Option (C)	B	Recommended (B)	A
Heparin	10,000–25,000 units	Option (C)	C	Recommended (C)	–
Lidocaine	200 mg alkalinized in 10 mL	Option (B)	C	Recommended (B)	–
Hyaluronic acid	40 mg in 50 mL	–	C	Option (C)	B
Chondroitin sulfate	20 mL of 2%	–	C	Option (D)	B
Pentosan polysulfate	200 mg in 30 mL saline	–	D	Option (C)	A

discussed including treatment dosage and grade of recommendation per the EAU, AUA, ICI, and CUA guidelines [1–3, 6].

Oral Therapies

The only oral therapy that is approved by the Food and Drug Administration (FDA) for the treatment of IC/BPS is pentosan polysulfate sodium (PPS). Several other categories of medication have been used in the management of ICS/BPS including analgesics, antidepressants, antihistamines, immunosuppressants, and glycosaminoglycans. While a few of these have been studied in randomized controlled trials, many of these therapies are used empirically.

Pentosan Polysulfate Sodium (PPS)

PPS is the most studied oral medication for treatment of IC/BPS with multiple randomized trials on over 500 patients. It is the only oral medication approved by the FDA for treatment of IC/BPS. PPS is a semisynthetic mucopolysaccharide that chemically and structurally resembles glycoaminoglycans [7]. Recommended dosage for IC/BPS is 100 mg three times daily. Though the mechanism of action in IC/BPS treatment is unknown, it is thought to replenish the damaged glycosaminoglycan layer overlying the urothelium and act as a buffer to control cell permeability thereby preventing irritating solutes in the urine from reaching the cells and to reduce the urothelial response to inflammatory stimuli by binding to inflammatory stimulants in the urine [8, 9].

Multiple randomized controlled trials of high quality that included PPS and placebo arms have yielded conflicting results. The first multicenter double-blind randomized placebo-controlled trial in 1987 evaluated 115 patients with IC. Patients were randomized to 200 mg twice daily PPS versus placebo over 4 months. While 56% of patients in the PPS arm versus 49% of patients in the placebo arm reported clinical improvement, this was not statistically significant [[10]] Two subsequent double-blind randomized controlled trials of 258 patients treated over 3 months with either 100 mg PPS three times daily versus placebo found 28–32% of patients in PPS arm reported a significant improvement in symptoms compared to 13–16% of placebo [11, 12]. In an underpowered study comparing PPS and hydroxyzine versus placebo, there was no statistically significant difference between PPS, hydroxyzine, or placebo; however, a nonsignificant trend was seen in symptom score improvement in the PPS group versus placebo (28% versus 13%) [13].

Recently, in 2015, Nickel et al. randomized 368 patients to 100 mg PPS once daily, 100 mg PPS three times daily, or placebo for 24 weeks without significant difference in symptom improvement noted in any group [14].

In a recent meta-analysis of the randomized placebo-controlled trials, a 12.4% difference in the responder rates between PPS-treated and placebo-treated patients were observed which was statistically significant. This meta-analysis found that treatment with PPS led to a statistically significant improvement in overall symptom response assessment, pain, and urgency [15•].

Recently, it should be noted that in a retrospective case series of 38 patients treated at a single Eye center with a diagnosis of IC/BPS on long-term PPS, six patients (16%) were diagnosed with pigmentary maculopathy after presenting with vision complaints. At presentation, all patients had been treated with PPS for a median of 186 months. While it is

premature to conclude that a definite causal relationship exists between PPS exposure and this maculopathy, it is a new condition that does not resemble other hereditary or acquired maculopathies and should be considered in counseling patients prior to beginning PPS or in those patients who have been on PPS for a prolonged period of time [16]. It is recommended that patients with a past or current history of PPS use who complain of vision changes be referred for comprehensive ophthalmic examination [17].

Overall, PPS appears to be beneficial in improving overall symptoms, pain and urgency in approximately one-third of patients with a diagnosis of IC/BPS after a 3- to 6-month treatment course. As noted, contemporary new research suggests that long-term treatment with PPS may be associated with irreversible vision loss and as such, this risk should be considered in contrast to its marginal benefits in the majority of patients.

Amitriptyline

Amitriptyline is a tricyclic antidepressant that acts via the blockage of acetylcholine receptors, inhibition of reuptake of released serotonin and norepinephrine, and blockage of histamine H1 receptors [18]. Its mechanism of action in IC/PBS is in part proposed to be through blocking H1-histaminergic receptors and stabilizing mast cells, thereby decreasing mast cell degranulation within the bladder wall [19]. It may also facilitate improved storage of urine through beta-adrenergic receptor stimulation. While its primary side effect is sedation, this too may have a therapeutic effect in patients with IC/BPS in improving nocturnal symptoms when taken at night. However, given its sedative effects, it is recommended to start the medication at a low dose of 10 mg taken before bed and titrate weekly to a target dose of 75–100 mg [20].

Amitriptyline for the management of IC/BPS has been studied in two randomized controlled trials and a handful of observational studies which demonstrate a benefit of amitriptyline over placebo. As such, this is a common medication to be initially prescribed to patients with IC/BPS. The first randomized controlled trial was of 50 patients who were given placebo or were allowed to self-titrate amitriptyline from 25 mg up to 100 mg. After 4 months, 63% of patients on amitriptyline reported clinically significant improvement in symptoms compared to 4% of the placebo group [21]. In a long-term observational follow-up study of patients who could tolerate amitriptyline, 46% of patients had excellent or good improvement in symptoms at a mean dose of 55 mg. Side effects occurred in 84% of patients. The most common side effects were dry mouth, weight gain, constipation, sedation, nausea, and blurred vision. The dropout rate was 31% due to nonresponse to treatment or side effects [22]. In the second randomized controlled trial, 271 treatment naive patients with IC were randomized to receive placebo or amitriptyline. Of the patients who tolerated a dose of at least 50 mg of amitriptyline daily, a significantly higher improvement in symptoms was noted compared to placebo (66% versus 47%) [23].

Cimetidine

It is hypothesized that an increase in mast cells in the bladder wall of patients with IC/BPS may lead to hypersensitivity reactions; as such, histamine receptor antagonists such as cimetidine have been studied in the treatment of IC/BPS. Cimetidine is a H2 histamine receptor antagonist and is thought to mitigate symptoms by decreasing activation of mast cells [24]. In 1987, it was used for the first time in the treatment of IC with reported improvement in symptoms [25]. Subsequently, three observational studies reported symptomatic relief of 57, 66, and 71% of patients with IC [26–28]. In a small randomized controlled trial, 34 patients were randomized to oral cimetidine 400 mg twice a day or placebo for 3 months. Those who received cimetidine reported statistically significant improvement in suprapubic pain and nocturia as well as overall improvement in symptom scores compared to placebo [29].

Hydroxyzine

Similar to cimetidine, hydroxyzine is a histamine H1 receptor antagonist with additional anticholinergic properties. Its additional anxiolytic and sedative properties make it a popular medication in the treatment of IC/BPS. Hydroxyzine was first reported to be beneficial in the management of IC/BPS in 1993 when Theoharides published three observational studies reporting a 40–55% improvement in symptoms in patients on hydroxyzine 50–75 mg, with increased benefit among patients who also had a history of allergies [30–32]. Conversely, the underpowered, pilot randomized controlled trial comparing PPS, hydroxyzine, and placebo reported no statistically significant difference in improvement between hydroxyzine and placebo (23% vs 13%) [13]. Side effects, though reported in up to 82% of patients, were mild and reported in similar proportion in the placebo group. These included fatigue, drowsiness, gastrointestinal disturbances, and pain [13].

Cyclosporine A

Cyclosporine A (CyA) is a calcineurin inhibitor that inhibits T cell activation by blocking the transcription of cytokines. It is widely used for its immunosuppressive properties in organ transplantation and the treatment of autoimmune disorders. Given the similarities and overlap of IC/BPS with autoimmune disorders, it was hypothesized

that CyA may have beneficial effects in this population. In 1996, 11 patients were treated with CyA for 3–6 months with an initial dose of 2.5–5 mg/kg daily, followed by a maintenance dose of 1.5–3 mg/kg daily. Bladder pain decreased or disappeared in ten patients, voiding frequency decreased, and mean and maximum voided volumes increased significantly. Symptoms recurred within 2 months in most patients after cessation of treatment [33]. In a retrospective review from three centers, 44 patients were treated with CyA, 34 of which had Hunner lesions. While only 30% of those without Hunner lesions had improvement in symptoms, 85% of those with Hunner lesions noted significant improvement in symptoms. Unfortunately, six patients stopped treatment due to adverse events for an ultimate success rate of 68%. The most common adverse events were a rise in serum creatinine and hypertension which improved after cessation of CyA [34]. In another small observational study, of 16 patients enrolled, ten patients completed the 6-week study with significant improvement in symptoms, and the remaining six withdrew due to bothersome side effects including diarrhea, abdominal pain, and elevated bilirubin levels. Notably, symptoms returned to baseline within 2 weeks of cessation of CyA [35]. In a long-term follow-up of 23 patients, over mean follow-up of 60 months were treated with 3 mg/kg divided into two daily doses. The mean number of voids decreased from 20 to 10 per day, bladder capacity more than doubled, and bladder pain resolved in 86.9% of patients on CyA. In this population, side effects were minimal and included hypertension in three, gingival hyperplasia in three, and induced hair growth in two [36]. In the only randomized trial, CyA was compared to PPS without a placebo for 6 months. CyA was found to be superior to PPS in all clinical outcome measures, with 75% of patients on CyA noting significant improvement compared to 19% on PPS. Adverse events were observed in 94% of patients on CyA compared to 56% of those on PPS, however, only three patients on CyA had an adverse event that was considered significant (increased blood pressure or serum creatinine) [37]. Taken together, these studies suggest that CyA significantly improves symptoms of IC/BPS, especially in those patients with Hunner lesions. However, given the small number of patients treated, the short follow-up and the comparatively significant adverse events, this should be reserved for those patients with severe or refractory symptoms. Patients on CyA should undergo regular blood pressure monitoring as well as routine assessment of renal and liver function [1].

Multimodal Pain Regimens

Chronic pain can significantly impacts quality of life, and as such, pain management is essential when treating patients with IC/BPS. The interstitial cystitis database reports that 93.6% of patients with IC/BPS have report pain as a symptom [38]. IC/BPS shares many features with other chronic visceral pain syndromes, and as such, pain management should be similar to the management of other chronic pain states [39]. Long-term use of nonopioid analgesics including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and antispasmodics may be used in a multimodal approach to pain management [1, 4••].

Gabapentin, an effective treatment option in neuropathic pain disorders, has been described in the treatment of IC/BPS. In 21 patients with refractory genitourinary pain treated with a mean dose of 1200 mg/day of gabapentin, pain relief was reported in 48% of patients [40]. In two observational studies of IC/BPS placed on multimodal treatment with gabapentin, amitriptyline, and NSAIDs, symptoms were noted to improve without any significant adverse effects [41, 42].

Phenazopyridine, when excreted in the urine, has local analgesic effects. In reviewing the Interstitial Cystitis Database, phenazopyridine is the third most common medication prescribed for the treatment of IC/BPS urinary symptoms at 14.3% [43]. Though there are no studies reporting efficacy of phenazopyridine in the treatment of IC, in a report of 1628 women with IC who completed a web-based survey on perceived outcomes of their treatment therapies, phenazopyridine was reported as the second most effective treatment next to opioids [44].

Opioids, though not the first choice for treatment of IC/BPS, should not be withheld as a last resort if other treatments have failed, but should be used as part of a multimodal therapy plan [4••]. With the recent opioid epidemic at the forefront of many providers minds, it is important to have a pain contract with your patient, ensuring that all narcotic prescriptions come from a single source, and that both the patient and provider have frequent conversations regarding goals of treatment. Given the complexities of long-term narcotic prescribing, collaboration with a pain clinic or pain specialist is often preferred.

Intravesical Therapies

Intravesical therapies can be administered as monotherapy or as part of a "cocktail." Many intravesical therapies aim to replace components of the damaged glycosaminoglycan layer of the urothelium including hyaluronic acid, heparin sulfate, pentosan polysulfate, and chondroitin sulfate [24]. Other intravesical agents contain anesthetic solutions, such as lidocaine, or have anti-inflammatory properties, such as dimethyl sulfoxide (DMSO) [45]. The variety of intravesical cocktails and variability of instillation regimens can make it difficult to select the appropriate treatment for patients with IC/BPS,

especially as research-based evidence is limited and primarily includes observational studies.

Dimethyl Sulfoxide (DMSO)

Dimethyl sulfoxide is an organosulfur compound that has anti-inflammatory properties and acts to relax muscles, dissolve collagen, decrease pain by nerve blockade, and provide smooth muscle relaxation. It is the only FDA-approved intravesical agent for the treatment of interstitial cystitis [46]. Though the instillation protocol is not standardized, typically 50 mL of 50% DMSO is instilled into the bladder, occasionally with 20 mL of 2% lidocaine, for 10–20 min before draining. This is repeated weekly for 6–8 weeks, and if a good result occurs, monthly maintenance can be initiated [24, 47].

A collection of small randomized controlled trials exist for DMSO in IC/BPS. In 1988, 33 patients received DMSO or saline instillations, with a 53% subjective improvement when compared to 18% of the placebo group [48]. When compared to Bacillus Calmette-Guerin instillations, Peeker et al. found that DMSO instillations resulted in a decrease in urinary frequency and pain compared to BCG [49]. Conversely, Sairanen et al. failed to note improvement in intravesical DMSO or BCG [50]. When comparing DMSO to chondroitin sulfate instillation, two randomized controlled trials found better improvement in symptoms with chondroitin sulfate compared to DMSO [51, 52•]. It should be noted that in the study by Tutulo et al., only six of the patients randomized to DMSO completed the trial. The majority of patients withdrew consent due to pain with instillation, intolerable garlic odor in breath, or lack of efficacy [51]. Among other case series and retrospective studies, an approximately 80% improvement in symptoms is reports with DMSO [4••].

DMSO can be administered in various cocktail formulations including heparin, sodium bicarbonate, triamcinolone, or lidocaine. See Table 2 for a list of various intravesical cocktails used in the treatment of IC/BPS.

Heparin

Heparin is found to have similarities to glycosaminoglycans (GAG) and as such is thought to aid in replacement of the damaged GAG layer of the bladder [53]. There is no systemic absorption of heparin when instilled in the bladder, and as such it has no effect on systemic coagulation and no report of significant side effects. Though not standardized, the typical protocol involves instillation of 10,000–40,000 units of heparin diluted in 10 mL of normal saline with or without lidocaine, retained for 30–60 min up to three times a week for 2–12 weeks [54, 55]. In two observational studies using intravesical instillation of heparin alone, 40–72.5% of patients noted significant relief of symptoms [56, 57]. Intravesical heparin is now commonly mixed with other agents in various cocktails including lidocaine, sodium bicarbonate, and DMSO. In a multicenter prospective, double-blind, crossover, placebo-controlled trial of 18 patients, the combination of alkalinized lidocaine and heparin was found to improve symptoms in 50% compared to 13% of control patients [58]. Furthermore, monthly maintenance instillations of heparin alone may reduce relapse after DMSO treatment; with one study showing only 20% relapse at 12 months after monthly heparin instillations compared to 52% of the control group that received a single treatment course of DMSO alone [59].

Alkalinized Lidocaine

Lidocaine is a local anesthetic with rapid onset that is best absorbed into the bladder when alkalinized with sodium bicarbonate [60]. Again, there is no standardized instillation protocol; the first case report was of 10 cc of 2% lidocaine mixed with 40 mL saline instilled daily for 2 weeks and then twice weekly for 4 weeks. This protocol resulted in pain improvement, decreased urinary frequency, and an increased bladder capacity in the short term [61]. Alkalization of intravesical lidocaine with sodium bicarbonate increases urothelial penetration of lidocaine, and in 35 patients who received 160 mg lidocaine alkalinized with 3 mL of 8.4% sodium bicarbonate and 50,000 units of heparin (15 mL total volume), 94% of patients reported a greater than 50% improvement in symptoms [58]. In one randomized multicenter trial of 102 patients, daily intravesical instillation of alkalinized lidocaine for 5 days resulted in 30% improvement in symptoms versus 9.6% of controls 3 days after the treatment course; unfortunately this improvement disappeared at the 10-day point [62].

In an attempt to prolong the effects of lidocaine instillations, a lidocaine-releasing intravesical system (LiRIS) was introduced. The LiRIS is a flexible device that is deployed into the bladder via cystoscopy and can remain in place for 2 weeks with continuous release of lidocaine into the bladder. In 16 women who underwent treatment with LiRIS, 64% of women noted improvement in symptoms 2 weeks after treatment. Also encouraging was the fact that 5 of 6 subjects with Hunner lesions had resolution of lesions after treatment [63].

In a review of the use of lidocaine in IC/BPS, it was concluded that only weak evidence exists to support the use of lidocaine instillations. There are no randomized controlled trials that have determined an optimal treatment protocol. However, for short-term relief of less than 2 weeks, it is reasonable to try daily instillations of 10–20 ml 2% lidocaine solution with or without alkalization for 7 days [64].

Hyaluronic Acid (HA) and Chondroitin Sulfate (CS)

Hyaluronic acid is a muco-polysaccharide that is thought to help repair the damaged GAG layer in the IC/BPS

Table 2 Intravesical cocktails used in the treatment of IC/BPS

Ingredients	Dwell time	Frequency
40,000 U heparin, 8 mL 2% lidocaine, 3 mL 8.4% sodium bicarbonate in 15 mL total	20 min	Three treatments per week for 2 weeks
20,000 U heparin, 8 mL 2% lidocaine, 4 mL 8.4% sodium bicarbonate	60 min	One instillation
20,000 U heparin, 5 mL 4% lidocaine, 25 mL 7% sodium bicarbonate	30 min	Weekly for 12 weeks
40 mL hyaluronic acid 1.6% and 20 mL chondroitin sulfate 2% in normal saline	60–120 min	Weekly for 6 weeks and then every other week for 6 months
50 mL 50% DMSO and 1 mL (10 mg) triamcinolone	15 min	Weekly for 6 weeks
40 mL 50% DMSO, 20 mL 0.25% bupivacaine, 100 mg hydrocortisone, 5000 U heparin	30 min	Twice weekly for 4 weeks, then weekly for 4 weeks
50 mL 50% DMSO, 10 mg kenalog, 20,000 U heparin, 4 mL 8.4% sodium bicarbonate	20 min	Weekly for 6 weeks
40 mL 0.5% Marcaine, 10,000 U heparin, 2 mL dexamethasone, 20 mL 7% sodium bicarbonate	20 min	Every other week for six treatments
300 mg pentosan polysulfate, 10 mL 4.2% sodium bicarbonate diluted in normal saline to 60 mL total	30 min	Weekly for 6–8 weeks

Adapted from Cox [3], Barua [45], Sant [46] and Meijlink [91]

bladder. Treatment with HA alone has been reported in a large number of observational studies, with a response rate of 30–87% according to the Canadian Urologic Association guidelines [3]. A prospective cohort of 126 patients treated with 40 mg HA weekly for 12 weeks resulted in an average five-point reduction in pain on the visual analog scale with 65.5% being symptom-free up to 5 years [65]. However, there exists three negative non-published double-blind, placebo controlled, multicenter randomized controlled trials that failed to show a benefit of HA compared to placebo. Though two of the studies showing a greater than 50% and 61% improvement in symptoms with HA; those on placebo had similar or greater improvement in symptoms [66]. In a meta-analysis of intravesical therapy for IC/BPS, 801 patients in 19 studies found that the largest effect was seen in patients who underwent treatment with HA, with a number needed to treat to achieve a response of 1.31. This was superior to all other intravesical instillations and was found to be superior in cost effectiveness as well [45].

Similarly, chondroitin sulfate, a sulfated GAG, is through to replenish the GAG layer of the bladder. In two small observational studies of patients treated with intravesical CS over a year, 73.1–92.3% of patient reported a response to treatment [67, 68]. In two underpowered randomized controlled trials, 38–39% of patients on CS had improvement in symptoms compared to 23–31% of placebo. This was not statistically significant [69, 70]. An individual patient data meta-analysis of 213 patients treated with CS monotherapy found that while symptom improvement was 54% higher in those treated with CS, the magnitude of improvement was small and not statistically significant (less than one point improvement in total ICSI score and urinary frequency improvement) [71].

One randomized, open-label study of 110 women compared instillations of HA and CS versus DMSO over 13 weekly instillations. HA/CS instillations were found to be as effective as DMSO, with significantly better pain reduction in those who underwent treatment with HA/CS compared to DMSO. Additionally there were significantly fewer treatment-related adverse events for HA/CS versus DMSO (1.35% vs 22.22%) [52•].

Pentosan Polysulfate Sodium

As previously discussed, PPS is a heparin analog and a mucopolysaccharide that is thought to aid in restoring the impaired GAG layer of the bladder when instilled intravesically. A small double-blind placebo-controlled study of 20 patients randomized to intravesical PPS (300 mg in 40 mL of normal saline) versus placebo found that 40% of patients on PPS instillations had significant symptom relief compared to 20% on placebo [72]. In a prospective open-label study of 29 patients who underwent instillation of 300 mg PPS intravesically twice a week for 10 weeks with voluntary maintenance therapy once a month, an improvement in pain on the visual analog scale and in symptom score was observed, with 72% of patients continuing the voluntary maintenance therapy [73]. A randomized placebo-controlled trial of 41 patients found that the addition of intravesical PPS to oral PPS resulted in a 46% reduction in symptom score compared to 24% of those on placebo over 6 weeks [74]. In a meta-analysis of intravesical therapy for IC/BPS, the number needed to treat to achieve a response to intravesical PPS was 2.67 [45].

Topical Therapies

There is a strong covariation of IC/BPS and vestibulodynia in women [75]. Vestibulodynia affects 25% of women with IC/BPS [76]. There appears to especially be overlap in the common complaint of urethral pain; possibly due to the urogenital sinus being the embryological origin of both bladder and genital tissues [77]. In patients who present with a significant component of vestibulodynia or urethralgia, the addition of topical therapies can be a helpful adjuvant, especially when administered before pelvic floor physical therapy, diagnostic tests, or intravesical instillations. While observational trials suggest good results with local therapies, clinical trials of topical agents show limited long-term efficacy [78]. Commonly used topical medications include: lidocaine 5% ointment, gabapentin 2–6% cream, amitriptyline 2% cream, and baclofen 2% cream [79]. Another option for the treatment of acute pain flares in IC/BPS or as an adjuvant treatment to pelvic floor physical therapy is the use of diazepam vaginal suppositories or pessaries. Dosage is usually 5–10 mg of diazepam compounded in a paraffin base [80]. In 26 patients, when received vaginal diazepam suppositories with high tone pelvic floor dysfunction, 25 noted improvement and six out of seven sexually active patients resumed intercourse [81].

Pharmacotherapies with Emerging Data

Sildenafil

Phosphodiesterase type 5 inhibitors such as sildenafil can relax contraction of smooth muscle, and have been found to play a role in the treatment of lower urinary tract symptoms. As such, a recent double blind, placebo-controlled randomized trial compared sildenafil 25 mg once daily to placebo in 48 women with IC/BPS. They found that IC symptom score and maximum cystometric capacity significantly improved at week 12 of treatment at 3 months after treatment when compared to placebo. Adverse events were mild and included headache and flushing [82].

Rosiptor (AQX-1125)

Rosiptor (AQX-1125) is an oral SH2-containing inositol-5′-phosphatase 1 (SHIP1) activator that triggers SHIP1, thereby inhibiting the phophoinositide-3-kinase pathway that is involved in activation and chemotaxis of inflammatory cells. This is thought to have anti-inflammatory properties that may prove beneficial in the treatment of IC/BPS. In a phase II study, 37 women with IC/BPS were randomized to receive daily oral AQX-1125 or placebo for 6 weeks and were monitored for 4 weeks after treatment. A significant improvement in pain and symptom score was noted when compared to placebo as well as a decrease in urinary frequency. More adverse events were seen in the placebo arm than AQX-1125 and no serious adverse events occurred [83•]. Unfortunately, in the phase III study of 298 women and 87 men with IC/BPS treated with 100 or 200 mg AQX-1125 daily, there was no difference in pain, symptom score, or urinary frequency when compared to placebo [84•]. This study, despite its negative results, is educational in highlighting the importance of further elucidating the pathophysiology of IC/BPS and properly phenotyping this syndrome in order to better develop successful interventions.

Gefapixant (AF-219)

Gefapixant (AF-219) is a P2X3 antagonist, which inhibits the P2X3 receptor, a purinoceptor that plays a role in sensitization of bladder afferent neurons. This medication is thought to desensitize bladder afferent overstimulation in IC/BPS. A randomized double-blind placebo controlled study of 36 women treated with AF-219 in a titratable dose regimen was found to have improvement in pain symptoms and urinary urgency compared to placebo [24].

Tanezumab

Tanezumab, a humanized monoclonal antibody that specifically inhibits nerve growth factor (NGF), is an exciting emerging therapy in the treatment of chronic pain. NGF is upregulated in various animal models of bladder inflammation and is proposed as a biomarker for IC/BPS [85]. In a randomized, double-blind placebo controlled phase II trial, 34 patients received a single injection of 200 μg/kg of tanezumab and 30 patients received placebo injections. At week six, patients on tanezumab had a significant reduction in daily pain score and urinary frequency versus placebo. The most common adverse events were headache (20.6% vs 16.7% placebo) and paresthesia (17.6% vs 3.3% placebo) [86]. In a pooled analysis of three small clinical trials, 208 patients were randomized to tanezumab or placebo pain improvement was noted in patients who had pelvic pain and a concomitant somatic syndrome but not in those with pelvic pain alone [87•].

Clinical Phenotyping

Clinicians have recently become aware that patients with IC/BPS are not a homogenous group, and that varying clinical phenotypes exist. This in part explains why many

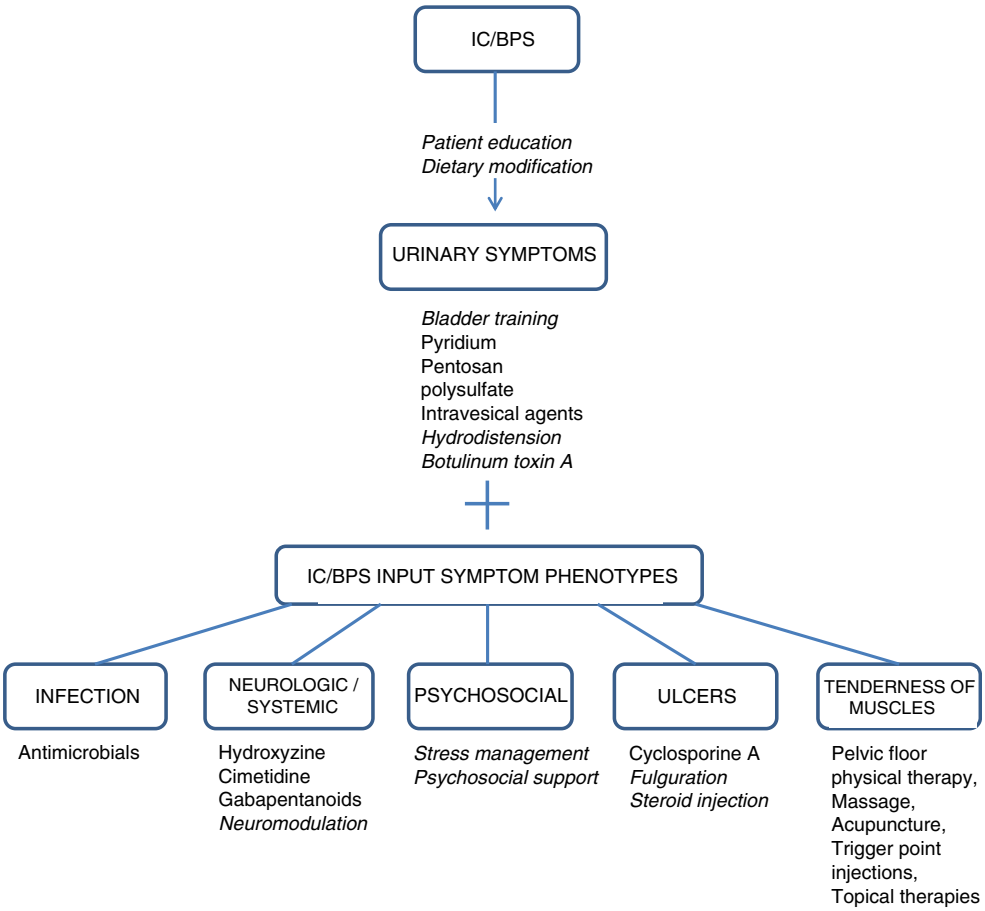

Fig. 1 Proposed management algorithm for the treatment if interstitial cystitis/bladder pain syndrome based on the INPUT phenotyping classification system

promising therapies have failed in large randomized placebo controlled trials and in clinical practice. As a result of an increased attempt to better characterize patients with IC/BPS, the UPOINT phenotyping classification system has been proposed as a new tool to guide individually based therapy for patients with IC/BPS. The six domains include: urinary, psychosocial, organ specific, infection, neurologic, and tenderness of skeletal muscles [88]. This system was validated in men with chronic pelvic pain syndromes but is more limiting in patients with IC/BPS since by definition all patients have both the urinary and organ specific phenotype [89]. As such, a new phenotype has been developed which included removing the urinary and organ-specific domains from UPOINT and adding a Hunner ulcer domain. This INPUT phenotyping classification system includes: infection, neurologic/systemic, psychosocial, ulcers, and tenderness of muscles. When applied to 239 patients with IC/BPS, incidence of domains was 11% infection, 51% neurologic/systemic, 91% psychosocial, 18% ulcers, and 85% tenderness with mean total domains of 2.46 [90••]. The aim of these classification systems is to guide the clinician in the creation of a multimodal treatment plan specific to the phenotype domains of each patient. Figure 1 provides a list of these phenotypes and possible targeted treatments best suited for each phenotype.

Conclusion

While multiple treatment options exist for the treatment of IC/BPS, the lack of understanding regarding the pathophysiology and difficulty diagnosing IC/BPS makes treatment difficult. Though there is consensus among the national and international guidelines that the treatment of IC/BPS should be done in a step-wise approach, beginning with the most conservative treatment options, the pendulum may be swinging towards individualized multimodal treatment plans based on a patient's unique phenotype.

Compliance with Ethical Standards

Conflict of Interest Lindsey Cox declares that she has no conflict of interest.

Alyssa Greiman declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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