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REVIEW

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Efficacy and safety of oral pharmacological and supplementary therapies in bladder pain syndrome: a systematic review

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Abstract

Treatment goals in bladder pain syndrome (BPS) or interstitial cystitis (IC) focusing on relieving symptoms to improve quality of life and avoiding adverse events (AEs) since curative treatment for BPS/IC is not available. The readily available pharmacologic options for BPS/IC including oral, intravesical, and transdermal therapy. The purpose of this study is to review randomized trial studies over the last 15 years examining the efficacy and safety of oral pharmacological and supplementary therapies for BPS/IC. A systematic search was conducted in PubMed and Medline Library. Only randomized-controlled trials and randomized comparative trials published between 2005 and 2020 on the efficacy and safety of oral therapies for BPS/IC were included. The keywords used were "bladder pain syndrome", or "interstitial cystitis", and "random" or "trial". From 629 articles, nine were included in this review. Oral therapies included consist of cyclosporine A (CyA), amitriptyline, amitriptyline plus alpha lipoic acid (ALA) and omega-3 fatty acids (*n*-3 PUFA), PD-0299685, sildenafil, pentosan polysulfate sodium (PPS), AQX-1125, and hydrogen-rich water. Among retrieved trials, amitriptyline in combination with ALA and *n*-3 PUFA, sildenafil, and cyclosporine A proved their efficacy for BPS/IC. Sildenafil was generally well tolerated, while amitriptyline and CyA must be used with caution, the supplementation of ALA/*n*-3 PUFAs possibly lower dosage of amitriptyline, subsequently reduce its AEs. CyA was superior to PPS but possessed greater AEs. Further studies focusing on etiopathology and phenotype differentiation of this syndrome will greatly contribute to the development of effective therapy.

Keywords: Bladder pain syndrome, Interstitial cystitis, Oral therapy

Introduction

Bladder pain syndrome (BPS) can be described as a chronic bladder pain condition without any identifiable etiology. The Society for Urodynamics and Female Urology (SUFU) explained this syndrome as an unpleasant sensation (pain, discomfort, or pressure) considered to be related to the lower urology system for more than 6 weeks, without identifiable causes [1]. NHANES III survey from the USA recorded a prevalence of 470 per 100,000 population, which was 850 per 100,000 women and 60 per 100,000 men [2].

BPS/IC has various clinical presentations includes discomfort feeling, increased bladder pressure, pain, and increase sensitivity in the bladder and pelvic areas, increased voiding frequency and urgency, or a combination of several symptoms. The pain often aggravates during menstruation, intercourse, or bladder filling with symptoms improvement after bladder emptying [1, 3].

Genitourinary pain in general can be neuropathic, nociceptive, or have elements of both. BPS/IC is one of the quite challenging conditions in chronic urologic pain. Various theories exist on the potential etiology of chronic urologic pain. These include infection, voiding dysfunction, anatomic abnormalities, immune disorders,

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endocrine, neurological, musculoskeletal, and psychological associations [4]. The development of urologic pain chronicity as in BPS is still unclear.

Nerves regeneration following injury may have abnormal connections, leading to inappropriate propagation of pain signals proximally, further mediating cross-talk, and the perception of non-painful stimuli as painful. There are suggestions of visceral and dorsal root ganglion neuron cross-sensitization as the underlying mechanism. Besides, phenotypic progression has also been reported [4].

Initial management in BPS should include prompted education, managing the comorbid condition, and psychosocial therapy. The step ladder of treatment should start from the most feasible conservative approach and step further to the less conservative option if control of symptoms is still inadequate. There is no single specific therapy consistently effective for all cases. Treatment should be tailored for each individual and the goal should focus on optimizing patients' quality of life [1, 5].

The readily available pharmacologic options for BPS/IC include oral, intravesical, and transdermal therapy. Several categories of oral medication that commonly been used for BPS include analgesics, antidepressants, antihistamines, glycosaminoglycans, immunosuppressants, and also pentosan polysulfate sodium which readily approved by the Food and Drug Administration (FDA). Many of these therapies are used empirically, while only a few of them have been studied in randomized controlled trials over recent decades [6].

Current research approaches on BPS systemic therapy, including anti-nerve growth factor treatment, activation of SHIP1 (AQX-1125), anti-tumor necrosis factor-α treatment, α1 adrenoceptor antagonists, and P2X3 receptor antagonists are potential systemic treatments [2, 7]. Alongside its systemic effect, the safety profile from oral therapies should carefully be measured. The interest in complementary therapies for BPS is increasing which encompasses physical and systemic therapy yet their evidence of effectiveness is still lacking [8, 9].

In this review, we aimed to analyze the efficacy and safety profile of oral pharmacological and supplementary therapies for BPS/IC from RCT and randomized comparative trial over the last 15 years.

Materials and methods

A systematic literature search for articles regarding oral therapies for BPS/IC that were published between 2005 and 2020 was conducted on scientific databases, namely, PubMed and Medline, following the PRISMA reporting guidelines for systematic reviews [10]. The keywords used were (bladder pain syndrome), or (interstitial cystitis), and (random or trial). 629 studies were found (Fig. 1).

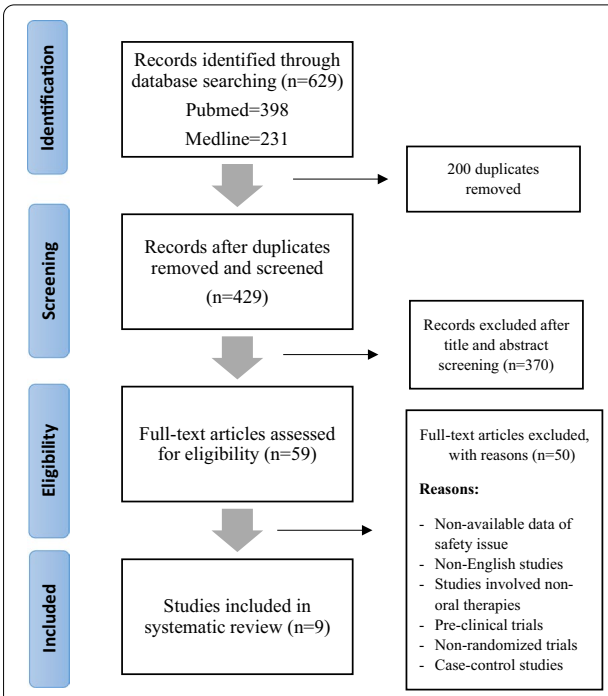

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram of included studies

The inclusion criteria for this systematic review comprise of:

1. Randomized studies either RCT or randomized comparative study whose results were published as a full article.
2. English publications only.
3. Trials on BPS oral therapies (including oral pharmacological and oral supplementary therapy).
4. Outcomes of the trials include efficacy and safety aspects.

The exclusion criteria for this systematic review comprise of:

1. Studies involving non-oral therapies for BPS.
2. Pre-clinical trials.
3. Case–control, cohort, cross-sectional, case report, literature review.
4. Trials with non-available data on the safety issue.

After applying the PRISMA protocol, a total of nine articles were retrieved (seven of them were randomized-placebo controlled trial studies, and two of them were randomized-comparative studies). Our main goal in this systematic review is to explore the characteristics of each study and equally analyze the efficacy and safety of oral

therapies on these trials. Data were collated on study characteristics (Table 1), including patient characteristics, details of oral therapy, outcome parameters, results, and adverse events.

Results

Out of the 629 citations identified by electronic literature searches, nine studies that fulfilled the inclusion and exclusion criteria were included in the systematic review (Fig. 1).

Quality assessment

The overall quality of the studies was good. We used JADAD Scale to assess the quality of our studies. The nine studies are randomized, blinded, and described the subject withdrawal. The quality assessment can be seen in Table 1 (JADAD Scale).

The characteristics of the included studies were assessed in several dimensions: types of oral therapy, sample size, study methods, intervention, and control or comparison groups, outcomes, and AEs (Table 2). In the design category, seven of the nine studies were randomized placebo-controlled trial study, while the rest were randomized comparative trials. The randomized comparative trials included in this review are a comparison study of cyclosporine A to PPS by Sairanen et al. [11] and a comparison between amitriptyline to amitriptyline combined with ALA and *n*-3 PUFA by Murina et al. [12].

Types of oral therapy included in this review comprise amitriptyline, amitriptyline plus ALA and *n*-3 PUFA, sildenafil, pentosan polysulfate sodium (PPS), cyclosporine A, PD-0299685, SHIP1 activator (AQX-1125), and hydrogen-rich water. Interstitial Cystitis Symptom Index (ICSI) was the most commonly used parameter for the outcome. Four from nine studies used Visual Analogue Scale (VAS) for their quantification of pain severity, the rest of the studies used Numeric Rating Scale (NRS).

Some of the randomized trials in this systematic review include drugs not mentioned in American Urological Association (AUA) guidelines [1], those include PD-0299685, sildenafil, SHIP1 activator, and supplementary therapies with ALA plus *n*-3 PUFA and hydrogen-rich water. The absence of a universal treatment for BPS triggers the existence of new drugs being studied to treat this syndrome.

Table 1 JADAD Scale

Author, years	Randomization	Blinding	An account of all patients	Total
Sairanen, 2005	2	1	1	4/5
Foster, 2010	2	2	1	5/5
Nickel, 2012	2	2	1	5/5
Matsumoto, 2013	2	2	1	5/5
Chen, 2014	2	2	1	5/5
Nickel, 2014	2	2	1	5/5
Nickel, 2016	2	1	1	4/5
Murina, 2017	2	2	1	5/5
Nickel, 2019	2	2	1	5/5

Quality assessment for randomized-controlled trial

Amitriptyline

Efficacy

Foster et al. conducted a randomized-controlled trial study comparing amitriptyline with placebo of 271 BPS patients. Both study groups were combined with the Educational and Behavioral Modification Program (EBMP). The results showed that from 231 subjects who were randomized, the response rate was higher in the amitriptyline group but not significant statistically ($p=0.12$). However, there was a significantly higher response rate in patients who achieved a minimum of 50 mg dose of amitriptyline ($p=0.01$) [13].

Safety

Most of the participants reported at least one AE, classified primarily as mild or moderate. The rate of AE on the amitriptyline group was 88% and 72% on the placebo group ($p=0.0013$). General malaise, dizziness, gastrointestinal and genitourinary problems were significantly more frequent in the amitriptyline group. From drug titration over 6 weeks, subjects who achieved 50 mg dose daily and continued it for 12 weeks were 46% on the amitriptyline group and 72% on placebo group. 20% of subjects from the amitriptyline group with 50 mg dose daily by 6 weeks reduced their dose for the rest of follow-up [13].

Amitriptyline in combination with alpha lipoic acid and omega-3 fatty acids

Efficacy

Murina et al. in 2017 published their randomized trial to study the effectiveness of amitriptyline combined with ALA and *n*-3 PUFA in patients with vestibulodynia/BPS. The VAS and the short-form McGill Pain Questionnaire (SF-MPQ) points significantly decrease after treatment in both amitriptyline and amitriptyline plus ALA and *n*-3 PUFA groups. Pain in the latter group improved with greater significance. The average dose of amitriptyline on this combined therapy to achieve efficacy was 22 mg, which was smaller than the average dose in general. The

Table 2 Characteristics of studies included in the systematic review of oral pharmacological and supplementary therapies in BPS/IC

References	Drug	Sample size (*n*)	Methods	Study duration/ follow-up	Intervention	Control	Outcome parameters (primary and secondary)	Results	Adverse event (AE)
Sairanen et al. [11]	Cyclosporine A compared to pentosan polysulfate sodium	64	Subjects were randomized in a 1:1 ratio to 1.5 mg/kg CyA twice daily or 100 mg PPS three times daily	6 months	Cyclosporine A ($n=32$)	PPS ($n=32$)	Daily micturition frequency, mean and maximal voided volume, nocturia episodes, ICSI, ICPI, VAS, subjective GRA	CyA was superior to PPS in all outcome parameters measured at 6 months	More AEs in the CyA group than in the PPS, 29 patients completed the 6-month follow-up in both groups
Foster et al. [13]	Amitriptyline	231	Subjects received an EBMP and were randomized in a 1:1 ratio to either amitriptyline-line or matching placebo	12 weeks	EBMP + Amitriptyline daily (dose escalation over 6 weeks from 10 to 75 mg per day) ($n=112/13$); withdrawn: 23	EBMP + Placebo ($n=119/136$); withdrawn: 17	GRA, pain, urgency and frequency score (0–10), ICSI, ICPI, 24 h and nighttime voiding frequency	Amitriptyline + EBMP improved GRA but not significant statistically, but a minimum 50 mg dose of amitriptyline per day suggested its effectivity compared to placebo (p 0.01)	The side-effect of amitriptyline was acceptable yet adherence to higher doses was low
Nickel et al. [15]	PD-0299685	161	Subjects were given either 30 mg PD-0299685 daily or 60 mg PD-0299685 daily or placebo	12 weeks	30 mg PD-0299685 ($n=40/54$); discontinued: 14 60 mg PD-0299685 ($n=31/55$); 24 discontinued	Placebo ($n=41/52$); discontinued: 11	NRS, ICSI, MVV, nocturnal frequency, MMF, UEF	PD-0299685 failed to improve pain and other urinary end points	Tolerability was poor, with a dose response for AEs of dizziness, somnolence and nausea
Matsumoto et al. [20]	Hydrogen-rich water	28/30 (2 withdrawal)	Subjects were randomized by a 2:1 ratio to receive hydrogen-rich water or placebo water	8 weeks	Hydrogen-rich water 3 packs/day ($n=18$)	Placebo water 3 packs/day ($n=10$)	ICSI, ICPI, Parson's Pelvic Pain, Urgency/Frequency Patient Symptom Scale, VAS score, standard 3-day voiding diary	The overall treatment outcome did not differ significantly between the 2 groups. The VAS scores in 2 patients of hydrogen-rich water group showed valuable improvement	No AEs in all subjects

Table 2 (continued)

References	Drug	Sample size (*n*)	Methods	Study duration/ follow-up	Intervention	Control	Outcome parameters (primary and secondary)	Results	Adverse event (AE)
Chen et al. [16]	Sildenafil	48	Subjects were randomized to daily low-dose sildenafil 25 mg or placebo	3 months	Daily low-dose sildenafil 25 mg ($n=24$)	Placebo ($n=24$)	ICSI, ICPI, VAS, micturition diary, PORIS	ICSI and ICPI were significantly improved in treatment group ($p<0.05$). Urodynamic index significantly improved at weeks 12 and 3 months after treatment ($p<0.05$). No significant change of the VAS between 2 groups except at week 12	All AEs were mild to moderate and temporary
Nickel et al. [17]	Pentosan polysulfate sodium (PPS)	368	Subjects received PPS 100 mg once (QID), PPS three times (TID) daily, or matching placebo	24 weeks	PPS 100 mg QID ($n=128$) PPS 100 mg TID ($n=122$)	Placebo ($n=118$)	ICSI, NRS, PORIS, GRA, urgency, frequency	No significantdifference between either PPS dose group and placebo or between the PPS dose groups for the primary endpoint	PPS was well tolerated, with similar percentages of discontinued subjects due to an AE (10.2–13.3%)
Nickel et al. [18] Phase 2 trial	AQX-1125	69	Subjects were randomized to single oral daily capsule of 200 mg AQX-1125 or placebo	6 weeks	Single daily capsule of 200 mg AQX-1125 ($n=37$)	Placebo ($n=32$)	NRS, ICSI, ICPI, BPIC-SS, SF-12v2, maximum daily pain and frequency	AQX-1125 significantly improved bladder pain and urinary symptoms at 6 weeks in moderate to severe BPS	AE rates were similar between AQX 1125 (51.4%) and placebo (78.1%). No serious AEs reported

Table 2 (continued)

References	Drug	Sample size (*n*)	Methods	Study duration/ follow-up	Intervention	Control	Outcome parameters (primary and secondary)	Results	Adverse event (AE)
Murina et al. [12]	Amitriptyline + alpha lipoic acid (ALA) plus omega-3 fatty acids	84	Subjects were randomized to amitriptyline or amitriptyline plus ALA 600 mg + *n*-3 PUFA	12 weeks	Amitriptyline + preparation containing ALA plus *n*-3 PUFAs twice daily (*n* = 43)	Amitriptyline (*n* = 41)	VAS, McGill-Pain Questionnaire, pelvic floor tonus, dyspareunia	Pain decreased significantly in both groups, with a greater effect seen in the intervention group. There were improvements in dyspareunia and pelvic floor muscle tone in the intervention group	The overall incidence of AEs was low, none led to treatment discontinuation
Nickel et al. [19] Phase 3 trial	SHIP1 activator	385	Subjects were randomized to 100 or 200 mg of an oral SHIP1 activator or placebo once daily	12 weeks	AQX-1125 100 mg (*n* = 114) AQX-1125 200 mg (*n* = 113)	Placebo (*n* = 114)	NRS, ICSI, BPIC-SS, SF-12v2, maximum daily pain and frequency	No difference in maximum daily bladder pain compared to placebo. No treatment benefit over placebo in the secondary end points of urinary voiding frequency, BPIC-SS, ICSI and GRA	Treatment was well tolerated at both doses

CyA cyclosporine A, *PPS* pentosan polysulfate sodium, *ICSI* Interstitial Cystitis Symptom Index, *ICPI* Interstitial Cystitis Problem Index, *VAS*: Visual Analog Scale, *GRA* Global Response Assessment, *EBMP* Education and Behavioral Modification Program, *NRS* Numeric Rating Scale, *MVV* Maximum Voided Volume, *MMF* Mean Micturition Frequency, *UEF* Urgency Episode Frequency, *PORIS* Patient's Overall Rating of Improvement of Symptoms, *BPIC-SS*: Bladder Pain/Interstitial Cystitis Symptom Score, *SF 12V2* short form 12 item (version 2)

overall incidence of side effects was (9.5%) and there was no subject dropout [12].

Safety

The overall incidence of AEs was low from this drug combination without any treatment discontinuation. Eight patients (9.5%) experienced drug AEs: three from the amitriptyline group and five from the amitriptyline plus ALA and *n*-3 PUFAs group. Sedation, constipation, and dry mouth were the most common AEs [12].

Cyclosporine A

Efficacy

Sairanen et al. in 2005 published their comparative study and concluded that CyA was superior to PPS in all clinical outcome parameters at 6 months [11]. They chose to compare CyA with PPS since PPS has been tested several times against placebo and accepted for BPS/IC therapy [14]. The number of responders from the study was significantly improved after 6 months compared to after 1 month of CyA therapy ($p=0.006$) [11].

Safety

There were more AEs in the CyA group compared to the PPS group. They consisted of increased blood pressure and serum creatinine with mild to moderate AEs, such as induced hair growth, gingival pain and hyperplasia, paresthesias in extremities, abdominal pain, muscle pain, flushing, and shaking. Despite that condition, 19 patients from the study decided to continue the CyA treatment after 6 months of study, while 4 patients continued on PPS treatment [11].

PD-0299685

Efficacy

Nickel et al. conducted a phase II a, randomized, double-blind, placebo-controlled study for PD-0299685. From the 161 subjects admitted in their study, PD-0299685 in 30 or 60 mg dose daily did not succeed to prove a positive impact for pain treatment and urinary parameters related to BPS/IC. Nickel et al. included a cohort with prolonged symptoms so they might represent a subgroup of cases that were refractory to treatment and subsequently it was difficult to demonstrate unequivocal efficacy [15].

Safety

The most common AEs from PD-0299685 were somnolence, dizziness, and nausea. They were reported at a greater proportion in the treatment group compared to placebo. A higher dose of 60 mg compared to 30 mg resulted in greater AEs incidences. Serious treatment-related AEs (deep vein thrombosis and suicide attempt) were reported in 2 of 54 participants in the 30 mg dose group [15].

Sildenafil

Efficacy

A randomized, double-blind, placebo-controlled trial published in 2014 by Chen et al. evaluate the efficacy of daily low dose (25 mg) sildenafil for BPS/IC. The study conducted on 48 women and resulted in a significantly improved ICSI, ICPI, and urodynamic index starting from the 4th week until 3 months after treatment. The efficiency of treatment reached 62.5%. However, the VAS score had significant changes only at the 12th week in the sildenafil group [16].

Safety

Chen et al. concluded that the daily low-dose of sildenafil was well-tolerated. All 48 patients completed the study. There was only mild to moderate AEs such as mild headache and flushing at the beginning of treatment but they only last temporary (2–4 days) [16].

Pentosan polysulfate sodium

Efficacy

Nickel et al. in 2014 reported their study on the efficacy and safety of the currently recommended dose of PPS (300 mg per day) with one-third of daily dose and with placebo. There was no statistically significant difference between either the PPS dose group and placebo or between the PPS dose groups for the primary endpoint [17].

Safety

They concluded that PPS was well tolerated with similar discontinue percentages between treatment and control group because of an adverse event. The majority of AEs were moderate in intensity. The most common treatment-emergent AEs were bladder pain, nausea, headache, and exacerbation of BPS symptoms [17].

SHIP1 activator (AQX-1125)

Efficacy

In 2016, Nickel et al. published their initial phase II pilot study to evaluate the efficacy of AQX-1125. The oral SHIP1 activator AQX-1125 administered once 200 mg daily for 6-week reduced pain, voiding frequency, and BPS symptoms [18]. The promising result of this phase II RCT prompted the initiation of the much larger and longer phase III dose-ranging RCT to evaluate the therapeutic benefit of this regimen. Nickel et al. in 2019 published their 12-week, RCT, phase 3 trial on SHIP1 activator. 298 female subjects with moderate to severe symptoms of BPS/IC were treated with 100 or 200 mg

SHIP1 activator once daily for 12 weeks. Treatment demonstrated no difference in maximum daily bladder pain compared to the placebo. There was no treatment benefit over that of placebo in the secondary endpoints [19].

Safety

Nickel et al. concluded that AQX-1125 was generally well tolerated at the 100 and 200 mg doses. Overall adverse event rates between the placebo group and the two AQX-1125 treatment groups were similar [19].

Hydrogen-rich water

Efficacy

Matsumoto et al. in 2013 published their study on the first RCT of hydrogen-rich water for the treatment of patients with BPS/IC. 30 participants were randomized in a 2:1 ratio to receive hydrogen-rich water or placebo water for 8 weeks. The results from their study do not support the use of hydrogen-rich water as supplementation for BPS/IC therapy. The score of bladder pain was significantly improved in both groups but did not differ significantly per statistic [20].

Safety

All patients reported no adverse events.

Discussion

Based on our systematic review, we obtained nine randomized studies on oral therapy for BPS. Amitriptyline plus ALA and *n*-3 PUFA, sildenafil, and cyclosporine A have proved their efficacy. Amitriptyline is considered the second-line treatment for BPS according to AUA guidelines. Amitriptyline as tricyclic antidepressants has analgetic effect and capability to improve depression. It blocks acetylcholine receptors, inhibits the reuptake of released serotonin and norepinephrine, and blocks histamine H1 receptors [6, 21]. Its pharmacologic action in BPS/IC is presumed by blocking H1-histamine receptors, helping to stabilize mast cells, so that mast cell degranulation within the bladder wall decreased [22]. Urinary storage improvement may be facilitated through the stimulation of beta-adrenergic receptor. The primary side effect of amitriptyline is sedation but this effect may alleviate BPS nocturnal symptoms when administered at night [6, 23].

van Ophoven et al. conducted a prospective RCT study of amitriptyline in 48 subjects with BPS/IC. Oral amitriptyline (25 mg titrated until 100 mg daily if tolerated) over 4 months was effective compared to placebo (63% versus 4%) [24]. A newer RCT study conducted by Foster et al. suggested that amitriptyline was effective at a minimum dose of 50 mg, but adherence to higher doses was poor. The most common side effects of amitriptyline are sedation, nausea, and drowsiness (found in up to 79% of cases) [1]. AEs experienced by some patients might influence patients' compliance and decrease their willingness to continue the treatment.

It is expected that combined therapy with ALA and *n*-3 PUFA can reduce the amitriptyline dose needed and reduce potential AEs [12]. Several studies regarding alpha-lipoic acid (ALA) reveal its antioxidant and anti-inflammatory effects. ALA may reduce pain and paresthesia, and has been used in several chronic neuropathic conditions as in diabetic neuropathy and carpal tunnel syndrome. Intake of Docosahexaenoic acid which belongs to predominant Omega-3 polyunsaturated fatty acid can increase the neuropathic and thermal pain threshold, it also provides anti-nociceptive effects [12, 25].

ALA can cross the blood–brain barrier and exert anti-inflammatory effects. Meanwhile, *n*-3 PUFAs also has several physiological roles in the nervous and cardiovascular systems. *n*-3 PUFAs are precursor of eicosanoids [26]. Multiple mechanisms with synergistic interactions of this drug combination might provide better pain relief compared to monotherapy [27].

The superiority of cyclosporine A compared to PPS was found in all clinical outcome parameters measured at 6 months but AEs were greater in the CyA arm [11]. The safety aspect of this drug must be cautiously considered. CyA acts as a calcineurin inhibitor which inhibits T cell activation by blocking cytokines genes transcription process and also stabilizing mast cells [28]. Before the comparative trial between CyA and PPS published in 2005, there was already a previous retrospective analysis on CyA which resulted in its highly efficient effect for BPS/IC [14]. The clinical efficacy of CyA improved with a longer treatment period which might be described by the inhibition of chronic inflammation that comes slowly as seen with relief from symptoms [11].

Sildenafil on a small daily dose improves BPS outcome and was well-tolerated [16]. BPS/IC encompasses a variety of symptoms, such as increased frequency voiding frequency and urgency. Phosphodiesterase type 5 inhibitors (PDE5I) may relax the contraction of smooth muscle caused by adrenergic activity or elevating potassium. Several studies reported that sildenafil was effective in treating an overactive bladder by the cyclic guanosine monophosphate (cGMP)-dependent protein kinase GRhoA/Rho-kinase signaling pathway Result from previous studies revealed the beneficial effect of PDE5I on various lower urinary tract symptoms (LUTS) benign prostatic hyperplasia and overactive bladder [29], those results suggested PDE5I can be a potential treatment for BPS/IC. Future studies with a larger population and longer follow-up are needed to confirm this promising result.

Regarding other therapies included in this review, SHIP-1 activator in phase II study showed satisfactory results, but in the phase III trial, there was no significant benefit over placebo [18, 19]. AQX-1125, being one of SHIP-1 activator is new pharmaceutical compounds that appears to be a potentially effective therapy in women with BPS/IC. AQX-1125 is a modulator of phosphoinositide signaling for diverse processes including cell growth, activation, and immune/inflammatory regulation [30]. There were discrepancies between the efficacy observed in the phase II and III trials of this drug [18, 19].

PPS that has been recognized for BPS did not succeed to show significant effect compared to placebo according to RCT by Nickel et al. [17]. Oral PPS was approved by AUA guideline as a treatment option in BPS. The proposed pharmacologic mechanism of PPS is that it rejuvenates the deficiency of glycosaminoglycan layer to protect the urothelium [31, 32]. Nonetheless, there is only a small amount of PPS absorbed by the alimentary system [33, 34]. Nickel et al. emphasized that early termination, study design, inclusion criteria, and high dropout rates might limit the study [17].

PD-0299685 study published by Nickel et al. concluded that the risk and benefit profile appeared to be unfavorable [15]. Drug tolerability was concluded as poor. PD-0299685 belongs to Calcium channel α2δ ligand. The α2δ subunit of ligand-gated $Ca2^{+}$ ion channels give an impact on chronic pain conditions since it mediates afferent nerve pain fibers. It has been studied in inflammatory pain with a nonclinical model and demonstrated efficacy, it may indicate benefit for conditions with chronic inflammatory pain [35]. There was also a small number of non-controlled trial reports indicating that α2δ ligand may be efficacious in BPS/IC.

The interest in complementary and alternative therapies for BPS is high, while the effectiveness is still questionable. Oxidative stress is hypothesized as one of the BPS causes. Several investigations have shown that hydrogen acts as an antioxidant for preventive and therapeutic purposes [36–38]. Ohsawa et al. reported that hydrogen selectively reduces cytotoxic oxygen radicals so that it may act as a therapeutic antioxidant [39]. From the first RCT on hydrogen-rich water, Matsumoto et al. did not support the use of hydrogen-rich water for BPS/IC [20].

Conclusions

From this systematic review, we delineate that as there are many options of oral therapies for BPS/IC, amitriptyline in combination with ALA and *n*-3 PUFA, sildenafil, and cyclosporine A provide good efficacy for BPS/IC. From the safety aspect, ALA and *n*-3 PUFA supplementation is expected to reduce the minimum dose of amitriptyline needed and reduce its adverse events. Sildenafil was generally well tolerated, while CyA should be administered with caution as its superiority over PPS possessed greater incidence of adverse events.

BPS/IC cases are heterogeneous with varying clinical phenotypes. Future studies focusing on etiopathology and phenotype differentiation of this syndrome will greatly contribute to the development of effective therapy.

Abbreviations

BPS: Bladder pain syndrome; IC: Interstitial cystitis; AEs: Adverse events; RCTs: Randomized-controlled trials; CyA: Cyclosporine A; ALA: Alpha lipoic acid; *n*-3 PUFA: Omega-3 fatty acids; PPS: Pentosan polysulfate sodium; SUFU: The Society for Urodynamics and Female Urology; FDA: Food and Drug Administration; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; ICSI: Interstitial Cystitis Symptom Index; ICPI: Interstitial Cystitis Problem Index; VAS: Visual Analog Scale; GRA: Global Response Assessment; EBMP: Education and Behavioral Modification Program; NRS: Numeric Rating Scale; MVV: Maximum Voided Volume; MMF: Mean Micturition Frequency; UEF: Urgency Episode Frequency; PORIS: Patient's Overall Rating of Improvement of Symptoms; BPIC-SS: Bladder Pain/Interstitial Cystitis Symptom Score; SF 12V2: Short form 12 item (version 2); SF-MPQ: Short-form McGill Pain Questionnaire; PDE5I: Phosphodiesterase type 5 inhibitors; cGMP: Cyclic guanosine monophosphate; LUTS: Lower urinary tract symptoms.

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Author contributions

IPEW was the first one to come up with the idea for this systematic review and was a major contributor in writing the manuscript. VTD collect and analyze the data for the available publication and previous researches regarding this topic also contribute in writing the manuscript. IASW and KBU contributed to review the data analyzed. All authors read and approved the final manuscript.

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Consent for publication

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Competing interests

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