Current Bladder Dysfunction Reports (2020) 15:192–202
https://doi.org/10.1007/s11884-020-00592-2

BPS/INTERSTITIAL CYSTITIS (D CASTRO-DIAZ AND Y IGAWA, SECTION EDITORS)

Systemic Therapy for Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC): Systematic Review of Published Trials in the Last 5 Years

Pedro Abreu-Mendes[1,2] · Rui Pinto[1,2,3] · Paulo Dinis Oliveira[1,2]

Published online: 27 June 2020
© Springer Science+Business Media, LLC, part of Springer Nature 2020

Abstract

Purpose of Review Systemic drug therapy licensed and present in worldwide guidelines for bladder pain syndrome/interstitial cystitis (BPS/IC) has been relatively stable for the last years. This systematic review aims to assess trials enrolling BPS/IC patients, published in the last 5 years. The authors abided by the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement to define retrieved trials. The keywords used in the search were "interstitial cystitis", "bladder pain syndrome" and "trial". Five additional papers were added: three published before 2015, due to the added value to the present work, and two published in abstract form only, retrieved from previous systematic reviews.

Recent Findings The pursuit of better and novel treatment modalities for BPS/IC patients is constant. Different classes of drugs were tried as potential systemic therapy in BPS/IC patients. Among retrieved trials, positive results were reported with sildenafil, certolizumab, amitriptyline, gefapixant, and cyclosporine A. Other drugs failed to prove their efficacy. When using other licensed drugs for BPS/IC, several trials showed inconclusive results or failed to meet the criteria at interim analyses.

Summary The interpretation of BPS/IC trial results is not straightforward especially when compared to other pathologies, due to difficulty in characterizing and phenotyping patients. Overall, both positive and inconclusive trials should motivate peers to continue the search for novel therapies in this condition. Trials with better designs and with a larger number of individuals are needed.

Keywords Interstitial cystitis · Bladder pain syndrome · Pharmacotherapy · Systemic therapy · Systematic revision · Trials

Introduction

By the 2007 ESSIC definition, bladder pain syndrome/interstitial cystitis (BPS/IC) is "chronic (> 6 months) pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like a persistent urge to void or frequency. Confusable diseases as the cause of the symptoms must be excluded" [1].

Inherent to its diagnosis, this umbrella-like syndrome includes a large spectrum of possible clinical presentations. The most important task upon phenotyping is to evaluate the presence of Hunners' lesions (HL) in patients' bladder, which differentiates the classical IC from BPS [2]. It was shown that the microenvironment in bladder biopsies with or without HL is different [3]. Patients with the latter appear to have more generalized complaints and symptoms while the former exhibit a more localized bladder disease. A recent study published by an ESSIC (The International Society for the Study of IC) working group compared BPS with IC patients [4•]. The basis of comparison between conditions was the macroscopic differences at cystoscopy, the microscopic and molecular differences within the bladder wall (microenvironment), and the differences in potential local treatments. This paper assumed IC as being, in fact, a confusable disease and defied the actual grouping of both conditions, proposing to review them as one condition, BPS/IC. Simultaneously, more holistic and multidisciplinary evaluation tools urge [5•, 6]. For example, the classification of patients by clusters, according to their association of

This article is part of the Topical Collection on *BPS/Interstitial Cystitis*

✉ Paulo Dinis Oliveira
paulodinisoliveira@gmail.com

[1] Department of Urology, Hospital São João, Porto, Portugal

[2] Department of Surgery and Physiology, Faculty of Medicine of University of Porto, Praça de Gomes Teixeira, 4099-002 Porto, Portugal

[3] i3S Institute for Investigation and Innovation in Health, Porto, Portugal

complaints, might permit a more individualized management of each patient.

The available therapies for BPS/IC patients and its treatment algorithm have been unchanged for the past decade. First-line options are based on dietary and lifestyle habits modification, according to the European Association of Urology (EAU) guidelines and also to the American Urology Association (AUA) and Urology Association of Asia (UAA) [7–9, 10•]. Oral pharmacotherapy is suggested when conservative measures fail, in all the guidelines. Drug recommendations in the three guidelines above have minor differences. Polysulfate pentosane (PPS) and amitriptyline are recommended in all; antihistaminic drugs, like cimetidine and hydroxyzine, are only listed in the EAU and AUA guidelines. Cyclosporine A (CyA) is suggested both by EAU and Asian guidelines, but are just fifth line therapy in the AUA guidelines. The use of both oral corticoids or citrate is solely listed in Asiatic guidelines. Simultaneously to these different classes of drugs, oral pain killers can be used rationally and logically: beginning with drugs with low analgesic strength on to escalating doses and potency of neuromodulators and opioids. In the EAU guidelines, other classes of systemic drugs are classified as "treatments of less value to BPS", including L-arginine (which is "not recommended" in Asian guidelines), oxybutynin, and prostaglandins.

After pharmacological failure, and according to Hanno's algorithm from AUA, invasive procedures are the next step: hydrodistention (used both for diagnostic and therapeutic purposes), intravesical instillation or injection of drugs, neuromodulation, and even surgery [8]. It is even accepted that a patient can undergo concurrent treatments on his best interest.

Nowadays, there is a paucity of new "good drugs" in trials for BPS/IC patients'. Most of the trials and studies on which the guidelines are based have been published more than 10 years ago.

Several problems have been identified in BPS/IC trials for new therapeutic drugs [11]. A common setback associated with placebo-controlled randomized trials is the failure to overcome the placebo effect with statistical significance when studying both groups' improvement. This drawback seems to be inherent to the definition of the disease as well as to the inclusion/exclusion criteria. It is very difficult to enroll a significant number of patients for each arm of the study and even more striving to stratify them. Studies involving patients with similar characteristics have a better internal validity but worsening its external validity. Moreover, due to the known heterogeneity of these patient's symptoms, negative trials can occur even with effective drugs but with a very unspecific cohort of patients.

In this review, we aimed to analyze the last 5 years RCT and open-label trials, involving systemic therapies for BPS/IC. Analysis of methods in each trial setup was utterly important, and results interpreted taking them into account.

Methods

We systematically searched MEDLINE and the Cochrane Central Register of Controlled Trials in the period of January 2015 to December 2019 using the terms "Interstitial cystitis" or "bladder pain syndrome" and "trial". Titles and abstracts were retained for selection after search results were combined; duplicated papers were eliminated. Relevant references were identified by filtration of the reference sections of included articles and other recent systematic reviews. This study was guided according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [12]. The papers were screened by two reviewers, to determine inclusion or exclusion and to perform the methodological analysis.

The inclusion criteria comprised randomized studies whose results were published both as a full article or as abstracts (in congresses or in the supplements of major journals). English publications only were included, and time frame was previously mentioned. Systemic therapies only (oral, endovenous or sub-cutaneous) were included. Pre-clinical trials and any trial involving other therapies were excluded: psychotherapy, physiotherapy, intravesical, neuromodulation, or surgery.

After applying the PRISMA protocol, a total of 7 articles with randomized control trials (RCT) were retrieved (one of them included a total of 3 RCT, published in one single article, since the drug was the same—tanezumab), 1 randomized crossover trial and 2 open-label trials [13•, 14, 15, 16•].

Parallel to the PRISMA oriented search, five other trials were added. Three of them were published before 2015 but their inclusion adds value to the work, providing some background information for the research done in the last 5 years. Also, two of them are the only papers about the drugs in question: adalimumab RCT from 2013 and one sildenafil RCT from 2014 [17, 18]. Two studies were identified as citations in recent systematic reviews: a phase III RCT with AQX-1025 and an RCT with Gefapixant, both from 2019 [19•, 20].

In this systematic review, our main goal is to equally analyze these trials, showing the basic characteristics of each study, systematically and exploring each trial particularities.

Results

The majority of trials regarding pharmacological therapy for BPS/IC in the last 5-year period included drugs not mentioned in guidelines. The existence of new drugs being tried in the treatment of this condition is a sign of the lack of efficacy of

the treatments licensed in the present and the absence of a universal treatment.

The majority of the trials include adult patients, refractory to oral and/or intravesical therapeutics, with moderate to severe symptoms O'Leary-Sant Interstitial Cystitis Symptom and Problem Indexes (OSS) > 18. Except for one RCT, which used an association between amitriptyline and a macronutrient, all the trials included in this revision assessed monotherapy regimens.

Most trials are pilot studies, with a low number of participants, with broadening inclusion criteria and short time under therapy.

The Tables 1 and 2 resume the most important features of each study (Table 1—RCT's and randomized crossover trial; Table 2—open-label trial). Some specific details related to each trial, like interim analysis or inclusion/exclusion criteria (examples), are mentioned in the text.

Randomized Control Trials

Phosphodiesterase 5 Inhibitor (PDE5i)

Tadalafil, 2014 The role that PDE5i can have in the management of LUTS is well known, and validated through inclusion in respective guidelines [21]. In 2014, Chen et al. evaluated the efficacy and safety of low-dose sildenafil (25 mg/day) in BPS/IC patient's refractory to previous therapeutics, in 48 patients [18]. The inclusion criteria were very specific, including only patients without HL and with a positive modified potassium sensitive test [22]. The rationale of this last criterion is related to the theory behind the use of sildenafil—patients with higher potassium concentration through submucosa, muscular, and interstitial layer can have their tissues damaged, leading to mast cell degranulation. C-fibers would ultimately be stimulated leading to detrusor contraction. Using a PDE5i, theoretically, the activation of C fiber is decreased, bladder afferent activity is reduced and detrusor muscle tone relaxes. In this RCT, the outcomes measured were OSS, Patient Overall Rating of Improvement in symptom questionnaire (PORIS), VAS score, nocturia, and frequency. Urodynamics were also assessed. All the parameters, including urodynamic ones, favored sildenafil arm at the end of the study, at 12-week and 24-week, except for pain VAS score. No serious complications were registered.

More studies are needed to evaluate the best dose and the type of patient who would benefit the most of this treatment.

Tumor Necrosis Factor α Antagonist (Anti TNFα)

One of the possible mechanisms suggested for BPS/IC is the autoimmunity. TNFα is a proinflammatory cytokine released by immune cells, responsible for perpetuating acute inflammatory states leading to chronic inflammation, as seen in autoimmune diseases.

Adalimumab, 2013 After one of his patients resolved his BPS/IC complaints with adalimumab therapy for a concomitant Crohn's disease, Hanno et al. evaluated the efficacy of adalimumab in BPS/IC patients. TNFα is highly expressed in patients with HL; adalimumab is a monoclonal antibody which inhibits TNFα [23]. In a phase III placebo-controlled RCT, adalimumab failed to demonstrate positive proof of concept compared to placebo, due to a significant placebo effect [17]. A statistically significant improvement from baseline was seen in both placebo and adalimumab, without differences between the arms. The overall improvement in both arms was unusually high (> 45%). One possible setback of the study was the inclusion criteria: naïve patients were educated in lifestyle changes at the beginning of the study. These patients being evaluated in the placebo arm distort the reality, since they received the first line of treatment plus a placebo. This study was considered inconclusive.

Certolizumab Pegol, 2018 In this trial, Hanno et al. included a run-in period with behavior modifications before randomization—absent in the adalimumab trial [24•]. A total of 20 patients were excluded, with a significant improvement after general measures. Certolizumab pegol is, as adalimumab, a licensed drug for several autoimmune diseases. However, certolizumab has, due to its unique structure, less AE, increased plasma half-life, and better distribution in inflamed tissue [25, 26]. This study failed to achieve its primary endpoint at week 2. Nevertheless, at week 18 certolizumab showed significant results versus placebo in all parameters evaluated: GRA, VAS, OSS, frequency, and more than 30% reduction in pain from baseline. No serious AE were recorded.

Anti-Nerve Growth Factor (anti-NGF)

NGF is a signaling protein produced by the bladder smooth muscle and urothelium and its expression is increased in the bladder of BPS/IC [27, 28]. NGF is seen as a potential biomarker for this disease but also as a potential therapeutic target [29].

Tanezumab, 2016 Curtis et al. published a paper representing the pooled analysis of 3 small placebo-controlled trials involving tanezumab [13•]. Tanezumab is a highly selective and specific humanized monoclonal antibody against NGF [30].

Although 2 previous trials involving tanezumab were already published [13•, 31], in this paper from 2016, the data from the A409103 study were known. A total of 205 patients, both male and female, were randomized to placebo or different doses of tanezumab, s.c., twice administrated in an 8-week interval (1 mg, 2.5 mg, 10 mg or 20 mg). This study was

Table 1 RCT's and randomized crossover trial

Drug, year, author	Number (female/male and HL/non-HL)	Study groups (dose)	Outcomes (primary and secondary) and timeframe evaluation	Results	Lost to follow-up	Adverse events (AE)
Randomized controlled trials						
Sildenafil (po); 2014; H. Chen	55 (all women, all non-HL)	24 pts. sildenafil 5 mg po vs 24 pts. placebo	OSS, VAS, PORIS, urodynamic evaluation. At baseline, week 12 (last dose) and week 24	Decrease of the ICSI and ICPI scores; frequency and nocturia significantly decreased; decreases in VAS scores at 12 weeks	None	1 pt. presented mild headache; 4 pts. with flushing in the beginning of taking sildenafil with symptoms remitting after 4 days
Adalimumab (sc); 2013; P. Hanno	43 (not specified)	21 pts. adalimumab s.c. 80 mg vs 22 pts. placebo	OSS (P.E.);PUF, GRA (S.E.) At week 2, 6 and 12	Failed to demonstrate positive proof of concept compared to placebo.	4 (2 placebo; 2 adalimumab)	4 pts. with irritation in injection site (adalimumab)
Certolizumab pegol (sc); 2018; P. Hanno	42 (all women)	28 pts. certolizumab pegol 400 mg vs 14 placebo	GRA at week 2 (P.E.); OSS, VAS, and frequency. At weeks 2, 10 and 18	All parameters in favor of certolizumab at 18 weeks, ($p > 0.05$). But the primary endpoint at week 2 failed	3 (2 in certolizumab and 1 in placebo)	Certolizumab—7 UTI; 4 irritation in injection site; Placebo—4 UTI, 1 nausea/vomiting
Tanezumab (sc); 2016; J. Curtis	205 patients (both with or without HL)	41 pts. tanezumab 1 mg vs 37 pts. tanezumab 2.5 mg vs 40 tanezumab 10 mg vs 40 pts. tanezumab 20 mg vs 42 pts. placebo	Change from baseline in average daily pain (NRS) (P.E.) ICSI score (S.E.)	The study was stopped—all doses met futility criteria ($p \geq 0.477$). No dose-response was observed	5 (4 in tanezumab 10 mg sc and 1 in tanezumab 20 mg sc)	Headache, arthralgia, paresthesia, and UTI were the most common. A total of 13 pts. discontinued treatment due to serious AE
Fulranumab (sc); 2017; H. Wang	31 pts. (mostly women, HL were used to balance groups randomization)	14 pts. fulranumab 9 mg vs 17 pts. placebo	Change from baseline in average daily pain (NRS) (P.E.); OSS, PUF, PPBC, frequency (S.E). Monthly for 26 week	No statistically significant difference between fulranumab and placebo at the primary efficacy endpoint. (the study was prematurely ended)	7 pts. (3 in fulranumab arm and 4 in the placebo arm)	AE were common in both arms (> 50%). No severe AE were recorded. No osteonecrosis or osteoarthritis was recorded
Amitriptyline(AMT) plus alpha-lipoic acid (ALA) and omega-3 polyunsaturated fatty acid (n-3), 2017; *F. murina*	84 female patients, with vestibulodynia or BPS (only female, no mention to HL)	41 pts., amitriptyline (max. dose of 30 mg) vs 43 pts. amitriptyline plus ALA and n-3 PUFAs	VAS and SF-MPQ (P.E.); Pelvic Floor Tonus, dyspareunia (S.E.). Baseline and day 60	Both arms were effective in all outcomes. AMT plus ALA and n-3 showed better results in all measured outcomes ($p < 0.05$)	Not mentioned	AE were uncommon, 3 in AMT arm and 8 in AMT plus ALA and n-3. Most commonly sedation and constipation. (the mean dose of AMT was 22 mg/day)
AQX 1125, 2016, J. Curtis (Phase II)	69 women (only female, both with or without HL)	37 pts. AQX-1125 200 mg id vs 32 pts. placebo control, for 6 weeks.	Change from baseline in average daily pain (NRS) (P.E.). BPIC-SS, OSS, SF-12v2, maximum daily pain and frequency (S.E.) During a total of 10 weeks	The statistically significant decrease in pain scores, at 6 weeks, was in favor of AQX in every item. The OSS and number of voids decrease was also in favor of AQX ($p < 0.05$). The SF-12v2 showed no differences	7 (4 in AQX 1125 arm, 3 in the placebo arm)	AE were common, but no serious adverse events were recorded. Two AQX-1125 pts. (skin rash and dyspepsia) and 2 placebo pts. withdrew due to AE

Table 1 (continued)

Drug, year, author	Number (female/male and HL/non-HL)	Study groups (dose)	Outcomes (primary and secondary) and timeframe evaluation	Results	Lost to follow-up	Adverse events (AE)
AQX 1125, 2019, J. Curtis (Phase III)	385 pts. (298 female and 87 male; HL presence not mentioned)	Patients were randomized to AQX (100 mg or 200 mg) p.o. or placebo.	Change from baseline in average daily pain (NRS) (P.E.). BPIC-SS, OSS, SF-12v2, maximum daily pain and frequency (S.E.) During a total of 12 weeks	Absence of treatment benefit over placebo, in P.E. and S.E.	Not mentioned	"Generally well tolerated"
Pentosan Polysulfate sodium, 2015, J. Nickel	368 pts. (36 males; 94 pts. with HL)	128 pts. PPS 100 mg p.o. id vs 121 pts. PPS 3id p.o. vs 118 pts. placebo, for 24 weeks	P.E. was a 30% reduction in the ICSI total score (from baseline to 24 week). VAS (0 to 10), PORIS, GRA, urgency, and frequency as S.E.	The study was stopped for futility during an interim analysis. The post hoc analysis in patients with IC, showed favorable results to placebo, over both arms of PPS	High discontinuation numbers: 55 in placebo, 54 in PPS 100 mg id and 53 in PPS 100 mg 3id	Well tolerated. Similar percentages of pts. across arms discontinuing due to an AE (10.2–13.3%). Most AE were mil
Gefapixant (AF 219), 2019, R. Moldwin	74 women (no information on HL)	36 pts. Gefapixant 50 mg 2id (until 300 mg/day) po vs 36 pts. placebo. During 4 weeks.	Pain improvement assessed through GRA (P.E.). Urinary urgency (S.E.). No other information.	The treatment arm reported improvement in pain and in urgency	No information	Side effects were mild. The most common being dysgeusia and hypogeusia
Randomized crossover trial Montelukast, 2017, R.M. Ward	64 women (not mentioned HL)	8 weeks in the treatment arm, 2 weeks in washout, 8 weeks in alternative treatment (could start with placebo or montelukast p.o.)	ICSI, ICPI, and PUF	Improvement noticed in both arms. 57% identified correctly when taking active treatment. Overall, the results were inconclusive	22 pts. (dropouts were more common in women with controlled symptoms at baseline)	5 pts., 2 in montelukast (rash and palpitations occurring) and 3 in the placebo

P.E. primary endpoint; *S.E.* secondary endpoints; *HL* Hunners' lesions; *sc* sub-cutaneous; *OSS* O'Leary-Sant Interstitial Cystitis Symptom and Problem Indexes; *ICSI* O'Leary-Sant IC Symptom Index; *ICPI* O'Leary-Sant IC Problem Index; *PUF* Pelvic Pain and Urgency/Frequency Questionnaire; *GRA* Patient's Global Response Assessment; *po* per-os; *HD* hydrodistention; *VAS* visual analog scale of pain; *PORIS* Patient Overall Rating of Improvement in Symptom; *UTI* urinary tract infection; *NRS* numeric rating scale; from 0 to 10; *PPBC* Patient's´ Perception in Bladder Condition; VAS visual analog scale; *SF-MPQ* McGill-Melzack Pain Questionnaire; *BPIC-SS* Bladder Pain Interstitial Cystitis Symptom Score; *SF-12v2* Short-Form 12 Health Survey

Table 2 Open-label trials

Drug, year, author	Number (female/male and HL/non-HL)	Study groups (dose)	Outcomes (primary and secondary) and timeframe evaluation	Results	Lost to follow-up	Adverse events (AE)
Open-label trials						
Cyclosporine A, 2014, J. Chade	45 pts. (43 female, HL not mentioned)	1.5 mg/kg of cyclosporine A, twice a day, for 5 years	ICIPI, ICSI, QoL, Urodynamics	Decrease in ICIP from 36 at baseline to 8.4 at 5 years; statistically significant	Not mentioned	Not mentioned
Cyclosporine, 2017, I.M. Crescenze	26 pts. (54% were female, 7 pts. had HL)	Dose 3 mg/kg CyA divided into two doses per day rounded to the nearest 50 mg. Follow-up at 2–4–6–8 months	P.E. was moderate/marked improvement evaluated by GRA at 3 months and/or > 50% improvement in ICSI and ICPI scores	ITT: Overall ICSI scores dropped from a median 15.0 (9–19) to 12.0 (2–19) at 3 months ($p < 0.01$). ICPI scores dropped from a median of 14.0 (8–16) at baseline to 11.0 (0–16) at 3 months ($p < 0.01$). On GRA 31% (8/26) at 3 months during treatment	4 patients did not reach primary endpoint and withdrew from the study	3 pts. discontinued the study before month 3 due to increasing pain, hypertension, and lack of effect. Other 2 pts. with hypertension and hyperglycemia, but not discontinued. Mean calculated GFR dropped initially but was restored after treatment
m-Pea-Pol, 2019, M. Cervigni	32 pts. (30 women, 11 pts. in 25 had HL)	1: 400 mg m-PEA plus 40 mg polydatin twice daily for 3 months followed by once p.o., daily for 3 months (6 months total)	VAS (P.E.). ICPI, ICSI, PUF, bladder diary (S.E.)	30% reported moderate or marked improvement on GRA, while 15% and 19% reported > 50% improvement in ICSI and ICPI scores, respectively, after 3 months of therapy	6 lost to follow-up at 6 months	None of the participants reported adverse events attributable to m-PEA-Pol

pts Patients, *HL* Hunners' lesion, *CyA* cyclosporine A, *ITT* Intention to Treat Analysis, *GRA* Patient's Global Response Assessment, *m-Pea Pol* Micronized Palmitoylethanolamide-Polydatin

stopped in consequence of a previously determined interim analysis to analyze ineffective doses or ineffective treatment, at all, at week 8. The primary endpoint was based on the change from baseline in mean average daily bladder pain score (from 0 to 10) from baseline to week 8.

Results from A409103 trial were published, as a pooled analysis with 2 previous studies, the first assessing BPS/IC patients and a second assessing chronic prostatitis/urologic chronic pelvic pain syndromes (CP/UCCP) patients [13•]. In both, a possible moderate pain-relieving action by tanezumab was accepted. In this retrospective pooled analysis, authors concluded that, probably, tanezumab is a more efficient drug in patients with BPS/IC localized to the bladder rather than in patients who present non-urological associated syndromes. The authors also noticed that retrospective analysis always carries a great level of uncertainty and prospective studies should be conducted to evaluate the best patient profile to tanezumab.

Fulranumab, 2017 In 2017, Wang et al. conducted an RCT to evaluate the efficacy and safety of fulranumab, an anti-NGF [32]. During the recruitment phase, the FDA suspended all studies involving anti-NGF due to the risk of a rapidly progressing osteoarthritis/osteonecrosis [33]. Despite the premature ending, the results of the placebo-controlled trial with 31 patients were published. Both male and female patients were recruited, and the presence of HL or bladder glumerulations was used to balance randomization. Patients were randomized to receive a placebo or 9 mg of fulranumab s.c. every 4 weeks, for 12 weeks. The primary endpoint was change from baseline in average daily pain (from 0 to 10); secondary endpoints were OSS, PUF, PPBC, and frequency. Fulranumab compared to placebo showed no significant difference for any of the endpoints. No patient discontinued treatment due to AE, and no case of osteoarthritis/osteonecrosis was recorded. Aside from the difficulty of designing and balancing the randomization in studies involving BPS/IC, the premature ending of this study conditioned the use of permuting blocks. Consequently, the arms were imbalanced with significant differences between group characteristics, making it even harder to take any conclusion.

Tricyclic Antidepressants

Amitriptyline Plus Alpha-Lipoic (ALA) Acid, Plus Omega 3 Polyunsaturated Fatty Acid (n-3 PUFAs) This controlled trial by Murina et al. evaluated the efficacy of adding ALA and n-3 PUFAs to amitriptyline therapy in patients with vulvodynia for > 3 months and BPS/IC [34•]. Amitriptyline is a drug used in the oral treatment for BPS/IC patients for the last decades, is considered a first-line therapy [7, 35]. Amitriptyline inhibits synaptic reuptake of serotonin and norepinephrine, blocks acetylcholine receptors, and blocks H1 histamine receptors. It is widely used in neuropathic pain conditions [36]. ALA has shown to have antioxidant and anti-inflammatory activity, improving pain in patients with neuropathic pain syndromes [37]. N-3 PUFAs have been linked with an anti-nociceptive effect by reducing the threshold for thermal pain and neuropathic pain [38]. In this study, 84 female patients with vulvodynia and BPS/IC were randomized to receive amitriptyline monotherapy or amitriptyline plus ALA and n-3 PUFAs. The endpoints were evaluated at baseline and day 60. Primary endpoints were the VAS and the McGill-Melzack Pain Questionnaire (SF- MPQ) and the secondary were the dyspareunia and pelvic floor tonus. Combination therapy was significantly superior in both primary endpoints. The reduction in dyspareunia at day 60 was also in favor of the combination therapy. The curious fact of this study is the mean dose of amitriptyline used: approximately 22 mg in both arms, far from the usual doses between 50 and 75 mg/day seen at clinical practices and other studies for both vulvodynia and BPS/IC [7, 39]. Patients initiated with 6 mg nightly, escalating doses 6 mg every week until 30 mg/day. Knowing that AE is one of the reasons for patients abandoning amitriptyline therapeutic, the possibility to use ALA and n-3 PUFAS to reduce the dose of amitriptyline should be evaluated in further studies [7].

SH2-Containing Inositol-5′-Phosphatase 1 (SHIP1) Activator

AQX 1125, "Rosiptor," 2016 and 2019 AQX 1125, named Rosiptor, is an oral drug that activates the SHIP-1. The activation of AQX 125 will inhibit the phosphoinositide-3-kinase pathway, responsible for local inflammatory response [40]. Therefore, the rationale behind this drug was a decrease in the inflammatory response hence an interest in BPS/IC patients. In 2016, Curtis et al. evaluated the efficacy and safety of rosiptor in 69 female patients, with and without HL, in a 2-arm RCT [41]. Thirty-two patients were in the placebo arm and 37 in Rosiptor arm (100 mg/day), during week 6. Patients were monitored until week 10. The primary endpoint was the baseline average pain, and secondary endpoints were based on on-line daily questionnaires (OSS, Bladder Pain Interstitial Cystitis Symptom Score (BPIC-SS), Short-Form12 Health Survey (SF-12v2)). The results showed a significant improvement at every endpoint evaluated. Rosiptor was well tolerated, with a total of 4 patients abandoning treatment due to AE, 2 in each arm. The results of this phase II trial were positive and thrilling. However, in the following phase III trial, published in 2019, the results were not so good [19•]. In a 3-arm RCT, a total of 298 females and 87 males, with and without HL, were randomized to Rosiptor 100 mg, 200 mg, or placebo for 12 weeks [19•]. No difference was seen between Rosiptor and placebo in pain or frequency results. It was not explained if any phenotyping was made to balance groups. Once again, the main finding of this study seems to be the need to correctly phenotype patients to apply the best therapeutic accordingly.

P2X3 Receptor Antagonists

AF-219, "Gefapixant", 2019 The P2X3 receptors are a family of ion channels, present in the cell membrane, involved in the sensitization of bladder afferent neurons. They respond to ATP. The rationale behind this drug would be the capability to downregulate these receptors, through an antagonism mechanism.

Therefore, AF-219 is a P2X3 antagonist which, by inhibiting this purinoreceptor, inhibits its role in bladder afferent sensitization. The bladder afferent overstimulation is assumed to be one possible mechanism behind the BPS/IC.

The results of a recent placebo-controlled RCT, involving 76 women with BPS/IC were shown at ICS conference, 2015. The results reported an improvement in pain in gefapixant arm over placebo, as in global response and urinary urgency [20].

Pentosan Polysulfate (PPS), 2015 PPS is a licensed treatment for BPS/IC (in the USA, Canada, and Europe), being present in both guidelines [7, 8]. The use of PPS and the trials involving it in BPS/IC patients are being done for the last decades. Historically, this semi-synthetic mucopolysaccharide drug derived from hemicellulose, enoxaparin-like has a more consistent effect in patients with IC than with BPS, reducing pain, urgency, and frequency [42–44]. The rationale of using this drug is would be its capability to repair damaged glycosaminoglycan (GAG) layers lining the urothelium and by buffering irritating solutions that may alter cell permeability [45].

In 2015, Curtis et al. evaluated once again the effects of PPS in BPS/IC, in a placebo-controlled RCT involving 368 patients, mostly female, with 94 of the total cohort presenting HL [46]. This trial compromised 3 arms: placebo, once-daily PPS 100 mg, or three-times daily PPS 100 mg, in 1:1:1, without any concurrent therapy for BPS/IC. The primary endpoint was a 30% reduction in the ICSI total score, and the secondary endpoints were VAS, PORIS, GRA, urgency, and frequency (from baseline to 24 week). During the study, after a predefined interim analysis, the results met criteria to be stopped due to futility—the absence of a statistically significant difference between either PPS dose group and placebo or between the PPS dose group in the primary endpoint, and neither in secondary endpoints.

A post hoc analysis of the 94 patients with IC was conducted and no difference between the arms was found. The high number of dropouts was a limitation, in each arm of almost 50%. Approximately 10% of patients in the PPS arm discontinuing the drug due to AE, very similar to placebo.

The results of this study contradict a recent meta-analysis by van Ophoven et al., showing the efficacy of PPS over placebo in pain, frequency, and urgency [47•]. Besides the previously explained limitations of the study, the role and value of PPS as part of a combined therapy, rather than in monotherapy, should be accessed in future prospective studies. PPS effect in bladder complains appears to be more relevant after a 3–6 months' therapy course, which can explain the reason why the interim analysis failed [20].

A recent paper related to PPS eye-related AE was published [48•]. A series of 6 patients diagnosed with pigmentary maculopathy following PPS treatment during 180 months (mean). It is premature to assume drastic measures but prescribers should be cautious, and patients with a story of long-time PPS therapy should undergo an eye examination.

Randomized Crossover Trial

Anti-Leukotriene

Montelukast, 2017 In 2019, R.M. Ward et al. conducted a randomized crossover trial with a leukotriene drug, montelukast, versus placebo involving a total of 64 patients [14]. Previous studies showed increased levels of leukotriene E4 in patients with BPS/IC [49]. The rationale behind the use of anti-leukotrienes, like montelukast, is to decrease leukotriene E4 levels, which activate leukotriene receptors present in the detrusor muscle, leading to local activation of masts cells [50]. This activation can, theoretically, contribute to BPS/IC symptomatology. In this randomized crossover trial of montelukast versus placebo, 64 women with BPS/IC underwent a scheme of 8 weeks in the treatment arm, 2 weeks in washout, and 8 week in alternative treatment. Symptoms were evaluated with OSS and PUF questionnaire. Improvement was noticed in both arms, both in women who started with montelukast and women who started with a placebo, without significant differences. Based on clinical changes, only 57% of patients were able to correctly identify if the drug being taken was montelukast or placebo. A total of 22 patients discontinued the trial, and those were more likely to have their symptoms controlled initially. The results were inconclusive, and once again, this treatment seems to be an option to identified patients with a phenotype associated with elevated leukotrienes.

Open-Label Trials

Cyclosporine A, 2014 and 2017

The reason to use immunosuppression drugs in BPS/IC is, once again, related to the notion of ongoing inflammatory processes in the bladder wall and the suspicion of an autoimmune involvement. CyA is an immunosuppressive agent, inhibiting the activation of T cells by reducing the enzymatic activity of calcineurin [51]. The main concern about using these drugs is its potential serious AE [52]. It was previously studied as therapeutic for BPS/IC, with a systematic review conducted in 2016, concluding that further higher-quality studies were needed to more consistent conclusions [53].

Two open-label trials will be discussed; one was published in the form of an abstract in 2014 by Chade et al. [54], and a second trial published by Crescenze et al. [15].

The trial of 2014 evaluated the long-term evolution of both symptoms and urodynamic outcomes, after 5-years of CyA therapy with daily doses of 3 mg/kg, divided into 2 doses. When used as an immunosuppressive agent after solid-organ transplant, the dose is 5–10 mg/kg/day. Forty-five patients were enrolled, 2 men with BPS/IC diagnosis; the presence of HL was not relevant in this trial. The mean ICSI experienced a drastic reduction, from a baseline value of 36 to 8.4 at 5 years. Urodynamically, the initial filling sensation of 103 ml baseline and the mean bladder capacity of 207 at baseline were 170 ml and 320 ml at 5 years, respectively. All patients scored ICPI score above 8 initially and in the 5th year; only 22% maintained ICPI > 8. In terms of AE, they refer the absence of significant abnormalities in terms of kidney and liver functions. This trial showed good long-term results with CyA in BPS/IC with an equal safety profile.

In 2017, Crescenze evaluated the outcomes of 3 months of therapy with 2 daily doses of 1.5 mg/kg. A total of 22 patients, 7 of them with HL, completed 3 months of treatment with 4 patients discontinuing the treatment. The primary endpoints were a moderate or marked improvement as evaluated by GRA at 3 months and/or improvement of at least 50% in ICSI and ICPI. At each visit, CyA levels, renal function, and blood pressure were evaluated. Nuclear GFR (glomerular function rate) was also compared from baseline to the end of treatment. Overall ICSI scores significantly dropped from a median of 15.0 at baseline to 12.0 at 3 months, and ICPI scores also significantly dropped from a median of 14.0 at baseline to 11.0, at 3 months. These improvements were stable at the evaluation at 1 month after treatment. A marked/moderate improvement in GRA was seen in 35% of patients at the end of treatment, dropping to 16% of patients 1 month after treatment ends. The authors performed a univariate analysis, and the only predictive factor with favorable response to CyA, especially in the improvement in ICSI was the presence of HL. The UNIPOINT analysis was not an important predictive factor of therapeutic response, in this study.

As for AE, 1 patient was diagnosed with hypertension and 1 patient with elevated serum glucose. Despite a non-significant deterioration in renal function parameters during treatment (creatinine serum, GFR and nuclear assessment of GRF), 1 month after treatment, all of them were completely normalized.

This trial showed interesting results, and the trend of an important symptom improvement particularly in patients with HL was in line with the results of a retrospective study published in 2012 [55]. Probably, the inflammatory environment is more significant in patients with. Also, when used with lower doses and with careful monitoring, CyA can be used in patients' refractory to previous first-line therapies.

N-Acylethanol-Amines

Micronized Palmitoylethanolamide-Polydatin (m-PEA-Pol), 2019 The inflammation present in bladder urothelium and interstitial tissue, possibly involved in bladder pain, as demonstrated by elevated urinary levels of inflammatory markers, is again the main reason to use palmitoylethanolamide (PEA) in BPS/IC [56]. Mast cells participate in both phases of the disease development, earlier and later, primarily causing nociceptive pain through tissue inflammation and also perpetuating the afferent stimulus to somatosensory fibers, ultimately leading to central sensitization. PEA is an endogenous occurring anti-inflammatory lipid, capable of acting on nociceptive pathway receptors, reducing mast cell degranulation, and ultimately modeling the threshold of inflammation and pain [57]. Despite being extensively studied, its mechanism of action is still not fully understood.

In this pilot open-label trial, 30 women and 2 men were enrolled with BPS/IC diagnosis [16•]. The regimen was 400 mg of m-PEA-Pol twice daily for 3 months followed by once daily for 3 months and evaluated until 8 months. The primary endpoint was the reduction in VAS score, and secondary were ICPI, ICSI, PUF questionnaire, and changes in voiding diary. The results in all endpoints were statistically significant in every outcome, showing improvement in symptoms. The improvement was maintained 2 months after stopping the drug. Despite being a pilot study, without a control arm, this trial should arouse investigators to design and conduct controlled trials to evaluate this drug as a new weapon to this condition.

As shown, several trials were performed, some of them with novel drugs, others with off-label use of known drugs or even using licensed drugs to BPS/IC. The results are inconsistent and sometimes contradictious. Problems are transverse to the majority of the reported studies: distinct phenotyping of patients although similar diagnostic criteria were used, the small number of patients recruited and rarely stratified, distinct outcomes measures used to evaluate therapeutic response, and the short-term effect of drugs, not the long-term, was evaluated most of the times. Also, some of the trials mentioned were just presented as an abstract but given the low number of trials, the results of every study conducted in the timeframe mentioned should be referred. Despite the overall low quality of the studies, they enriched the knowledge in this condition.

The lack of consistency in trials involving monotherapy treatment hampers the possibility of trials with combined therapy. The difficulty to correctly phenotype each patient at various levels is known and seems to be the first drawback clouding adequate management of this condition. Consequently, the right treatment regimen for each patient is difficult to be reached without a sequence of previously failed

combinations, usually following general guidelines for this condition. The placebo effect is another barrier that is also difficult to deal with in clinical trials, inherent to a subjective complaint such as pain.

Conclusion

Among all the evaluated trials, particular positive results were observed in the trials with sildenafil, certolizumab, amitriptyline, gefapixant, and cyclosporine A. Soon, it is expectable these drugs will be included/validated in BPS/IC treatment algorithm.

Hopefully, future studies will improve the capacity to phenotype BPS/IC, namely through genomics and proteinomics, alongside clinical features, providing useful information for further studies.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol. 2008;53(1):60–7.
2. Whitmore KE, Fall M, Sengiku A, Tomoe H, Logadottir 0, Kim YH. Hunner lesion versus non-Hunner lesion interstitial cystitis/bladder pain syndrome. Int J Urol. 2019;26(S1):26–34.
3. Maeda D, et al. Hunner-type (classic) interstitial cystitis: a distinct inflammatory disorder characterized by pancystitis, with frequent expansion of clonal B-cells and epithelial denudation. PLoS One. 2015;10(11):e0143316.
4.• Fall M, et al. Hunner lesion disease differs in diagnosis , treatment and outcome from bladder pain syndrome: an ESSIC working group report. Scand J Urol. 2020;0(0):1–8. **A recent paper by field specialist inquiring the need to separate BPS from IC.**
5.• Crane A, Lloyd J, Shoskes D. Improving the utility of clinical phenotyping in interstitial cystitis/painful bladder syndrome: from UPOINT to INPUT. J Urol. 2017;197(4S):9250–4. **A new phenotyping type proposed to BPS/IC patients.**
6. Lai HH, Thu JHL, Moh FV, Paradis A, Vetter J. Clustering of patients with interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome. J Urol. 2019;202(3):546–51.
7. Engeler SED, Baranowski AP, Berghmans B, Borovicka J, Cottrell AM, Dinis-Oliveira P, et al. A.C. de C Williams Guidelines Associates: L. Pacheco-Figueiredo, B. Parsons, 'EAU guidelines on chronic pelvic Pain'. Eur Urol. 2019.
8. Hanno PM, Erickson D, Moldwin R, Faraday MM. Diagnosis and treatment of interstitial cystitis/bladder pain syndrome: AUA guideline amendment. J Urol. 2015;193(5):1545–53.
9. Homma Y, Ueda T, Tomoe H, Lin ATL, Kuo HC, Lee MH, et al. Clinical guidelines for interstitial cystitis and hypersensitive bladder syndrome: guidelines. Int J Urol. 2009;16(7):597–615.
10.• Malde S, Palmisani S, Al-Kaisy A, Sahai A. Guideline of guidelines: bladder pain syndrome. BJU Int. 2018;122(5):729–43. **An interesting paper that compares different guidelines around the world, in terms of BPS/IC management.**
11. Propert KJ, Payne C, Kusek JW, Nyberg LM. Pitfalls in the design of clinical trials for interstitial cystitis. Urology. 2002;60(5):742–8.
12. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339(jul21 1):b2535.
13.• Nickel JC, et al. Tanezumab reduces pain in women with interstitial cystitis/bladder pain syndrome and patients with nonurological associated somatic syndromes. J Urol. 2016;195(4):942–8. **A pooled analysis of 3 RCT evaluating pain reduction in BPS/IC not only but especially female patients treated with a monoclonal antibody against NGF.**
14. Yurke B, Stoler D, Laboratories TB, Hill M. Montelukast trial. Female Pelvic Med Reconstr Surg. 2019;25(5):S1–S25.
15. Crescenze IM, Tucky B, Li J, Moore C, Shoskes DA. Efficacy, side effects, and monitoring of oral cyclosporine in interstitial cystitis-bladder pain syndrome. Urology. Sep. 2017;107:49–54.
16.• Cervigni M, Nasta L, Schievano C, Lampropoulou N, Ostardo E. Micronized palmitoylethanolamide-polydatin reduces the painful symptomatology in patients with interstitial cystitis/bladder pain syndrome. Biomed Res Int. 2019, 2019. **A recent RCT assessing pain reduction in BPS/IC patients treated with Micronized Palmitoylethanolamide-Polydatin.**
17. Bosch PC. A randomized, double-blind, placebo controlled trial of adalimumab for interstitial cystitis/bladder pain syndrome. J Urol. Jan. 2014;191(1):77–82.
18. Chen H, Wang F, Chen W, Ye, Zhou Q, Shao F, et al. Efficacy of daily low-dose sildenafil for treating interstitial cystitis: results of a randomized, double-blind, placebo-controlled trial—treatment of interstitial cystitis/painful bladder syndrome with low-dose sildenafil. Urology. 2014;84(1):51–6.
19.• Nickel JC, et al. Targeting the SHIP1 pathway fails to show treatment benefit in interstitial cystitis/bladder pain syndrome: lessons learned from evaluating potentially effective therapies in this enigmatic syndrome. J Urol. 2019;202(2):301–8. **A phase III trial to treat BPS/IC with negatives results, failing to show benefit as the phase-II trial.**
20. Greiman A, Cox L. Pharmacotherapy for interstitial cystitis/bladder pain syndrome. Curr Bladder Dysfunct Rep. 2019.
21. Burkhard ATFC, Bosch JLHR, Cruz F, Lemack GE, Nambiar AK, Thiruchelvam N, et al. EAU guidelines on urinary incontinence. EAU Guidel. 2019;(March):1–100.
22. Daha LK, Riedl CR, Lazar D, Hohlbrugger G, Pflüger H. Do cystometric findings predict the results of intravesical hyaluronic acid in women with interstitial cystitis? Eur Urol. 2005;47(3):393–7.
23. Felsen D, et al. Inflammatory mediator profile in urine and bladder wash fluid of patients with interstitial cystitis. J Urol. 1994;152(2 Part 1):355–61.
24.• Bosch PC. A randomized, double-blind, placebo-controlled trial of certolizumab pegol in women with refractory interstitial cystitis/bladder pain syndrome. Eur Urol. 2018;74(5):623–30. **An RCT with certolizumab pegol, a novel anti-TNFa, assessing pain and urgency improvement in female BPS/IC patients, with positive results.**
25. Nesbitt A, Fossati G, Bergin M, Stephens P, Stephens S, Foulkes R, et al. Mechanism of action of certolizumab pegol (CDP870): in vitro comparison with other anti-tumor necrosis factor α agents. Inflamm Bowel Dis. 2007;13(11):1323–32.

26. Bourne T, Fossati G, Nesbitt A. A PEGylated Fab′ fragment against tumor necrosis factor for the treatment of Crohn disease: exploring a new mechanism of action. BioDrugs. 2008;22(5):331–7.
27. Steers WD, Tuttle JB. Mechanisms of disease: the role of nerve growth factor in the pathophysiology of bladder disorders. Nat Clin Pract Urol. Feb. 2006;3(2):101–10.
28. Lowe EM, Anand P, Terenghi G, Williams-Chestnut RE, Sinicropi DV, Osborne JL. Increased nerve growth factor levels in the urinary bladder of women with idiopathic sensory urgency and interstitial cystitis. Br J Urol. 1997;79(4):572–7.
29. Frias B, Lopes T, Pinto R, Cruz F, Duarte Cruz C. Neurotrophins in the lower urinary tract: becoming of age. Curr Neuropharmacol. 2011;9(4):553–8.
30. Nickel JC, Atkinson G, Krieger JN, Mills IW, Pontari M, Shoskes DA, et al. Preliminary assessment of safety and efficacy in proof-of-concept, randomized clinical trial of tanezumab for chronic prostatitis/chronic pelvic pain syndrome. Urology. 2012;80(5):1105–10.
31. Evans RJ, Moldwin RM, Cossons N, Darekar A, Mills IW, Scholfield D. Proof of concept trial of tanezumab for the treatment of symptoms associated with interstitial cystitis. J Urol. 2011;185(5):1716–21.
32. Wang H, Russell LJ, Kelly KM, Wang S, Thipphawong J. Fulranumab in patients with interstitial cystitis/bladder pain syndrome: observations from a randomized, double-blind, placebo-controlled study. BMC Urol. 2017;17(1):2.
33. Hochberg MC. Serious joint-related adverse events in randomized controlled trials of anti-nerve growth factor monoclonal antibodies. Osteoarthr Cartil. Jan. 2015;23:S18–21.
34.• Murina F, Graziottin A, Felice R, Gambini D. Alpha lipoic acid plus omega-3 fatty acids for vestibulodynia associated With painful bladder syndrome. J Obstet Gynaecol Canada. 2017;39(3):131–7. **An RCT assessing combination therapy associated with amitriptyline, with positive results, with possible amitriptyline dose reduction.**
35. Pilowsky I, Hallett EC, Bassett DL, Thomas PG, Penhall RK. A controlled study of amitriptyline in the treatment of chronic pain. Pain. 1982;14(2):169–79.
36. Giusto LL, Zahner PM, Shoskes DA. An evaluation of the pharmacotherapy for interstitial cystitis. Expert Opin Pharmacother. 2018;19(10):1097–108.
37. Lee FH, Raja SN. Complementary and alternative medicine in chronic pain. Pain. 2011;152(1):28–30.
38. Nakamoto K, Nishinaka T, Mankura M, Fujita-Hamabe W, Tokuyama S. Antinociceptive effects of docosahexaenoic acid against various pain stimuli in mice. Biol Pharm Bull. 2010;33(6):1070–2.
39. Leo RJ, Dewani S. A systematic review of the utility of antidepressant pharmacotherapy in the treatment of vulvodynia pain. J Sex Med. 2013;10(10):2497–505.
40. Stenton GR, Mackenzie LF, Tam P, Cross JL, Harwig C, Raymond J, et al. Characterization of AQX-1125, a small-molecule SHIP1 activator. Br J Pharmacol. Mar. 2013;168(6):1506–18.
41. Nickel JC, Egerdie B, Davis E, Evans R, Mackenzie L, Shrewsbury SB. A phase II study of the efficacy and safety of the novel oral SHIP1 activator AQX-1125 in subjects with moderate to severe interstitial cystitis/bladder pain syndrome. J Urol. 2016;196(3):747–54.
42. Nickel JC, et al. Pentosan polysulfate sodium therapy for men with chronic pelvic pain syndrome: a multicenter, randomized, placebo controlled study. J Urol. Apr. 2005;173(4):1252–5.
43. Fritjofsson Å, Fall M, Juhlin R, Persson BE, Ruutu M. Treatment of ulcer and nonulcer interstitial cystitis with sodium pentosanpolysulfate: a multicenter trial. J Urol. Sep. 1987;138(3):508–12.
44. Mulholland SG, Sant GR, Hanno P, Staskin DR, Parsons L. Pentosan polysulfate sodium for therapy of interstitial cystitis. Urology. 1990;35(6):552–8.
45. Anderson VR, Perry CM. Pentosan polysulfate. Drugs. 2006;66(6):821–35.
46. Nickel JC, Herschorn S, Whitmore KE, Forrest JB, Hu P, Friedman AJ, et al. Pentosan polysulfate sodium for treatment of interstitial cystitis/bladder pain syndrome: insights from a randomized, double-blind, placebo controlled study. J Urol. 2015;193(3):857–62.
47.• van Ophoven A, Vonde K, Koch W, Auerbach G, Maag KP. Efficacy of pentosan polysulfate for the treatment of interstitial cystitis/bladder pain syndrome: results of a systematic review of randomized controlled trials. Curr Med Res Opin. 2019;35(9):1495–503. **Although not directly assessed in this paper, is a recent valuable systematic review over the effect of PPS in BPS/IC patients.**
48.• Pearce WA, Chen R, Jain N. Pigmentary maculopathy associated with chronic exposure to pentosan polysulfate sodium. Ophthalmology. 2018;125(11):1793–802. **A recent paper with a case series of patients developing maculopaty follwing long-term treatment with PPS.**
49. Larsen S, Hald T, Bouchelouche P. Clinical biomarkers. Urology. 2001;57(June):2001.
50. Bouchelouche K, Horn T, Nordling J, Larsen S, Hald T. The action of cysteinyl-leukotrienes on intracellular calcium mobilization in human detrusor myocytes. BJU Int. 2001;87(7):690–6.
51. Reynolds NJ, Al-Daraji WI. Calcineurin inhibitors and sirolimus: mechanisms of action and applications in dermatology. Clin Exp Dermatol. 2002;27(7):555–61.
52. Sternthal MB, Murphy SJ, George J, Kornbluth A, Lichtiger S, Present DH. Adverse events associated with the use of cyclosporine in patients with inflammatory bowel disease. Am J Gastroenterol. 2008;103(4):937–43.
53. Wang Z, Zhang L. Treatment effect of cyclosporine a in patients with painful bladder syndrome/interstitial cystitis: a systematic review. Exp Ther Med. 2016;12(1):445–50.
54. Chade J, Chade D, Lucon AM, Bruschini H, Srougi M. 5-year follow-up of patients with refractory interstitial cystitis treated with cyclosporine A: a prospective single-institution study. Eur Urol Suppl. 2014;13(1):e462.
55. Forrest JB, Payne CK, Erickson DR. Cyclosporine a for refractory interstitial cystitis/bladder pain syndrome: experience of 3 tertiary centers. J Urol. 2012;188(4):1186–91.
56. Furuta A, Yamamoto T, Suzuki Y, Gotoh M, Egawa S, Yoshimura N. Comparison of inflammatory urine markers in patients with interstitial cystitis and overactive bladder. Int Urogynecol J. 2018;29(7):961–6.
57. Skaper SD, Facci L, Fusco M, della Valle MF, Zusso M, Costa B, et al. Palmitoylethanolamide, a naturally occurring disease-modifying agent in neuropathic pain. Inflammopharmacology. 2014;22(2):79–94.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.