REVIEW ARTICLE

Efficacy and safety comparison of pharmacotherapies for interstitial cystitis and bladder pain syndrome: a systematic review and Bayesian network meta-analysis

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Abstract

Introduction and hypothesis The objective was to compare the clinical efficacy and safety of pharmacological interventions for interstitial cystitis and bladder pain syndrome (IC/BPS) with direct and indirect evidence from randomized trials.

Methods We searched PubMed, the Cochrane library, and EMBASE for randomized controlled trials (RCTs) that assessed the pharmacological therapies for IC/BPS. Primary efficacy outcomes included ICSI (O'Leary Sant Interstitial Cystitis Symptom Index), ICPI (O'Leary Sant Interstitial Cystitis Problem Index), 24-h micturition frequency, visual analog scale (VAS), and Likert score for pain. Safety outcomes are total adverse events (AEs, intravesical instillation, and others), gastrointestinal symptoms, headache, pain, and urinary symptoms. A systematic review and Bayesian network meta-analysis were performed.

Results A total of 23 RCTs with 1,871 participants were identified. The ICSI was significantly reduced in the amitriptyline group (MD = −4.9, 95% CI: −9.0 to −0.76), the cyclosporine A group (MD = -7.9, 95% CI: −13.0 to −3.0) and the certolizumab pegol group (MD = −3.6, 95% CI:−6.5 to −0.63) compared with placebo group. Moreover, for ICPI, cyclosporine A showed superior benefit compared to placebo (MD = −7.6, 95% CI: −13 to −2.3). VAS score improved significantly in cyclosporine A group than pentosan polysulfate sodium (MD = 3.09, 95% CI: 0.13 to 6.07). None of the agents revealed a significant alleviation of 24-h micturition frequency. In terms of safety outcomes, the incidence rate on urinary symptoms for botulinum toxin A was the only variate higher than chondroitin sulfate (MD = −2.02, 95% CI: −4.99 to 0.66) and placebo (MD = −1.60, 95% CI:−3.83 to 0.17). No significant difference was found among the other treatments.

Conclusions Cyclosporine A might be superior to other pharmacological treatments in efficacy. Amitriptyline and certolizumab pegol were capable of lowering the ICSI as well.

Keywords Interstitial cystitis · Bladder pain syndrome · Pharmacological therapy · Clinical trials · Systematic review · Network meta-analysis

Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a urinary bladder disease characterized as lower urinary tract

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symptoms over 6 weeks with an unpleasant sensation such as discomfort, pain, and pressure [1]. The prevalence of IC/BPS is around 45 out of 10,000 in women and 8 out of 100,000 in men [2]. Pain is a vital symptom of IC/BPS, which is not only suprapubic pain associated with bladder filling but also pelvic pain (urethra, vagina, rectum, etc.) [3]. However, the unitary of definition and management, the optimal treatment, and treatment duration are still absent worldwide [4].

Moreover, various pharmacological therapies with IC/BPS as the target have been discussed, such as intravesical instillation including chondroitin sulfate [5], alkalinized lidocaine [6, 7] and bacillus Calmette–Guerin (BCG) [8]; intravesical injection including onabotulinum toxin A [9–11]; oral medication including tricyclic antidepressants, hydroxyzine,

cimetidine, and pentosan polysulfate (PPS) sodium [12, 13]; subcutaneous medication including certolizumab pegol, adalimumab, fulranumab; and intravenous medication including tanezumab. However, the highest curative rate is only about 60% [10]. It has been found that IC/BPS is a multifactorial disease, as along with autoimmunological responses [14], there is damage of the glycosaminoglycan (GAG) layer of the urothelium [15], neurological pain, and inflammatory activities [16]. PPS reduces urothelial permeability by reinforcing the GAG layer. Lidocaine has shown an obvious improvement in IC/BPS symptoms because of its anti-inflammatory function. Heparin-related drugs function as part of GAG family, which promotes the growth of urothelium. Intravesical injection of botulinum toxin A (BoNTA) has shown an improvement in IC/BPS symptoms through detrusor paralysis [17]. Therefore, more effective methods are necessary for patients who do not respond to current therapies.

Although several pairwise meta-analyses and a network meta-analysis have been published [18–20], only the outcome of intravesical pharmacotherapies with a limited information supply was provided. Many other drugs have different application methods, and there are no ranking recommendations at present [21]. Hence, we performed this systematic review and Bayesian network meta-analysis to investigate all available pharmacological therapies for more evidence on efficacy and safety for patients with IC/BPS.

Materials and methods

Methodology

We conducted a network meta-analysis based on a Bayesian model of randomized controlled trials (RCTs), comparing pharmacotherapies for IC/BPS. Our network meta-analysis was carried out under the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement for network meta-analysis of health care interventions. In addition, the current meta-analysis was registered on PROSPERO (no. CRD42020176627). Commentaries, review articles, editorials, and letters were excluded. All duplicates were excluded, following the literature research.

Search strategy

A search of PubMed, the Cochrane library, EMBASE, and other sources covering English-language articles with full text from August 2003 to June 2020 was carried out. Both text word terms and subject headings ("Interstitial Cystitis" *or* "Bladder Pain Syndrome" *and* "RCT")

were used including MeSH terms in combination with keyword searching (see Supplementary Table 1). All results were restricted to RCTs.

Eligibility and exclusion criteria

Participants of our network meta-analysis were all diagnosed with IC/BPS or refractory IC/BPS. The diagnostic criteria decided by the study authors were based on urinary symptom scores such as an ICSI (O'Leary Sant Interstitial Cystitis Symptom Index) of at least 5, an ICPI (O'Leary Sant Interstitial Cystitis Problem Index) of at least 4, and chronic bladder pain over 6 months, accompanied by urinary urgency, urinary frequency (≥8 voids daily) [22, 23]. In addition, patients with urinary tract infection, bladder outlet obstruction, overactive bladder, or other urological diseases were excluded.

Studies were included if they were prospective RCTs, assessing pharmacotherapy of IC/BPS with a duration of no less than 4 weeks. The intervention arms of our network meta-analysis were all pharmacological therapies. Accordingly, we searched mainly regarding several pharmacological therapies including antidepressants, tumor necrosis factor, anesthetics, toxins, etc. All the interventions were listed in Supplementary Table 1. For studies concerning multiple publications, the most intact or recent version in our analysis was included.

Unavailable data, observational studies, commentaries, and review articles were excluded. Bibliographies of the studies included were hand-searched to ensure completeness. Conference abstracts were not included because of absent or insufficient data. All duplicates were excluded. The comparators were placebo or other related pharmacological treatments eligible in our network meta-analysis.

Outcome measures

The primary outcome was efficacy (ICSI, ICPI, 24-h micturition frequency, visual analog scale [VAS] for pain, Likert score for pain). Secondary outcomes were total adverse events (AEs, intravesical instillation, and others), gastrointestinal symptoms, headache, pain, and urinary symptoms.

Study selection and data extraction

According to the criteria above, two authors (XP Di and DY Luo) performed the study selection independently and strictly. Disagreements were resolved by discussion. Moreover, all baseline information was analyzed thoroughly to avoid bias; such information included age, design, sample size, drugs, as well as efficacy, safety, and adverse events.

Fig. 1 Flow chart of study identification and the selection procedure. *RCT* randomized controlled trial
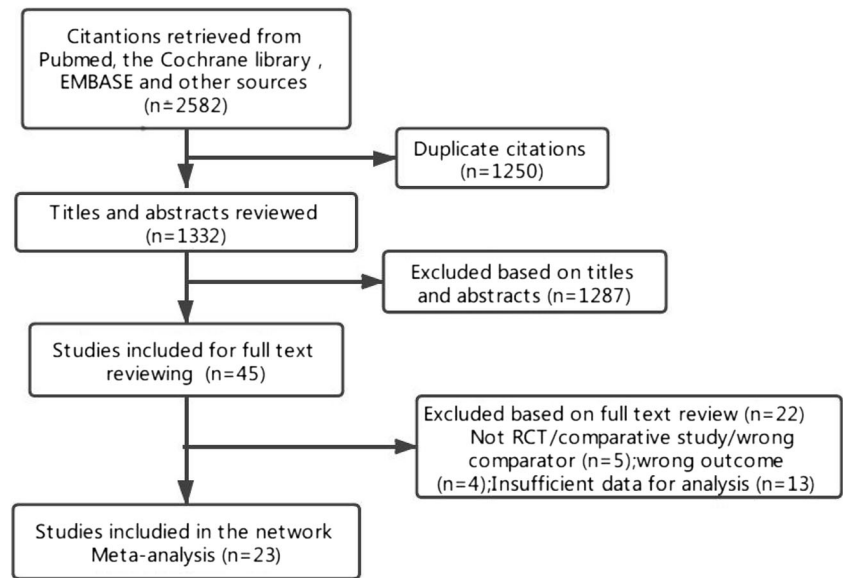
Risk of bias assessment

The risk of bias was assessed via the Cochrane Collaboration tool [24] in RevMan version 5.3. Then, selection bias (allocation

Fig. 2 Network plot of pharmacological therapies included in the network meta-analysis. The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of each circle represents the amount of randomized assigned participants (sample size). *ADA* adalimumab, *AMI* amitriptyline, *AQX1125* SH2-containing inositol-50-phosphatase1ctivator, *BCG* bacillus Calmette–Guérin, *BoNTA* botulinum toxin A, *CER* certolizumab pegol, *CS* chondroitin sulfate, *CyA* cyclosporine A, *DMSO* dimethyl sulfoxide, *FUL* fulranumab, *HA* hyaluronic acid, *HA/CS* hyaluronic acid plus chondroitin sulfate, *LPX* lipotoxin, *PLA* placebo, *PPS* pentosan polysulfate, *PSD597* alkalinized lidocaine, *SIL* sildenafil, *TAN* tanezumab
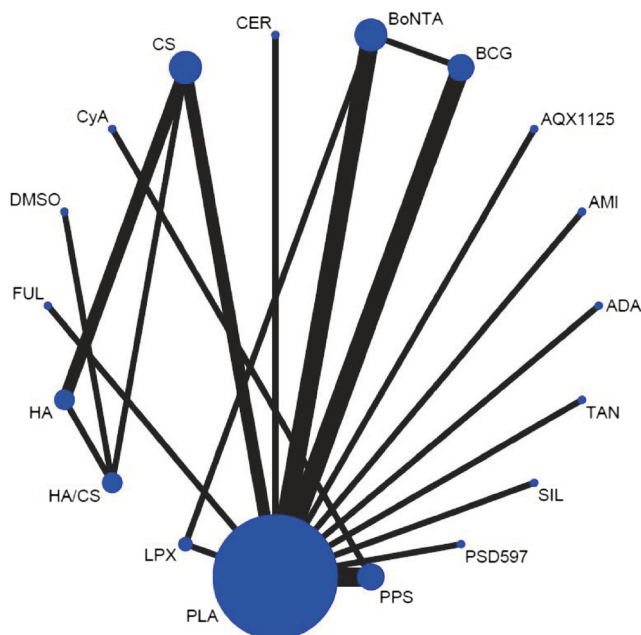
concealment, random sequence generation), performance bias, attrition bias, reporting bias, and other susceptible sources of bias were analyzed by XP Di and DY Luo separately.

Data analysis

Before the meta-analysis, we summarized the base-line information and outcomes of the studies included. Mean differences (MDs) for continuous variables and risk ratios (RRs) for dichotomous variables with 95% confidence intervals (CIs) were used to present the integrated data.

Both traditional meta-analysis and network meta-analysis were performed. First, a pairwise meta-analysis was performed on a random-effects model. Any outcome covering more than 10 studies was analyzed using Begg's test to detect publication bias in STATA version 15.1. Once publication bias was detected, Egger's test or the trim-and-fill method was used for further detection. $p \leq 0.05$ indicates significant heterogeneity. Then, a network meta-analysis based on Bayesian frameworks was conducted for direct and indirect treatment comparisons. Considering the heterogeneities among groups, the most recommended random-effects model for analysis was applied. The Markov chain Monte Carlo method was used with four chains in 'GeMTC' packages of R version 3.6.1 (https://www.r-progect.org/) [25]. Moreover, we ran models for 150,000 iterations to ensure convergence of the model, which was ensured by density and convergence plots, after discarding the first 20,000 iterations and thinning of 1. We estimated relative probability rankings of each treatment and assessed the hierarchy of competing interventions using the Surface Under the Cumulative Ranking (SUCRA) curve.

As the inclusion criteria were different between studies, a sensitivity analysis was conducted by comparing the Deviance Information Criterion (DIC) between the consistent

Table 1 Characteristics of studies on pharmacological therapies for interstitial cystitis and bladder pain syndrome included in the network meta-analysis

Reference	Region	Study interval	Intervention	Number of patients	Gender, n (%, female)	Age, mean (SD)	Application method	Follow-up
Van Ophoven et al. [26]	Germany	–	Amitriptyline Placebo	25 25	44 (88)	50.5 (14.4) 60.2 (17.5)	Oral	4 months
Chen et al. [27]	China	June 2009 ~ June 2011	Sildenafil Placebo	24 24	48 (100)	38.3 (5.4) 37.8 (4.4)	Oral	3 months
Bosch [28]	USA	2015 ~ 2017	Certolizumab pegol Placebo	28 14	42 (100)	50 54	Subcutaneous	18 weeks
Bosch [29]	USA	March 2011 ~ March 2013	Adalimumab Placebo	21 22	34 (79.07)	45.2 (14.0) 46.5 (13.4)	Subcutaneous	12 weeks
Wang et al. [30]	USA, Canada	March 2010 ~ June 2011	Fulranumab Placebo	14 17	26 (83.87)	50.6 (10.68) 46.2 (13.56)	Subcutaneous	12 weeks
Evans et al. [31]	USA	March 2008 ~ April 2009	Tanezumab Placebo	34 30	(89)	21 ~ 85	Intravenous	6 weeks
Nickel et al. [32]	Canada, USA	July 2013 ~ January 2015	AQX-1125 Placebo	37 32	69 (100)	52.1 (14.9) 53.1 (12.9)	Oral	6 weeks
Giannantoni et al. [33]	Canada	–	CS Placebo	50 48	98 (100)	44.4 (14.59) 46.8 (14.06)	Intravesical instillation	11 weeks
Cervigni [34]	Italy	June 2011 ~ September 2013	HA/CS DMSO	74 36	110 (100)	50.95 (14.97) 48.78 (17.70)	Intravesical instillation	6 months
Mayer et al. [8]	USA	September 2011 ~ January 2003	BCG Placebo	131 134	214 (80.75)	18.1 (13.9) 47.3 (13.2)	Intravesical instillation	34 weeks
Kuo et al. [11]	Taiwan	–	BoNTA Placebo	40 20	52 (86.67)	52.9 (14.3) 50.2 (13.2)	Intravesical injection	8 weeks
Davis [35]	USA	April 2004 ~ August 2006	PPS Placebo	21 20	41 (100)	36.9 38.7	Intravesical instillation	18 weeks
Sairanen et al. [36]	Finland	–	Cyclosporine A PPS	32 32	52 (82.81)	56.2 (14.7) 59.7 (13.0)	Oral	8 months
Nickel et al. [37]	USA, Canada	September 2003 ~ June 2011	PPS-qd PPS-tid Placebo	118 128 122	332 (90.22)	45.6 (15.73) 42.7 (15.7) 44.6 (14.58)	Oral	24 weeks
Gülpmar [38]	Turkey	January 2012 ~ February 2014	CS HA	21 21	42 (100)	41.7 (10.7) 48.9 (17.18)	Intravesical instillation	6 months
El-Bahnasy [39]	Egypt	–	BCG BoNTA	18 18	36 (100)	Over 18	Intravesical instillation Intravesical injection	23 weeks
Nickel [40]	USA, Canada	–	PSD597 Placebo	50 52	99 (97.06)	44.5 (13.8) 49.0 (14.5)	Intravesical instillation	29 days
Manning [41]	Australia	January 2004 ~ February 2009	BoNTA Placebo	26 27	53 (100)	54 53	Intravesical injection	3 months
Nickel [42]	Canada	–	CS Placebo	33 32	64 (98.46)	45.5 (16.07) 44.4 (14.87)	Intravesical instillation	12 weeks
Irani [43]	Iran	January 1999 ~ September 2002	BCG Placebo	15 15	30 (100)	40.8 (13.96) 36 (12.84)	Intravesical instillation	24 months
Propert [44]	USA	–	BCG Placebo	22 16	(80)	–	Intravesical instillation	68 weeks
Chuang and Kuo [9]	Taiwan	July 2014 ~ August 2016	Lipotoxin BoNTA Placebo	31 28 31	80 (88.89)	53.9 (12.9) 47.8 (9.9) 55.9 (8.6)	Intravesical instillation	4 weeks
Özkıdık [45]	Turkey	–	HA CS HA/CS	24 24 24	62 (86.11)	37.1 37.4 37.2	Intravesical instillation	24 months

qd once a day, *tid* third times a day, *AQX-1135* SH2-containing inositol-50-phosphatase1 ctivator, *BCG* bacillus Calmette–Guérin, *BoNTA* botulinum toxin A, *CS* chondroitin sulfate, *DMSO* dimethyl sulfoxide, *HA* hyaluronic acid, *HA/CS* hyaluronic acid plus chondroitin sulfate, *PPS* pentosan polysulfate, *PSD597* alkalinized lidocaine
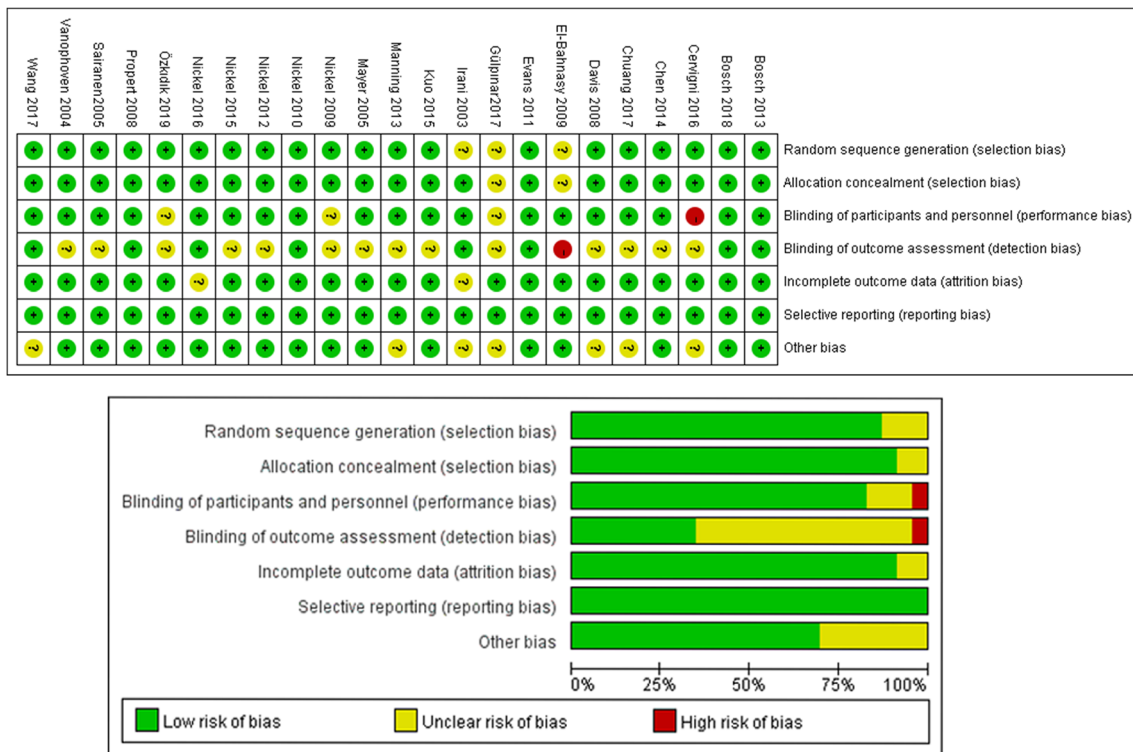
Fig. 3 Quality assessment for the risk of bias of eligible studies

and inconsistent models for each outcome (https://mtm.uoi.gr/index.php/tutorial/15-tutorial-articles/mtmmetaanalysis/31-generalstatisticalconsiderations).

Results

Search and selection

The literature search yielded a total of 2,582 articles, as shown in the PRISMA flowchart. One thousand three hundred and thirty-two titles and abstracts were reviewed after deletion of 1,250 duplicates. Fourty-five articles were eligible for fulltext review. Twenty-two of 45 articles were excluded according to the inclusion and exclusion criteria. Twenty-three RCTs with 1,881 participants were identified after careful revision (Table 1). A summary of the literature review was shown in Fig. 1. A weighted network plot was shown in Fig. 2.

Study and patient characteristics

Publication dates ranged from August 2003 to September 2019 from different regions or nations. The number of patients in each arm ranged from 14 to 134. The follow-up duration ranged from 29 days to 24 months. Most patients were women.

All studies were RCTs, with three triple-arm studies ($n = 530$) and 20 double-arm ($n = 1,351$) studies. Placebo was regarded as the most frequent comparator. Nineteen of 23 studies were double-blind trials. The application methods in most studies were intravesical instillation or injection, whereas 5 were orally administered [26, 27, 32, 36, 37], 3 were subcutaneously injected [28–30], and 1 was intravenously infused [31]. For intravesical injection, patients received injection of specific drugs about 1 mm into the urothelium at the posterior and lateral wall of the bladder. For subcutaneous injection, drugs or placebo were injected into the thigh (or abdominal wall).

For the primary outcome, 17 out of 23 studies provided the ICSI score. Meanwhile, 15 out of 23 studies provided an ICPI score. For secondary outcomes, 17 out of 23 covered 24-h micturition frequency, and 15 out of 23 reported the pain scores (VAS or Linkert). Fifteen studies depicted the AEs. Further details are shown in Table 1.

Quality of evidence and risk bias

According to the Cochrane risk of bias tool, the quality and risk of bias were carefully assessed. The results showed the high quality and low risk of eligible studies (Fig. 3). The allocation concealment was difficult to figure out, with the possibility of selection bias. Besides, no publication bias was detected in Begg's test (Fig. S1).
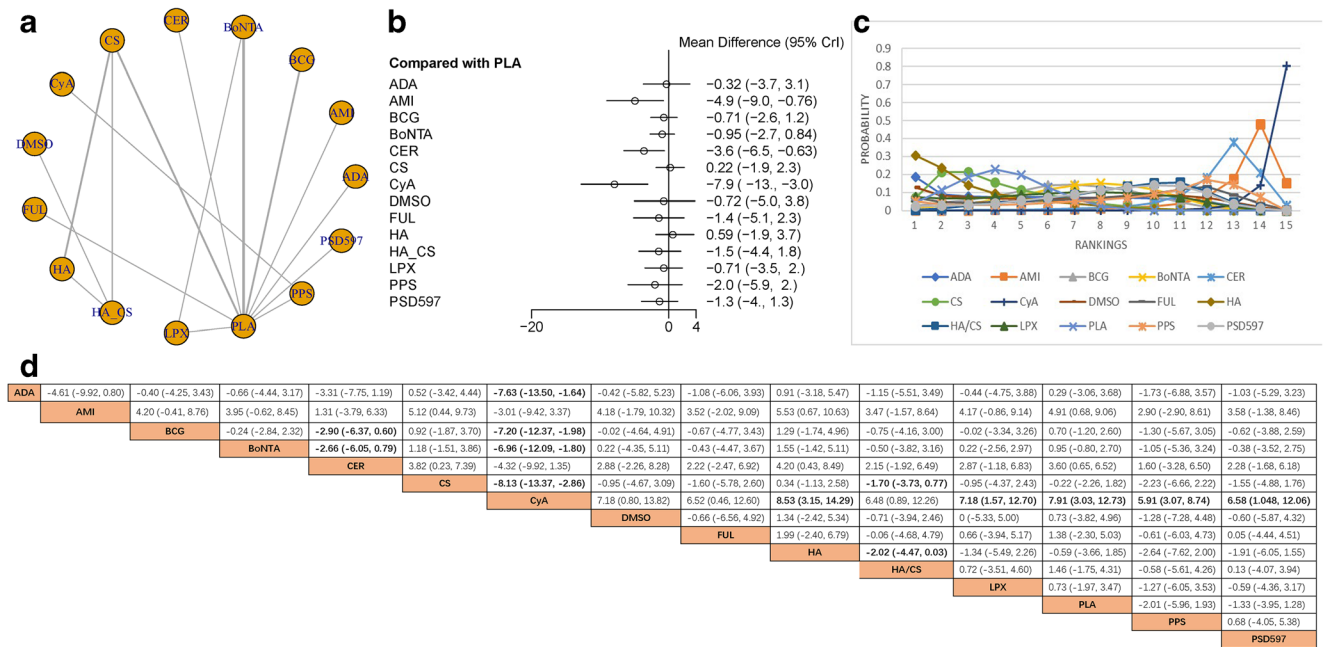
Fig. 4 Analysis of the O'Leary Sant Interstitial Cystitis Symptom Index (ICSI). **a** Network diagram. **b** Forest plot. **c** Surface Under the Cumulative Ranking (SUCRA) plot: with the placebo as the comparator. **d** League table. Forest plot of the ICSI shows the relative effect of interventions against placebo on the ICSI. The SUCRA curve plot demonstrates the possible hierarchy of pharmacological therapies on the ICSI, and the rankings from 1 to 15 represent the worst to the best. In the league table, when the mean difference with 95% CI displayed above the orange grid is positive, the efficacy of the column-defining treatment is identified as being better than that of the row-defining treatment, and vice versa

Meta-analysis results

Efficacy

Owing to the differences in application methods and drug dosages, network meta-analysis was performed based on both consistent and inconsistent models to ensure a satisfying convergence among studies.

ICSI

For the ICSI, a network meta-analysis of 17 trials was performed to compare 15 different treatments ($n = 1,266$, Fig. 4a). Compared with treatment with placebo, the ICSI changed significantly in the amitriptyline group (MD = −4.9, 95% CI:−9.0 to −0.76), the cyclosporine A group (MD = −7.9, 95% CI:−13.0 to −3.0), and the certolizumab pegol group (MD = −3.6,95% CI: −6.5 to −0.63) (Fig. 4b). Data from SUCRA revealed a possible rank as cyclosporine A > amitriptyline > certolizumab pegol > pentosan polysulfate sodium > hyaluronic acid plus chondroitin sulfate > botulinum toxin A > placebo > chondroitin sulfate > hyaluronic acid (Fig. 4c). More indirect comparisons were shown in Fig. 4d.
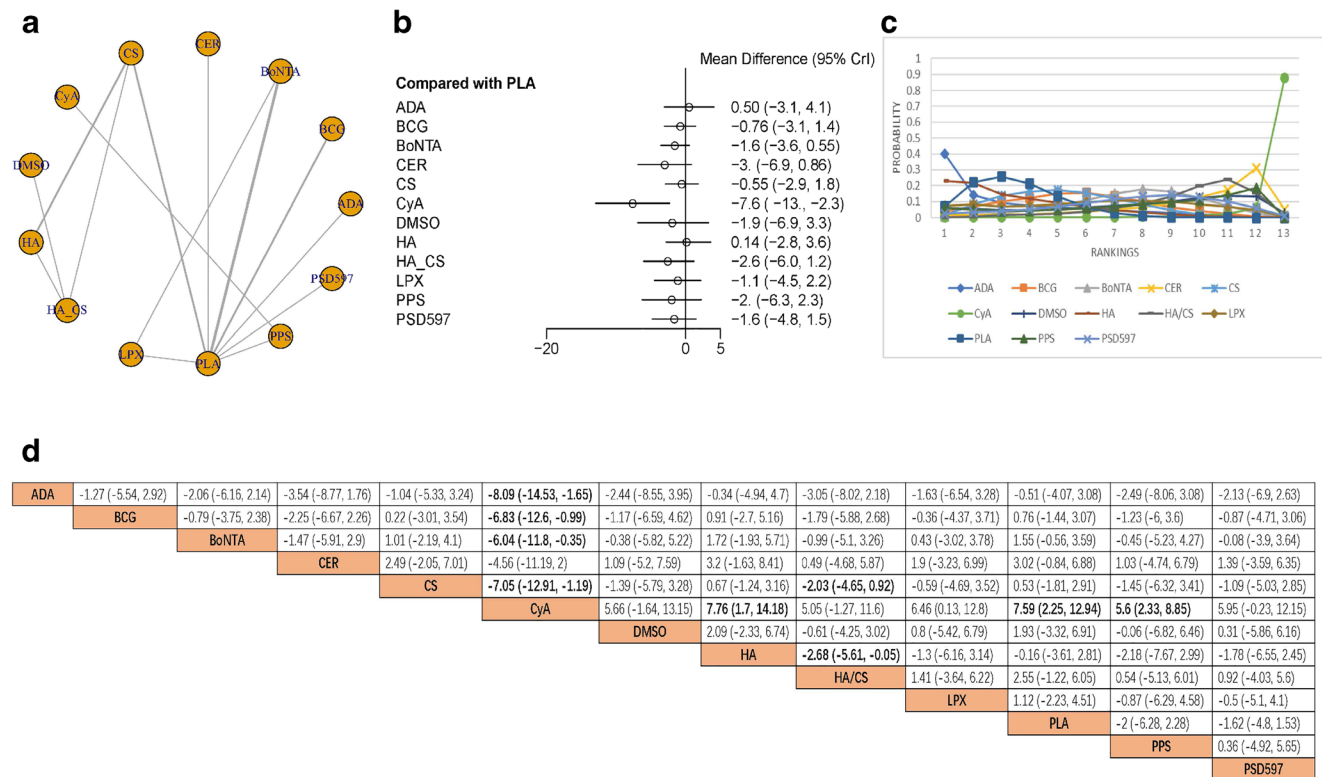
ICPI

Fifteen studies were included for the ICPI ($n = 1,185$, Fig. 5a). The ICPI improved significantly in the cyclosporine A group (MD = −7.6, 95% CI: −13 to −2.3; Fig. 5b). The derived hierarchy was cyclosporine A > certolizumab pegol > hyaluronic acid plus chondroitin sulfate > botulinum toxin A > chondroitin sulfate > placebo > adalimumab (Fig. 5c). More indirect comparisons were shown in Fig. 5d.

24-h micturition frequency

Based on available data from 17 studies ($n = 1,596$, Fig. 6a). None of the treatments was significantly superior to placebo or any other (Fig. 6b, d). The derived hierarchy in micturition frequency alleviation was cyclosporine A > botulinum toxin A > bacillus Calmette–Guérin (BCG) > placebo > chondroitin sulfate > pentosan polysulfate sodium > tanezumab (Fig. 6c). Cyclosporine A might show the greatest improvement in 24-h micturition frequency.

Pain scale (VAS and Likert)

As the VAS and the Likert scale are both pain scaling systems with different ceiling scores, the data were analyzed separately.

Fig. 5 Analysis of the O'Leary Sant Interstitial Cystitis Problem Index (ICPI). **a** Network diagram. **b** Forest plot: with the placebo as the comparator. **c** The Surface Under the Cumulative Ranking (SUCRA) plot. **d** League table. The SUCRA plot demonstrates the possible hierarchy of pharmacological therapies on the ICPI, and the rankings from 1 to 13 represent the worst to the best. In the league table, when the mean difference with 95% CI displayed above the orange grid is positive, the efficacy of the column-defining treatment is identified as being better than that of the row-defining treatment, and vice versa

Panel b (Compared with PLA — Mean Difference (95% CrI)):

Treatment	Mean Difference (95% CrI)
ADA	0.50 (−3.1, 4.1)
BCG	−0.76 (−3.1, 1.4)
BoNTA	−1.6 (−3.6, 0.55)
CER	−3. (−6.9, 0.86)
CS	−0.55 (−2.9, 1.8)
CyA	−7.6 (−13., −2.3)
DMSO	−1.9 (−6.9, 3.3)
HA	0.14 (−2.8, 3.6)
HA_CS	−2.6 (−6.0, 1.2)
LPX	−1.1 (−4.5, 2.2)
PPS	−2. (−6.3, 2.3)
PSD597	−1.6 (−4.8, 1.5)

Panel d (League table):

	BCG	BoNTA	CER	CS	CyA	DMSO	HA	HA/CS	LPX	PLA	PPS	PSD597
ADA	−1.27 (−5.54, 2.92)	−2.06 (−6.16, 2.14)	−3.54 (−8.77, 1.76)	−1.04 (−5.33, 3.24)	−8.09 (−14.53, −1.65)	−2.44 (−8.55, 3.95)	−0.34 (−4.94, 4.7)	−3.05 (−8.02, 2.18)	−1.63 (−6.54, 3.28)	−0.51 (−4.07, 3.08)	−2.49 (−8.06, 3.08)	−2.13 (−6.9, 2.63)
	BCG	−0.79 (−3.75, 2.38)	−2.25 (−6.67, 2.26)	0.22 (−3.01, 3.54)	−6.83 (−12.6, −0.99)	−1.17 (−6.59, 4.62)	0.91 (−2.7, 5.16)	−1.79 (−5.88, 2.68)	−0.36 (−4.37, 3.71)	0.76 (−1.44, 3.07)	−1.23 (−6, 3.6)	−0.87 (−4.71, 3.06)
		BoNTA	−1.47 (−5.91, 2.9)	1.01 (−2.19, 4.1)	−6.04 (−11.8, −0.35)	−0.38 (−5.82, 5.22)	1.72 (−1.93, 5.71)	−0.99 (−5.1, 3.26)	0.43 (−3.02, 3.78)	1.55 (−0.56, 3.59)	−0.45 (−5.23, 4.27)	−0.08 (−3.9, 3.64)
			CER	2.49 (−2.05, 7.01)	−4.56 (−11.19, 2)	1.09 (−5.2, 7.59)	3.2 (−1.63, 8.41)	0.49 (−4.68, 5.87)	1.9 (−3.23, 6.99)	3.02 (−0.84, 6.88)	1.03 (−4.74, 6.79)	1.39 (−3.59, 6.35)
				CS	−7.05 (−12.91, −1.19)	−1.39 (−5.79, 3.28)	0.67 (−1.24, 3.16)	−2.03 (−4.65, 0.92)	−0.59 (−4.69, 3.52)	0.53 (−1.81, 2.91)	−1.45 (−6.32, 3.41)	−1.09 (−5.03, 2.85)
					CyA	5.66 (−1.64, 13.15)	7.76 (1.7, 14.18)	5.05 (−1.27, 11.6)	6.46 (0.13, 12.8)	7.59 (2.25, 12.94)	5.6 (2.33, 8.85)	5.95 (−0.23, 12.15)
						DMSO	2.09 (−2.33, 6.74)	−0.61 (−4.25, 3.02)	0.8 (−5.42, 6.79)	1.93 (−3.32, 6.91)	−0.06 (−6.82, 6.46)	0.31 (−5.86, 6.16)
							HA	−2.68 (−5.61, −0.05)	−1.3 (−6.16, 3.14)	−0.16 (−3.61, 2.81)	−2.18 (−7.67, 2.99)	−1.78 (−6.55, 2.45)
								HA/CS	1.41 (−3.64, 6.22)	2.55 (−1.22, 6.05)	0.54 (−5.13, 6.01)	0.92 (−4.03, 5.6)
									LPX	1.12 (−2.23, 4.51)	−0.87 (−6.29, 4.58)	−0.5 (−5.1, 4.1)
										PLA	−2 (−6.28, 2.28)	−1.62 (−4.8, 1.53)
											PPS	0.36 (−4.92, 5.65)
												PSD597

Seven studies covering 706 patients were included for VAS assessment (Fig. 7a). None of the treatments was significantly superior to placebo (Fig. 7b). The derived hierarchy was cyclosporine A > amitriptyline > certolizumab pegol > botulinum toxin A > lipotoxin > placebo > fulranumab (Fig. 7c). The VAS score improved significantly in the cyclosporine A group compared with the pentosan polysulfate sodium group (MD = 3.09, 95% CI: 0.13 to 6.07; Fig. 7d). Cyclosporine A might show the greatest improvement in VAS score.

Seven studies were included for the Likert score ($n = 611$; Fig. 8a). None of the treatments was significantly superior to placebo or any other groups (Fig. 8b). The derived hierarchy was tanezumab > botulinum toxinA > PSD597 > BCG > placebo > chondroitin sulfate (Fig. 8c). Tanezumab might show the greatest improvement in Likert score. More indirect comparisons are shown in Fig. 8d.

Safety

The network meta-analysis converged well. Unlike efficacy, the incidence of total AEs might be influenced by doctor-related factors such as catheter insertion-related infection of the urinary system. In order to avoid the bias, the analysis of total adverse events was divided into the intravesical group and the other treatments group. Four typical AEs with high incidence rates were taken into consideration.

Total AEs (intravesical instillation and others)

Fifteen studies were included for AEs (Fig. 9a, b). No significant difference was found in both the intravesical intervention group and the other treatments group (Fig. S2). The derived hierarchy of the risk of total AEs of intravesical instillation was botulinum toxin A > BCG > placebo > PSD597 (Fig. 9c). The derived hierarchy of the risk of total AEs of other treatments was sildenafil > cyclosporine A > tanezumab > placebo > AQX1125 (Fig. 9d).

Gastrointestinal symptoms

The network meta-analysis on gastrointestinal symptoms included six studies of seven treatments ($n = 859$; Fig. S3A). We found no significant difference between any of the treatments (Fig. S3B, C). The probability of gastrointestinal symptoms ranked as pentosan polysulfate sodium > placebo > chondroitin sulfate (Fig. S3D).
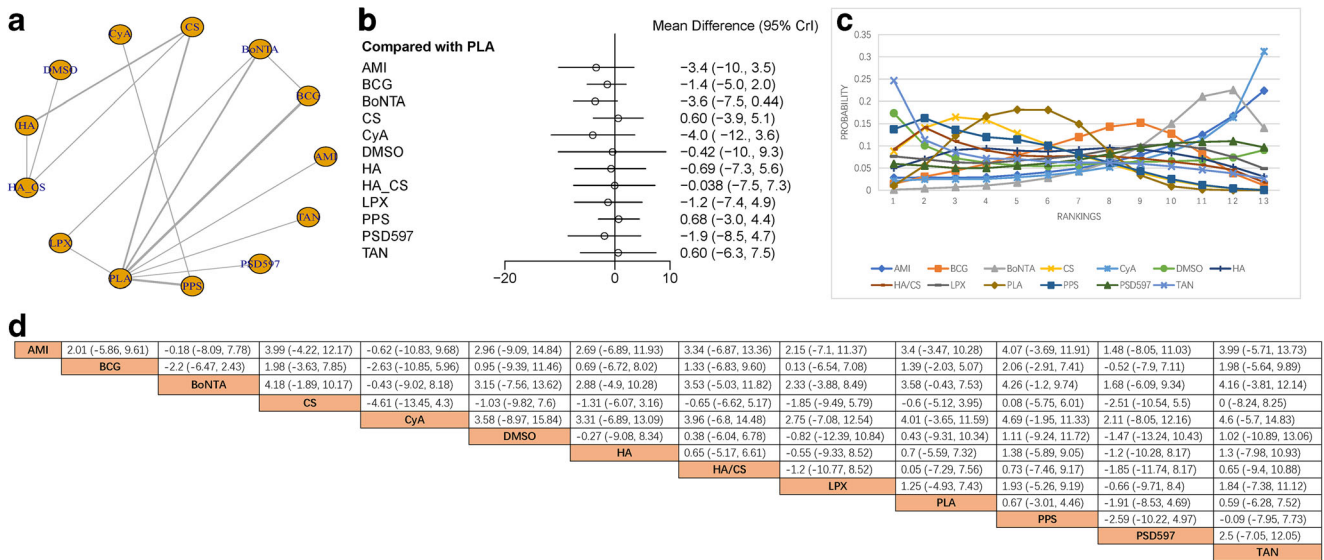
Fig. 6 Analysis of 24-h micturition frequency. **a** Network diagram. **b** Forest plot: with placebo as the comparator. **c** Surface Under the Cumulative Ranking (SUCRA) plot. **d** League table. The SUCRA plot demonstrates the possible hierarchy of pharmacological therapies on 24-h micturition frequency, and the rankings from 1 to 13 represent the worst to the best. In the league table, when the mean difference with 95% CI displayed above the orange grid is positive, the efficacy of the column-defining treatment is identified as being better than that of the row-defining treatment, and vice versa.

Headache

The network meta-analysis on headache included four studies of five treatments (*n* = 750, Fig. S4A). We found no significant difference between any of the treatments (Fig. S4B, C). Prevalence of headache ranked as sildenafil > placebo > BCG > AQX1125 (Fig. S4D).

Pain

The network meta-analysis on gastrointestinal symptoms included 6 studies on five treatments (*n* = 733, Fig. S5A). No significant difference was found between any treatments (Fig. S5B, C). The probability of pain incidence was ranked from high to low as BCG > pentosan polysulfate sodium > placebo > AQX1125 > fulranumab (Fig. S5D).

Urinary symptoms

The network meta-analysis on gastrointestinal symptoms included 6 studies on seven treatments (*n* = 635, Fig. S6A). Botulinum toxin A was superior to chondroitin sulfate (MD = −2.02, 95% CI: −4.99 to 0.66) and placebo (MD = −1.60, 95% CI: −3.83 to 0.17) respectively (Figure S6B, C). The probability of urinary symptoms events incidence rate was ranked from high to low as botulinum toxin A > pentosan polysulfate sodium > placebo > chondroitin sulfate (Fig. S6D).

Sensitivity analysis

As the inclusion criteria of the studies were different, we compared the parameters between a consistent and an inconsistent model of outcomes based on the methodology. It was found that the data were well matched and stable for network meta-analysis (Supplementary Table 2).

Discussion

To our knowledge, this is the first network meta-analysis to investigate the efficacy and safety of eligible pharmacotherapies in clinical use. Using a Bayesian framework, both direct and indirect evidence for pharmacological therapies for IC/BPS were acquired. Although some therapies, such as BCG, are no longer recommended in the guidelines because of unimpressive outcomes and severe adverse effects [14], all the studies were included in order to keep the analysis intact. It was found that besides current mainstream pharmacotherapies such as intravesical instillation or injection [46–48], immunoregulators such as cyclosporine A demonstrated a vital role, with relatively higher efficiency and fewer AEs. Cyclosporine A and certolizumab pegol showed a significantly improved ICSI and ICPI compared with other pharmacological therapies. Cyclosporine A and botulinum toxin A were more likely to reduce 24-h micturition frequency. Botulinum toxin A, sildenafil, and cyclosporine A improved the AEs from the hierarchy as well. Moreover, our findings revealed
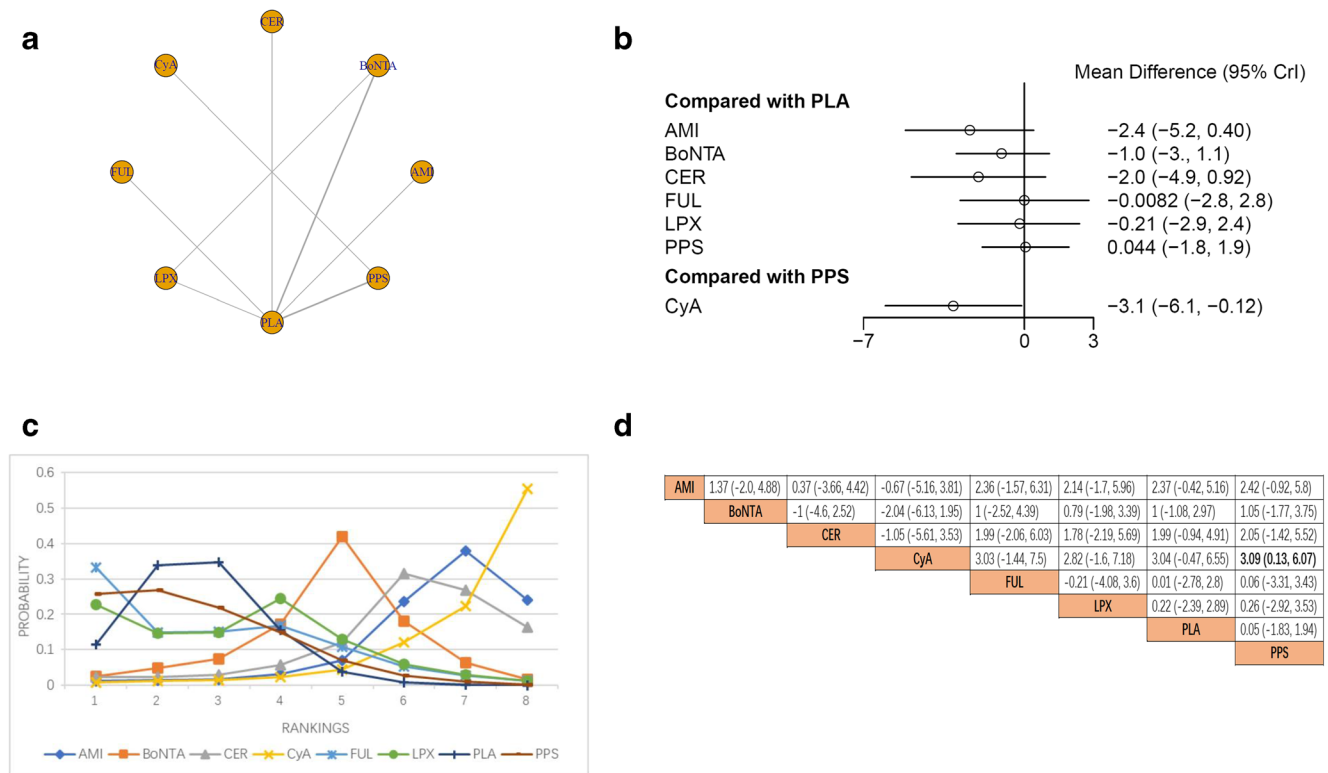
Fig. 7 Analysis of the visual analog scale (VAS) pain score. **a** Network diagram. **b** Forest plot: with placebo as the comparator. **c** The Surface Under the Cumulative Ranking (SUCRA) plot. **d** League table. The SUCRA plot demonstrates the possible hierarchy of pharmacological therapies on the VAS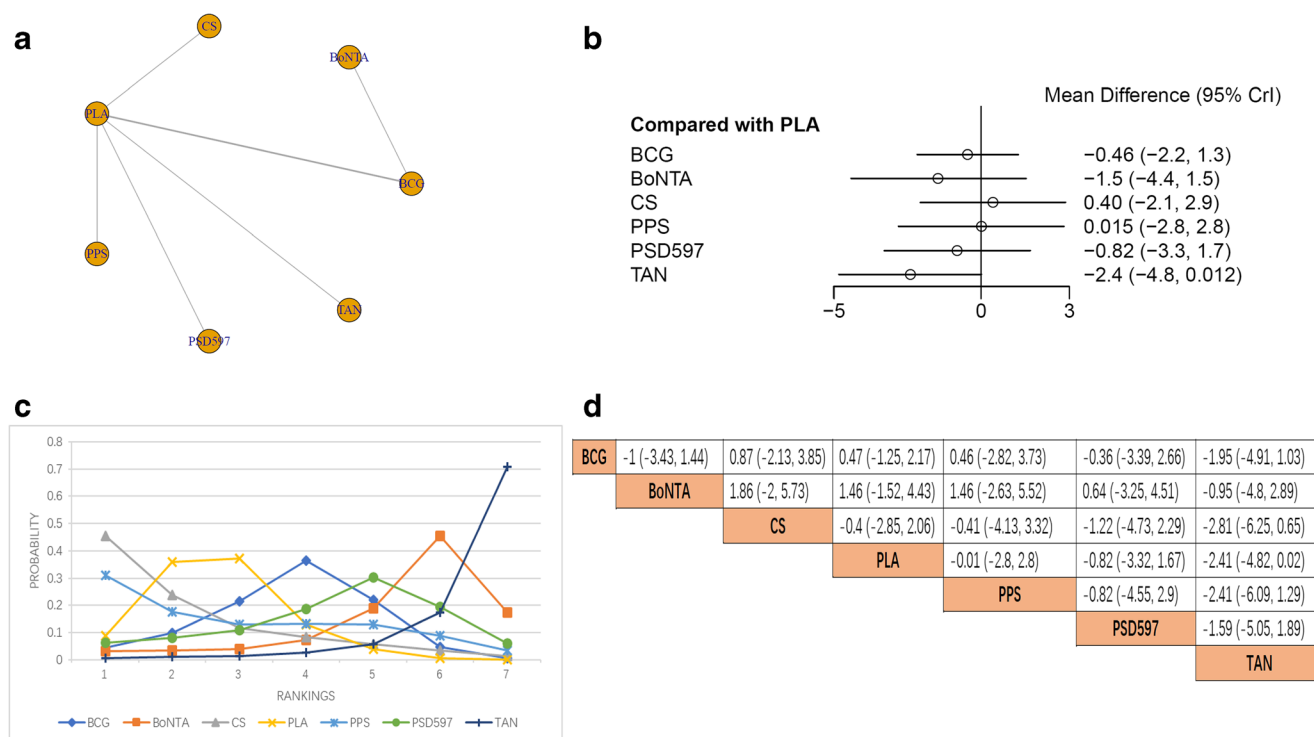, and the rankings from 1 to 8 represent the worst to the best. In the league table, when the mean difference with the 95% CI displayed above the orange grid is positive, the efficacy of the column-defining treatment is identified as being better than that of the row-defining treatment, and vice versa

that drugs such as TNFα inhibitors and antidepressants performed better than others as well.

The purpose of our network meta-analysis was a drug-based comparison of the efficacy and safety of 18 pharmacological therapies for IC/BPS. At this time, the etiology of IC was still unclear, some evidence revealed that an abnormal immune response takes place in IC/BPS, which means that immunological regulation in the bladder might be a treatment option for IC/BPS. Tirumuru et al. [49] demonstrated that BoNTA was probably a therapy with a short-term benefit. Crescenze et al. [50] suggested that cyclosporine A might be effective for refractory IC/BPS. Wang and Zhang [51] performed a meta-analysis suggesting that cyclosporine A might be an effective method with a long-term benefit. Giannantoni et al. [33] performed a systematic review of all the possible treatments for IB/BPS, but failed to reach a reliable conclusion because of great heterogeneity in their methodology, among other things. Their results only showed the potential efficiency of cyclosporine A with low-quality evidence. The absence of a comparison between intravesical therapy and other types of drug application methods restricted the utilization of drugs. Regarding safety, AEs of all therapies were evaluated. These adverse events, mostly mild and similar to those in previous studies, constituted the major drawback of these therapies for IC/BPS. There was no significant difference in almost all treatments that might be attributed to application method, drug metabolism, drug dose, etc.

In line with previous studies [36, 52], the results favored cyclosporine A as a potential option for IC/BPS over other treatments. Cyclosporine A is a calcineurin inhibitor that enables suppression of T cell activity and cytokine release [53]. Cyclosporine A has been successfully applied to the management of autoimmune diseases such as Crohn's disease and rheumatoid arthritis and psoriasis [54, 55]. Generally, cyclosporine A shares not only safety and high efficiency but also long-term therapeutic effect [56]. In addition, cyclosporine A was also considered as a novel choice for refractory IC/BPS [52, 57]. Although cyclosporine A is more likely to cause side effects such as increases in blood pressure and serum creatinine, abdominal pain, flushing, hyperplasia, hair growth, muscle pain, and shaking, there was no significant differences in mean systolic and diastolic blood pressure or serum creatinine during the half-year treatment with cyclosporine A [36]. The importance of drugs such as immunoregulators, antidepressants, or anesthetics for systematic treatment are highlighted.

Fig. 8 Analysis of the Likert pain score. **a** Network diagram. **b** Forest plot: with the placebo as the comparator. **c** The Surface Under the Cumulative Ranking (SUCRA) plot. **d** League table. The SUCRA plot demonstrates the possible hierarchy of pharmacological therapies on the Likert score, and the rankings from 1 to 7 represent the worst to the best.

In the league table, when the mean difference with 95% CI displayed above the orange grid is positive, the efficacy of the column-defining treatment is identified as being better than that of the row-defining treatment, and vice versa

The most outstanding point of our study is that we compared and ranked the efficacy and safety outcomes of eligible pharmacological interventions with direct and indirect evidence in patients with IC/BPS under a Bayesian network meta-analysis framework. Previous meta-analyses [18, 58–60] only focused on intravesical treatments with a relatively higher incidence of side effects.

Furthermore, one crucial aspect that we cannot neglect is the health care cost. Cervigni et al. [34] demonstrated that the incremental cost-effectiveness ratio (ICER) of HA/CS versus DMSO falls between 3,735€/quality-adjusted life years (QALY; an optimistic assumption) and 8,003€/QALY (a pessimistic assumption). One recent study [5] revealed similar efficacy–cost rates on HA and CS. Unfortunately, a cost-effectiveness analysis was not performed in our study as only two eligible studies analyzed health care cost. Further studies should include the direct and indirect analysis of the medical costs in order to acquire a better assessment of pharmacological treatments.

This network meta-analysis had some limitations. First, because most available data showed the comparison between drug and placebo, the lack of comparisons among drugs caused a lack of direct comparisons and looplessness. We tried fixed and random models under consistent and inconsistent models, and the outcomes showed high consistency and low heterogeneity. However, more high-quality RCTs on the direct comparison of drugs are still needed. Second, because of some unavailability of patient data, we were not able to carry out a subgroup analysis of age, gender, etc. Third, no consistent post-treatment follow-up duration for pharmacological therapies of IC/BPS resulted in the failure to compare the efficiency of drugs at different post-treatment times. The selection of outcomes (ICSI, ICPI, 24-h micturition frequency, AEs) is applicable for the purposes of the investigation, whereas other factors may strongly affect outcomes in patients with IC/BPS and have not been included in this systematic review. Given the various outcomes and recommendations of pharmacological therapies, it was found that the preferred intervention may be different because of the endpoints prioritized by patient and physician. Finally, owing to the small patient numbers in some studies, the results may be biased to some extent. For this reason, the efficacy of some therapies, such as cyclosporine A, must be validated in future studies with more patients for a reasonable conclusion. Despite the limitations described above, our network meta-analysis shows the best eligible evidence of the efficacy and safety outcomes
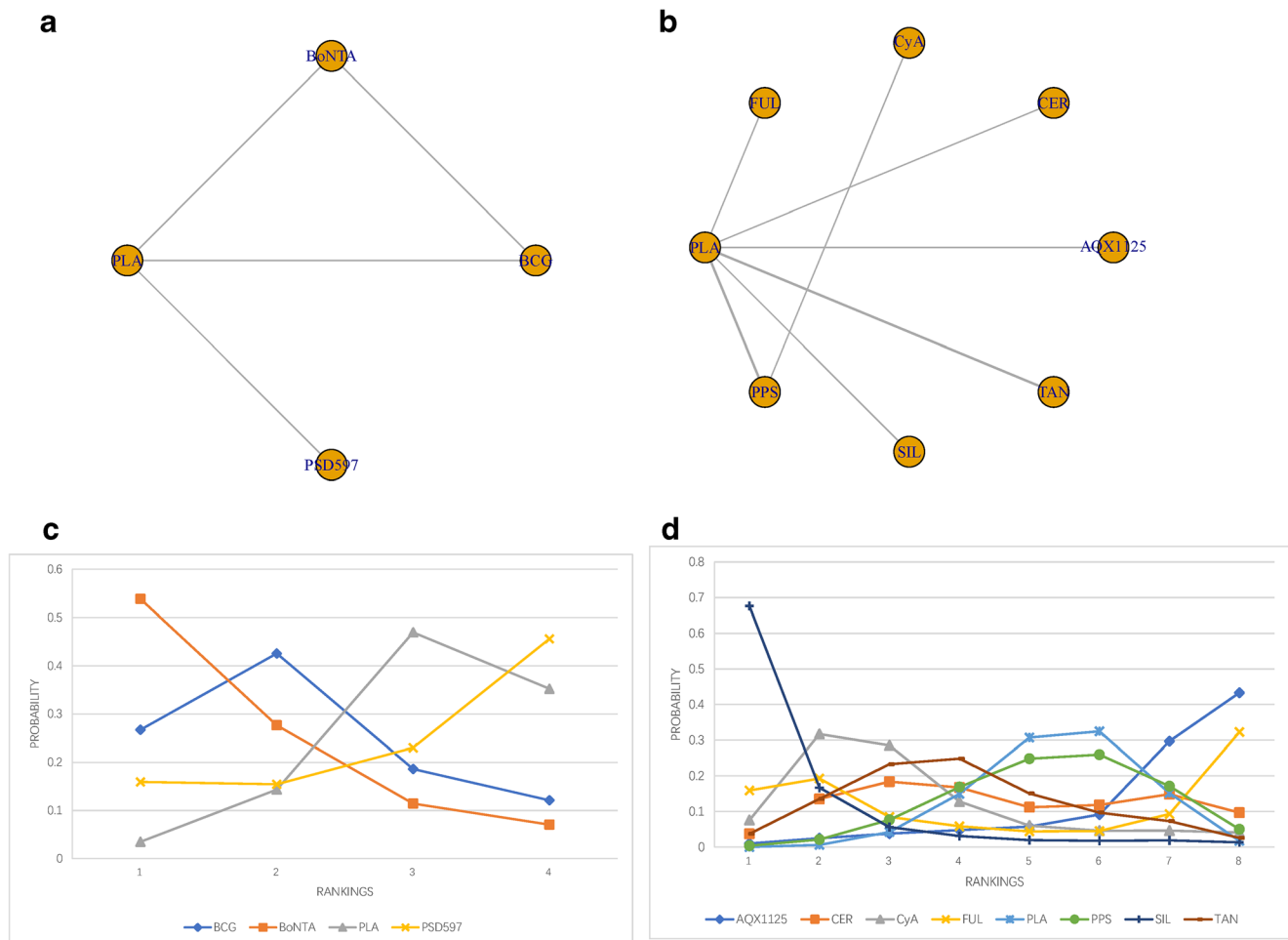
Fig. 9 Analysis of adverse events (AEs). **a** Network diagram of intravesical instillation. **b** Network diagram of the other treatments. **c** The Surface Under the Cumulative Ranking (SUCRA) plot of intravesical instillation. **d** The SUCRA plot of the other treatments. The

SUCRA plot demonstrates the possible hierarchy of pharmacological therapies on AEs, and the rankings from 1 to 4 or 8 represent the highest incidence rate to the lowest

of pharmacological interventions and enables us to provide a novel recommendation with less impairment of clinical use in patients with IC/BPS. Researchers have found that IC/BPS is no longer simply an inflammatory disease. In the future, we should concentrate more on multi-factorial treatments instead of monotherapy. More high-quality drug-based, dose-based, and duration-based head-to-head RCTs are needed.

Conclusion

In this systematic review and Bayesian network meta-analysis of pharmacological therapies for patients with IC/BPS, cyclosporine A may be identified as being highlighted to provide more effective benefit. Amitriptyline and certolizumab pegol were capable of lowering the ICSI as well. Alkalinized lidocaine and AQX1125 were more likely to be tolerated than other treatments. These findings may provide novel options for clinicians when making clinical decisions.

Compliance with ethical standards

Conflicts of interest None.

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