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## Platinum Priority – Female Urology – Incontinence

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# Contemporary Management of the Painful Bladder: A Systematic Review

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### Abstract

**Context:** Different types of behavioural, dietary, interventional, pharmacologic, and surgical therapies have been used to treat painful bladder syndrome/interstitial cystitis (PBS/IC). Because of the paucity of randomised placebo-controlled studies on different treatments, an evidence-based management approach has not yet been developed.

**Objective:** To critically review and synthesize data from a wide range of current therapeutic approaches to PBS/IC, to quantify the effect size from randomised controlled trials (RCTs), and to reach clinical agreement on the efficacy of treatments for PBS/IC. **Evidence acquisition:** We performed a systematic review of the literature to identify articles published between 1990 and September 2010 on the management of PBS/IC. We included articles restricted to the English language published since 1990 to date that reported on oral and intravesical treatment, multimodal or combined treatment, and surgical treatment. For all RCTs, standardised mean differences (SMDs) were extracted and combined in a meta-analysis applying a random-effect model that incorporated the heterogeneity of effects. The four outcomes assessed in all studies were a change in the Interstitial Cystitis Symptom Index (ICSI), pain, urgency, and frequency. Non-RCTs (nRCTs) were analysed with a narrative synthesis of the evidence from all research designs.

**Evidence synthesis:** We included 7709 adult patients from 29 RCTs and 57 nRCTs. Meta-analysis of RCTs showed that only cyclosporine A provided a simultaneous great effect size of SMD on ICSI, pain, and frequency. Amitriptyline at different dosages showed a great effect size of SMD on pain and urgency or on ICSI and frequency. The remaining RCTs showed sporadic significant changes in only one of the four considered parameters. The attributed levels of evidence for treatments reported in RCTs were 1b; grades of recommendations ranged from A to C. According to the Jadad score, 11 RCTs were high-quality studies. Meta-analysis of RCTs showed a great heterogeneity in the applied methodologies, clinical outcomes assessed, and the obtained results in different studies. The results from the nRCTs showed that the most frequently adopted treatment is oral pentosan polysulfate and that the use of botulinum A toxin intradetrusorial injections in PBS/IC is increasing. A high heterogeneity in drugs and treatment modalities, clinical outcomes, and obtained results was also found for nRCTs.

**Conclusions:** Limited evidence exists for the few treatments for PBS/IC. The lack of definitive conclusions is due to the great heterogeneity in methodology, symptoms assessment, duration of treatment, and follow-up in both RCTs and nRCTs.

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## 1. Introduction

Painful bladder syndrome/interstitial cystitis (PBS/IC) is a poorly defined clinical condition characterised by pelvic pain and urinary storage symptoms (eg, urinary urgency and frequency). The European Society for the Study of Interstitial Cystitis (ESSIC) [1] suggested the term *PBS/IC*, which is strictly consistent with the taxonomy guidelines of the European Association of Urology (EAU) [2]. In the ESSIC proposal, PBS/IC is defined as “chronic pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder, with at least one other urinary symptom such as persistent urge to void or urinary frequency.” The phrase “persistent urge to void” should replace the term *urgency* because it better describes urinary urgency experienced by patients with PBS/IC. In addition, confusable diseases as the cause of the symptoms have to be excluded [1]. The American Urological Association (AUA) guidelines recently provided a modified definition for the diagnosis and treatment of PBS/IC: “An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptom(s) of more than 6 weeks duration, in the absence of infection or other identifiable causes” [3].

There is no general agreement about the physiopathology of the disease, which has prevented identification of an objective marker and development of a clinical diagnostic protocol. Thus how patients are identified for epidemiologic studies differs greatly [4,5]. The close diagnostic criteria proposed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) can miss about 60% of patients and thus are only recommended for research purposes [6]. The EAU guidelines on chronic pelvic pain recently proposed an algorithm for diagnosing and treating PBS/IC that should help properly identify and treat patients with the disease [2].

The O’Leary-Sant Symptom and Problem score (Interstitial Cystitis Symptom Index [ICSI] and Problem Index [ICPI]) has been recognized as one of the most reliable and valid instruments to identify the most prominent voiding and painful symptoms in patients with PBS/IC and the extent of the perceived problem [7].

Treatment and management approaches vary widely, and different types of behavioural, dietary, interventional, pharmacologic, and surgical therapies have been used. This diversity reflects both the complexity of the condition in terms of aetiology and pathogenesis and the lack of clear diagnostic criteria for the disease. The Interstitial Cystitis Data Base study reported on >180 treatment modalities, with unsatisfactory results in most cases [8]. In addition, the lack of high-quality randomised placebo-controlled studies on different treatments has not permitted the development of an evidence-based management approach. To date, there is general agreement on the use of some agents, orally or intravesically administered, as indicated by the EAU guidelines on chronic pelvic pain and the AUA Guidelines for the Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome [2,3], particularly for amitriptyline, hydroxyzine, and pentosan polysulfate sodium (PPS) [2,3].

Our aim was to critically review and synthesise data from a wide range of current therapeutic approaches to PBS/IC, to quantify the effect size from randomised controlled trials (RCTs), and to reach clinical agreement on treatment efficacy for PBS/IC.

## 2. Evidence acquisition

### 2.1. Literature search

We performed a systematic review of the literature to identify articles published between 1990 and September 2010 on the management of PBS/IC. We conducted a Medline search using the search terms *painful bladder syndrome*, *interstitial cystitis*, *hypersensitive bladder*, *oral treatment*, *intravesical treatment*, *multimodal or combined treatment*, and *surgical treatment*. We also surveyed the references of review articles to identify any missed articles.

### 2.2. Inclusion and exclusion criteria

We included only articles in the English language published from 1990 to date. Then we included all original research and excluded review articles, abstracts, case reports, and nonhuman studies. Antonella Giannantoni and Silvia Proietti reviewed each title and, if unclear, the full article applying the inclusion and exclusion criteria. We excluded studies and articles with <10 patients.

### 2.3. Assessment of results

We previously analysed outcomes assessed in each individual study. Because the outcomes assessed in all studies were change in the ICSI index, pain, urgency, and frequency, each of the mentioned outcomes was assessed in all studies.

We decided to include urgency in the evaluation of the outcomes for PBS/IC despite recent observations that suggested leaving it out of the description of patients with PBS and considering “persistent urge to void,” which better describes urinary urgency in patients with PBS/IC [3]. Even if urgency is the key symptom of overactive bladder syndrome, which is considered a major confusable disease for PBS/IC, it still remains in its original meaning one of the most frequently assessed outcomes to evaluate therapies.

For all RCTs, we attempted to abstract the data as a standardized mean difference (SMD). This produces measures of effect for each treatment trial on a similar metric.

The SMD is obtained by dividing the difference in mean outcome between two groups with the pooled standard deviation of the measurement. These effect sizes indicate the mean difference between two variables expressed in standard deviation units. A score of 0 represents no change, and effect size scores can be negative or positive. The result of this calculation is that the outcome is measured in standard deviation units. This can be difficult to interpret, and the following rule of thumb has been suggested: A SMD of 0.2 standard deviation units is considered a small difference between the intervention groups; a SMD of

0.5, a moderate difference; and a value of 0.8, a large difference [9]. For many trials the calculation of SMD was not possible, and the studies were classified as positive or negative in terms of efficacy for that outcome.

SMDs were extracted from selected studies and combined in a meta-analysis applying a random-effect model that incorporated heterogeneity of effects [10]. Heterogeneity of studies was evaluated by the Cochrane  $Q$  test and  $I^2$  statistics, which describe the percentage of total variation across studies that is due to heterogeneity rather than chance [11]. Heterogeneity was considered significant if  $p < 0.10$  and  $I^2$  was  $>50\%$ . The Begg and Egger tests were used to test publication bias [12,13]. All calculations were performed using StatsDirect statistical software v.2.7.2. The quality of the RCTs was assessed using the Jadad score, with an overall score  $\geq 3$  indicating a high-quality study [14].

We used a narrative synthesis for the analysis of nonrandomised controlled studies (nRCTs) of the evidence from all research designs and included a description of the characteristics and main findings of the sample and studies for the outcomes measured.

Data were compiled into behavioural, oral, intravesical, surgical, and multimodal treatments with data from RCTs and nRCTs. Agents and/or treatment modalities were further classified into categories according to the levels of evidence applied by the EAU [15].

### 3. Evidence synthesis

Of the 299 trials identified using our search criteria, 86 articles met the requirements for inclusion in our final analysis. Those excluded ( $n = 213$ ) did not address the treatment of PBS/IC or did not report global or symptom-specific outcomes ( $n = 104$ ); included patients without a diagnosis of PBS/IC ( $n = 59$ ) (ie, those with bladder pain due to cyclophosphamide, recurrent urothelial neoplasm, prior pelvic radiotherapy, or neurogenic bladder); were not published in English ( $n = 34$ ); or involved  $<10$  patients ( $n = 16$ ).

#### 3.1. Randomised controlled trials

A total of 29 of 86 articles were RCTs. In 3 of 29 RCTs, different dosages of the same agent were used, so the statistical analysis was performed for each individual dosage [15–17]. Table 1 lists the 29 RCTs we analysed. Results on a single agent were evaluated in 26 RCTs, and a combination of two agents in 3 RCTs. Eight trials evaluated the comparison between two different agents/techniques [16,18–24]. The 29 trials spanned 1990–2011, reporting on a total of 2344 adult patients at baseline. A total of 1999 patients completed the studies. The number of patients included ranged from 16 to 380; mean ages ranged from 38 to 65 yr. Fourteen RCTs used the NIDDK research criteria for diagnosing IC; in one study the IC database study criteria were used (Table 1). Some studies did not include diagnostic systems but only clinical and cystoscopic parameters (Table 1). All trials reported an adequate work-up to exclude organic disease, including history, physical examination, laboratory tests, and radiologic and cystoscopic evaluation.

Of the 29 RCTs, 26 used a parallel and 3 used a crossover design. Length of the follow-up ranged from 4 to 96 wk, with a mean of 22.14 wk. Symptom severity assessed within each individual trial was similar at baseline between the intervention and control groups in all of the parallel RCTs. Both global as well as individual symptom improvement was reported in all studies. The definition of symptoms such as pain, urgency and frequency varied considerably across the trials. According to the Jadad score, 11 of the 29 studies were high-quality RCTs (Table 1).

#### 3.1.1. Treatment efficacy in randomised controlled trials

Table 1 shows the evidence on treatment efficacy for each individual therapeutic modality in their respective RCTs. Specific symptoms assessed and measures used varied considerably among different studies. Because the outcomes assessed in all studies were ICSI, pain, urgency, and frequency, we report the effect size of standardised mean difference (SMD) for these four outcomes.

#### 3.1.2. Effect size of standardised mean difference on Interstitial Cystitis Symptom Index

Four studies reported a great effect size ( $>0.8$ ) of SMD (Fig. 1). Specifically, a great effect size was observed for cyclosporine A (CyA) versus PPS, sacral versus pudendal neuromodulation, amitriptyline (from 10 to 75 mg) versus placebo, and hyperbaric oxygen versus normal air [19,22,24,25]. A medium size effect of SMD was detected in four studies: botulinum toxin serotype A (BoNT/A) 200 U plus hydrodistention (HD) versus HD alone, intravesical resiniferatoxin (RTX) 0.10  $\mu\text{M}$  versus placebo, amitriptyline (25–100 mg) versus placebo, and bacillus Calmette–Guérin (BCG) versus placebo [16,26–28]. Finally a small effect size of SMD was reported in nine studies: BoNT/A 100 U plus HD versus HD alone, RTX 0.05  $\mu\text{M}$  versus placebo, HD plus PPS versus HD alone or placebo, BCG versus placebo, BoNT/A periurethral injections versus placebo, intravesical chondroitin sulphate versus placebo, L-arginine (1.5 g and 2.4 g daily) versus placebo (two studies), and lidocaine plus sodium bicarbonate versus placebo [16,17,19,29–34]. In two studies comparing intravesical oxybutynin and intravesical PPS versus placebo, respectively, data were not extractable even if the reported effect was described as positive [35,36]; in one more study with no extractable data on RTX versus placebo, the effect was reported as negative [26].

#### 3.1.3. Effect size of standardised mean difference on pain

A great effect size of SMD was observed in six studies (Fig. 2): BoNT/A 200 U plus HD versus HD alone, CyA versus PPS, oral PPS plus subcutaneous heparin versus heparin alone, hyperbaric oxygen versus normal air, amitriptyline (25–100 mg) versus placebo, and RTX 0.001  $\mu\text{M}$  versus placebo [16,20,22,37,38]. A medium effect size of SMD was detected in five studies: RTX 0.10  $\mu\text{M}$  versus placebo, BCG versus placebo, BoNT/A periurethral injections, L-arginine (1.5 g/d), and cimetidine [26,28,30,33,39]. A small effect size of SMD was revealed in 11 studies: BoNT/A 100 U plus HD versus HD alone, RTX (0.01 and 0.05  $\mu\text{M}$ ) versus placebo,

**Table 1 – Randomised controlled trials in the treatment of painful bladder syndrome/interstitial cystitis**

Treatment Study Jadad score (JS)	Diagnostic criteria	Comparator	No. of patients at baseline	No. of patients at follow-up	Group 1 vs group 2 baseline	Group 1 vs group 2 follow-up	Design	Mean age, yr	Women, %	Follow-up duration, wk	Symptom index SMD (95% CI)	Pain SMD (95% CI)	Urgency SMD (95% CI)	Frequency SMD (95% CI)	Details of the study and side effects
Amitriptyline+ van Ophoven et al. [27] JS <3	NIDDK	Versus placebo	50	48	25 vs 25	24 vs 24	Parallel	55	88	16	−0.77 (−1.36 to −0.18)	−1.12 (−0.51 to 1.73)	−2.61 (−3.38 to −1.83)	−0.62 (−1.2 to −0.04)	Amitriptyline: increasing doses once daily from 25 to 100 mg for 4 mo Side effects: dry mouth in 79% of patients in amitriptyline group vs 21% in placebo group; constipation: 42% vs 8% in placebo group; sedation: 37.5% vs 1.5% in placebo group; nausea, 33% vs 8% in placebo group
Foster et al. [25] JS ≥3	Clinic and cystoscopic	Amitriptyline plus behavioural modifications vs placebo plus behavioural modifications	231	231	135 vs 136	112 vs 119	Parallel	38	80	12	−1.5 (−2.5 to −0.5)	−0.4 (−1.0 to 0.3)	−0.5 (−1.2 to 0.1)	−0.9 (−1.5 to −0.3)	Amitriptyline: increasing doses once daily (from 10 to 75 mg) for 12 wk Side effects: fatigue, gastrointestinal problems (dry mouth in 42% of amitriptyline group vs 24% in placebo group), dizziness, renal, and genitourinary problems in 88% of patients in amitriptyline group vs 72% in placebo group Dropout in amitriptyline group: 17%; in placebo group: 13%
Antibiotics Warren et al. [41] JS <3	NIDDK	Versus placebo	50	37	25 vs 25	18 vs 19	Parallel	52	90	18	NA	Not extractable (−)	Not extractable (−)	0.15 (−0.68 to 0.97)	3 wk of different antibiotics in a sequence during a 18-wk period; Rifampicin 300 mg once daily during the whole 18 wk Side effects: nausea and or vomiting, diarrhoea, headache, dizziness, rash in 80% of patients in antibiotics group vs 40% in placebo group
Bacillus Calmette-Guérin (BCG): intravesical Peters et al. [43] JS <3	NIDDK	Versus placebo	33	30	17 vs 16	15 vs 15	Parallel	42	100	24	NA	−0.63 (−1.36 to 0.11)	Not extractable (−)	−0.4 (−1.17 to 0.28)	BCG (50 mg): 6 weekly intravesical instillations Side effects: irritative symptoms in both groups
Peeker et al. [18] JS <3	NIDDK	Versus dimethyl sulphoxide	21	21	21	21	Crossover	51	95	12	NA	−0.13 (−0.74 to 0.48)	Not extractable (−)	−0.45 (−1.1 to 0.17)	BCG: 6 weekly instillations of $5 \times 10^8$ colony-forming units dimethyl sulphoxide: 50 ml in 6 weekly instillations Side effects: irritative and obstructive symptoms in 11 patients (52.3%) in BCG group vs 5 (23.8%) in DMSO group
Mayer et al. [29] JS ≥3	NIDDK	Versus placebo	265	248	131 vs 134	121 vs 127	Parallel	48	82	34	−0.18 (−0.42 to 0.07)	0.22 (−0.02 to 0.46)	−0.28 (−0.52 to −0.04)	−0.13 (−0.38 to 0.11)	BCG ( $5 \pm 3 \times 10^8$ ): 6 intravesical instillations within 6–10 wk Side effects: severe bladder symptoms, constitutional symptoms, gastrointestinal disturbances in 49% of patients in both groups

Proper et al. (2008) [28] JS <3	Clinical and cystoscopic	Versus placebo	44	33	27 vs 17	19 vs 14	Parallel	46	80	68	-0.51 (-1.2 to 0.20)	-0.44 (-1.13 to 0.26)	-0.45 (-1.14 to -0.25)	-0.48 (-1.17 to 0.22)	BCG first course: six intravesical instillations (during 6–10 wk); BCG second course: four instillations Side effects: not reported
BoNT/A: intravesical injection Kuo and Chancellor [16] JS <3	NIDDK	BoNT/A plus HD vs HD alone	70	67	200 U: 17 vs 24 100 U: 29 vs 24	200 U: 15 vs 23 100 U: 29 vs 23	Parallel	49	83	96	200 U: -0.50 (-1.16 to 0.16) 100 U: -0.39 (-0.94; 0.16)	200U: -0.86 (-1.54 to -0.18) 100 U: -0.44 (-0.99; 0.11)	NA	200U: -0.38 (-0.93 to 0.17) 100U: -0.38 (-0.94; 0.17)	BoNT/A (Botox): suburothelial injections of 100 U and 200 U plus HD 2 wk later Side effects: seven patients with BoNT/A 200 U and three with BoNT/A 100 U had dysuria and large PVR. Haematuria and UTIs in five patients
BoNT/A: periurethral injection Gottsch et al. [30] JS <3	Clinical and cystoscopic	Versus placebo	20	20	9 vs 11	9 vs 11	parallel	45	100	12	-0.29 (-1.17 to 0.60)	-0.66 (-1.56 to 0.26)	NA	0.09 (-0.79; 0.97)	BoNT/A (Botox): injections of 50 U diluted in 2 ml normal saline at the 3 and 9 o'clock positions in the region of the bladder neck No side effects
Cimetidine Thilagarajah et al. [39] JS <3	Clinical and cystoscopic	Versus placebo	36	34	18 vs 18	17 vs 17	Parallel	42	97	12	NA	-0.71 (-1.38 to -0.03)	-0.35 (-1.02 to 0.3)	-0.20 (-0.86 to 0.46)	Oral cimetidine: 400 mg: twice daily for 3 mo Side effects: not reported
Chondroitin sulphate Nickel et al. [31] JS <3	IC database study criteria	Versus placebo	65	58	33 vs 32	29 vs 29	Parallel	44	98	12	-0.29 (-0.78; 0.20)	0.37 (-0.12; 0.87)	NA	-0.35 (-0.84; 0.14)	Sodium chondroitin sulphate: 20 ml of 2.0% intravesical solution, weekly for 6 wk. Evaluation of results at 7 wk Side effects: at least one adverse effect in 76.9% of patients (gastrointestinal disorders, urethritis, renal and urinary disorders, urethral pain, macular rash, skin and subcutaneous tissue disorders)
CyA Sairanen et al. [20] JS ≥3	NIDDK	Versus PPS	64	58	32 vs 32	29 vs 29	Parallel	59	83	24	-1.87 (-2.48 to -1.25)	-1.34 (-1.92 to -0.77)	NA	-1.42 (-2.0 to -0.85)	Cyclosporine A: 1.5 mg/kg twice daily for 6 mo PPS: 100 mg three times daily for 6 mo Side effects: mild to moderate in 30 patients in the CyA arm (increased blood pressure and serum creatinine) and in 18 patients in the PPS arm (gastrointestinal disturbances, headache, fatigue, and gross haematuria in one) Dropout at 6 mo: 25% of patients in CyA arm and 12.5% in PPS arm
L-arginine Korting et al. [33] JS <3	NIDDK	Versus placebo	53	46	27 vs 26	21 vs 25	Parallel	49	100	12	-0.33 (-0.93 to 0.27)	-0.60 (-1.19 to -0.01)	-0.52 (-1.14 to 0.08)	-0.36 (-0.96 to 0.24)	L-arginine: 1500 mg/d orally for 3 mo Side effects: worsening in IC symptoms in three patients; no difference between the number of withdrawn patients

Table 1 (Continued)

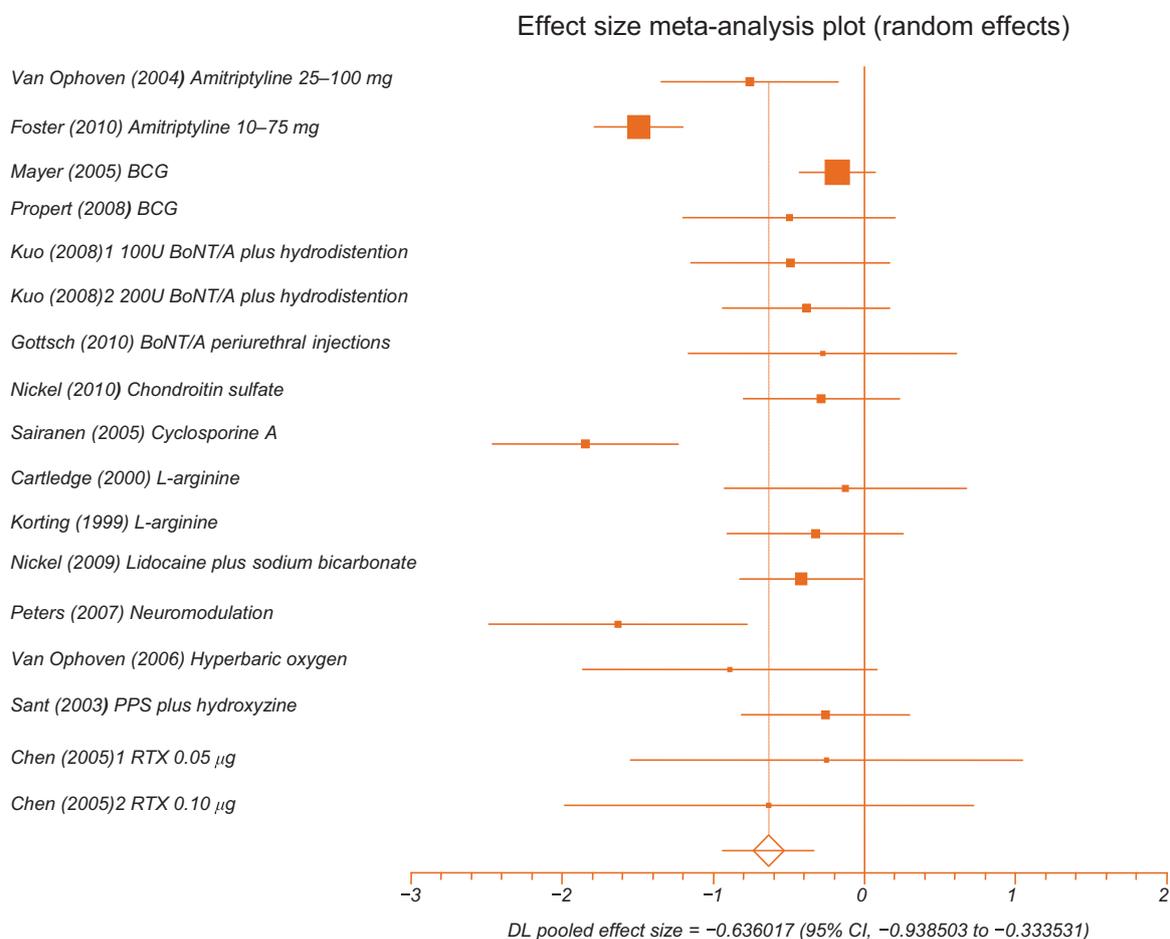
Treatment Study Jadad score (JS)	Diagnostic criteria	Comparator	No. of patients at baseline	No. of patients at follow-up	Group 1 vs group 2 baseline	Group 1 vs group 2 follow-up	Design	Mean age, yr	Women, %	Follow-up duration, wk	Symptom index SMD (95% CI)	Pain SMD (95% CI)	Urgency SMD (95% CI)	Frequency SMD (95% CI)	Details of the study and side effects
Cartledge et al. [32] JS <3	NIDDK	Versus placebo	16	12	12	12	Crossover	51	75	4	−0.13 (−0.82 to 0.57)	NA	NA	0.85 (0.13 to 1.58)	L-arginine: 2.4 g/d for 1 mo Side effects: severe headache, night sweats, flushing in three withdrawn patients
Lidocaine plus sodium bicarbonate: intravesical Nickel et al. [34] JS ≥3	Clinical and cystoscopic	Versus placebo	102	95	50 vs 52	45 vs 50	Parallel	47	97	29 d	−0.42 (−0.83 to 0)	−0.40 (−0.81 to 0.01)	−0.51 (−0.92 to −0.1)	0.07 (0 to 0.48)	Instillation of lidocaine 200 mg (PSD597) plus 8.4% sodium bicarbonate solution to a final volume of 10 ml, once a day for 5 consecutive days Side effects: bladder pain was the most common severe AE in 2%, 4%, and 2% of patients in PSD597, placebo, and open-label group, respectively
Neuromodulation Peters et al. [23] JS <3	Clinical and cystoscopic	Sacral vs pudendal nerve stimulation	22	14	14	14	Crossover	48	86	24	−1.68 (−2.94 to −0.43)	NA	NA	NA	Tined lead placed at the S3 nerve root; second electrode on the same side at the pudendal nerve. Each lead was tested for 7 d The best lead was implanted to a pulse generator Side effects: described as not significant
Oxybutynin: intravesical Barbalias et al. [35] JS ≥3	NIDDK	Versus placebo	36	31	24 vs 12	23 vs 8	Parallel	45	100	24	Not extractable (+)	NA	NA	−1.59 (−2.4 to −0.80)	Intravesical instillations of oxybutynin 10 mg diluted in 500 ml normal saline for 1 wk; then every week for 6 wk; then every month for 3 mo Side effects: not reported
Oxygen, hyperbaric van Ophoven et al. [37] JS ≥3	NIDDK	Versus normal air	21	19	14 vs 7	12 vs 7	Parallel	65	100	48	−0.93 (−1.89 to 0.02)	−1.08 (−2.05 to −0.11)	−0.47 (−1.38 to 0.46)	−0.73 (−1.67 to 0.21)	30 treatments (six times a week for 5 wk) of 100% oxygen inhalation, in hyperbaric chamber, 2.4 ata normal air: 1.3–1.4 ata
Pentosan polysulphate Mulholland et al. [40] JS <3	Clinical and cystoscopic	Versus placebo	110	98	54 vs 56	51 vs 47	Parallel	44	89	12	NA	−0.15 (−0.53 to 0.22)	Not extractable (−)	NA	PPS: 300 mg orally in divided doses of 100 mg, three times daily Side effects: gastrointestinal, headache, increased perspiration, severe mood swing in 6% of PPS patients vs 13% in placebo patients

Parsons et al. [36] JS ≥3	Clinical and cystoscopic	Versus placebo	148	130	74 vs 74	65 vs 65	Parallel	43	97	12	NA	Not extractable (+)	Not extractable (+)	NA	PPS: 300 mg orally in divided doses of 100 Side effects: gastrointestinal symptoms in more than one patient in PPS group. Three patients in PPS group and five in placebo group discontinued treatment
Sant et al. [19] JS ≥3	NIDDK	2 × 2 factorial study: hydroxyzine/PPS/placebo/hydroxyzine plus PPS	121	96	31 vs 29 vs 31 vs 30	24 vs 26 vs 23 vs 23	Four arms	45	89	24	−0.26 (−0.77–0.25)	−0.11 (−0.62–0.40)	0.06 (−0.45–0.56)	0.06 (−0.45–0.57)	PPS: 300 mg orally in divided doses of 100 mg, three times daily; hydroxyzine: 50 mg/d Side effects: gastrointestinal and constitutional symptoms in at least 80% of patients receiving either placebo or study drugs Overall dropout: 8%
Nickel et al. [21] JS <3	Clinical and cystoscopic	PPS 300 mg vs 600 mg vs 900 mg	380	230	128 vs 125 vs 127	78 vs 86 vs 73	Parallel	44	90	32	NA	NA	NA	NA	PPS: 300, 600, 900 mg orally per day, divided in doses of 100, 200, or 300 mg three times daily for 32 wk Side effects: diarrhoea (25%), headache (18%), nausea (15%), pelvic pain (12.9%), and abdominal pain (12.6%); 22.4% of patients discontinued treatment due to AEs
van Ophoven et al. [22] JS <3	Clinical and cystoscopic	PPS plus heparin vs PPS alone	58	43	41 vs 17	26 vs 17	Parallel	48	95	24	NA	−4.4 (−5.5 to −3.3)	0.22 (−0.38–0.84)	−2.72 (−3.56 to −1.88)	5000 IU subcutaneous heparin every 8 h for 2 d, followed by 5000 IU every 12 h for 12 d; maintenance dose was heparin 5000 IU/d Side effects: stronger menstrual bleeding than normal in 17 patients (65.4%)
Pentosan polysulphate: intravesical Bade et al. [44] JS ≥3	Clinical and cystoscopic	Versus placebo	20	19	10 vs 10	9 vs 10	Parallel	51	100	12	NA	NA	Not extractable (−)	−0.30 (−1.19–0.58)	Intravesical PPS: 300 mg in 50 ml of normal saline, twice a week for 3 mo No side effects
Davis et al. [24] JS ≥3	Clinical and cystoscopic	PPS (oral plus intravesical) vs oral PPS plus intravesical placebo	41	40	21 vs 20	20 vs 20	Parallel	38	100	18	Not extractable	Not extractable (+)	Not extractable (+)	Not extractable	Intravesical PPS: 200 mg in 30 ml of saline solution twice a week during the first 6 wk. Oral PPS: 200 mg/twice a day for 18 wk Side effects: headache: 66.7% in PPS group vs 60% in placebo group; bruise in arms: 52.4% in PPS group vs 55% in placebo group; mild hair loss: three patients in PPS group vs one in placebo group
Resiniferatoxin (RTX): intravesical Lazzeri et al. [38] JS <3	Clinical and cystoscopic	0.001 μM RTX vs placebo	18	18	9 vs 9	9 vs 9	Parallel	41	37	12	NA	−4.01 (−5.67 to −2.34)	Not extractable (+)	−1.57 (−2.64 to −0.50)	RTX: a single intravesical dose of 0.001 μM RTX Side effects: suprapubic burning sensation in one patient in RTX arm
Chen et al. [17] JS <3	NIDDK	0.10 μM RTX vs 0.05 μM RTX vs placebo	22	21	11 vs 8 vs 3	10 vs 8 vs 3	Parallel	44	77	12	0.05 μM −0.27 (−1.44 to 0.89) 0.10 μM −0.69 (−1.93–0.55)	0.05 μM 0.05 (−1.15 to 1.25) 0.10 μM 0.10 (−1.48–0.85)	0.05 μM −0.26 (−1.43 to 0.90) 0.10 μM 0.10 (−0.84–2.10–0.41)	0.05 μM −0.19 (−1.35 to 0.97) 0.10 μM 0.10 (−1.92–0.56)	RTS: a single dose of intravesical RTX (0.10 mM or 0.05 mM) Side effects: the most commonly adverse effect was pain during instillation (80%, 87.5%, and 25% in 0.10 μM or 0.05 μM RTX and in placebo group, respectively)

Table 1 (Continued)

Treatment Study Jadad score (JS)	Diagnostic criteria	Comparator	No. of patients at baseline	No. of patients at follow-up	Group 1 vs group 2 baseline	Group 1 vs group 2 follow-up	Design	Mean age, yr	Women, %	Follow-up duration, wk	Symptom index SMD (95% CI)	Pain SMD (95% CI)	Urgency SMD (95% CI)	Frequency SMD (95% CI)	Details of the study and side effects
Payne et al. [26] JS ≥3	Clinical and cystoscopic	0.01 μM RTX vs 0.05 μM RTX vs 0.10 μM RTX vs placebo	163	150	43 vs 41 vs 35 vs 44	38 vs 40 vs 33 vs 39	Parallel	47	86	12	Not extractable (–)	0.01 μM 0.02 –0.33 (–0.98–0.33) 0.05 μM –0.26 (–0.91–0.39) 0.10 μM –0.52 (–1.18–0.39)	0.01 μM –0.20 (–0.85–0.45) 0.05 μM –0.05 (–0.70, 0.60) 0.10 μM 0.12 (–0.53–0.77)	0.01 μM 0.00 (–0.42–0.42) 0.05 μM 0.06 (–0.37–0.48) 0.10 μM 0.19 (–0.25–0.64)	RTX: a single dose of intravesical RTX (0.10 μM or 0.05 μM or 0.01 μM) Side effects: dose-dependent increase in pain during instillation and systolic blood pressure during the acute period following instillation
Tanezumab (intravenous) Evans et al. [42] JS <3	Clinical and cystoscopic	Versus placebo	64	52	34 vs 30	29 vs 23	Parallel	21–85	89	16	Not extractable (+)	Not extractable (+)	Not extractable (+)	Not extractable (+)	Tanezumab: a single intravenous dose of 200 μg/kg Side effects: headache in 20.6% and paresthesia in 17.6% of patients in tanezumab group vs 16.7% and 3.3% in placebo group, respectively

SMD = standardised mean difference; CI = confidence interval; NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; NA = not available; DMSO = dimethylsulphoxide; BoNT/A = botulinum toxin serotype A; HD = hydrodistention; PVR = postvoid residual; UTI = upper urinary tract infection; IC = interstitial cystitis; CyA = cyclosporine A; PPS = pentosan polysulphate sodium; AE = adverse event; RTX = resiniferatoxin.  
(–) Reported as not effective; data not extractable.  
(+) Reported as effective; data not extractable.



**Fig. 1 – Change in Interstitial Cystitis Symptom Index.**

**BCG = bacillus Calmette-Guérin; BoNT/A = botulinum toxin serotype A; CI = confidence interval; PPS = pentosan polysulfate sodium; RTX = resiniferatoxin.**

RTX (0.05 and 0.10  $\mu\text{M}$ ), BCG versus dimethylsulfoxide (DMSO), hydroxyzine plus PPS versus hydroxyzine alone versus placebo, amitriptyline (10–75 mg) versus placebo, BCG versus placebo (two studies), chondroitin sulphate versus placebo, lidocaine plus sodium bicarbonate versus placebo, and oral PPS versus placebo [16–18,25,26,28,29,31,34,40]. Four studies did not show extractable results on pain: In one (antibiotics vs placebo), the reported effect was negative [41], and in the other three studies (intravesical PPS vs placebo, oral PPS 300 mg/d, and tanezumab vs placebo), the effect on pain was described as positive [24,36,42].

### 3.1.4. Effect size of standardised mean difference on urgency

Two studies reported a great effect size of SMD (Fig. 3): RTX 0.10  $\mu\text{M}$  versus placebo and amitriptyline (25–100 mg) versus placebo [17,27]. A medium effect size of SMD was detected in two studies: L-arginine (1.5 g/d) and lidocaine plus sodium bicarbonate versus placebo [33,34]. In nine studies we found a small effect size of SMD: RTX 0.05  $\mu\text{M}$  versus placebo, RTX (0.01, 0.05, and 0.10  $\mu\text{M}$ ) versus placebo, hydroxyzine plus PPS versus hydroxyzine alone or placebo, PPS plus heparin versus PPS alone, amitriptyline (10–75 mg) versus placebo, hyperbaric oxygen versus

normal air, BCG versus placebo in two different studies, and cimetidine versus placebo [17,19,22,25,26,28,29,37,39]. In nine studies data about effect size on urgency were not extractable; in four the effect was reported as positive (intravesical PPS, oral PPS 300 mg/d, RTX 0.001  $\mu\text{M}$ , and tanezumab vs placebo) [24,26,38,42], and in five the effect was negative (BCG vs DMSO, PPS vs placebo, antibiotics vs placebo, BCG vs placebo, and intravesical PPS vs placebo) [18,40,41,43,44].

### 3.1.5. Effect size of standardised mean difference on frequency

A great effect of size of SMD was observed in six studies (Fig. 4): CyA versus PPS, PPS plus heparin versus PPS alone, amitriptyline (10–75 mg) versus placebo, L-arginine (2.4 g/d) versus placebo, intravesical oxybutynin versus placebo, and RTX 0.001  $\mu\text{M}$  versus placebo [20,22,25,32,35,38]. A medium effect size of SMD was observed in three studies: RTX (0.1  $\mu\text{M}$ ) versus placebo, hyperbaric oxygen versus normal air, and amitriptyline (25–100 mg) versus placebo [17,27,38]. A small effect size of SMD was detected in 15 studies: BoNT/A 100 and 200 U plus HD versus HD alone, RTX 0.05  $\mu\text{M}$  versus placebo, RTX (0.01, 0.05, and 0.1  $\mu\text{M}$ ) versus placebo, BCG versus DMSO, hydroxyzine plus PPS, BCG versus placebo (two studies), BoNT/A

## Effect size meta-analysis plot (random effects)

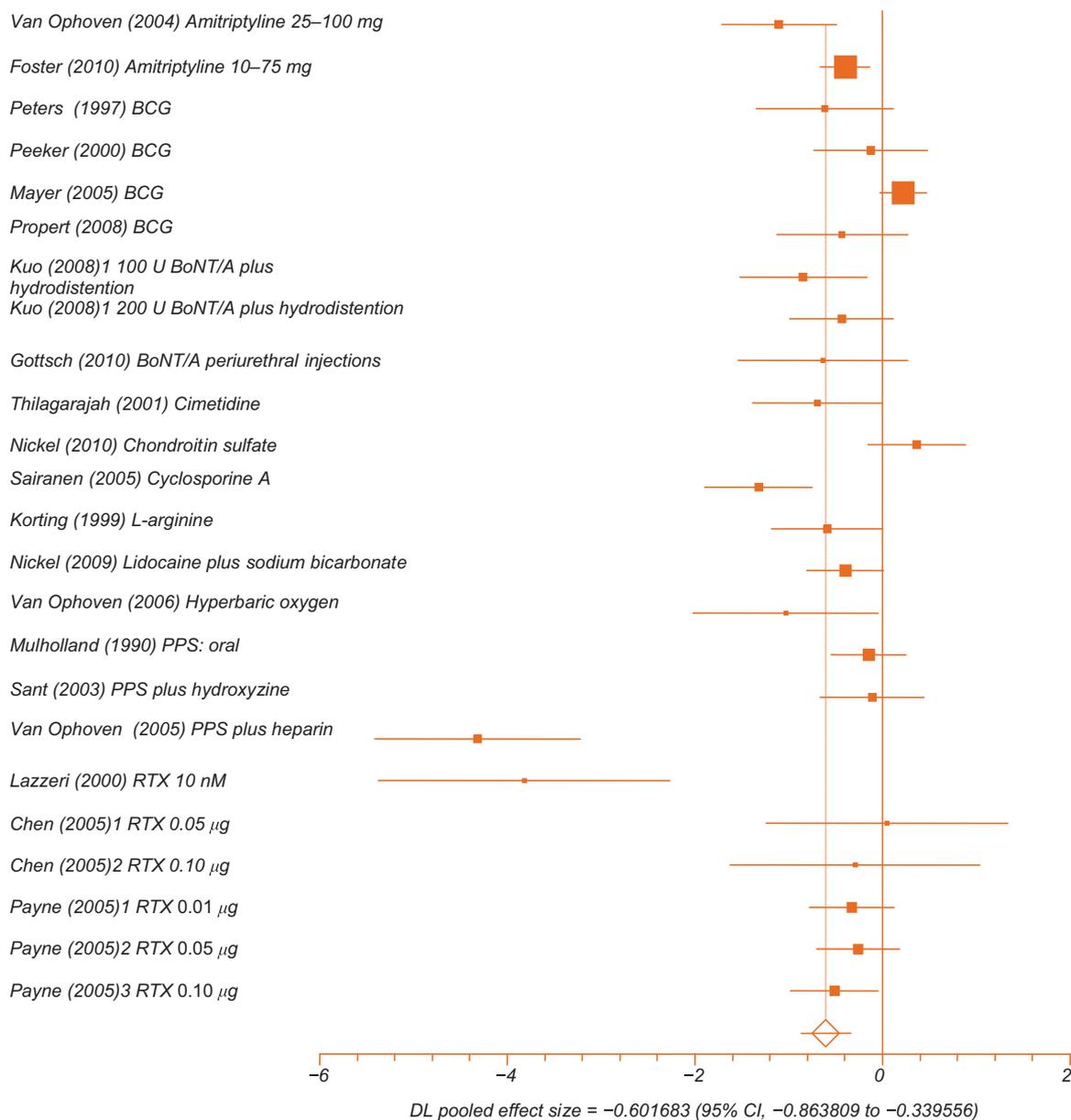


Fig. 2 – Pain.

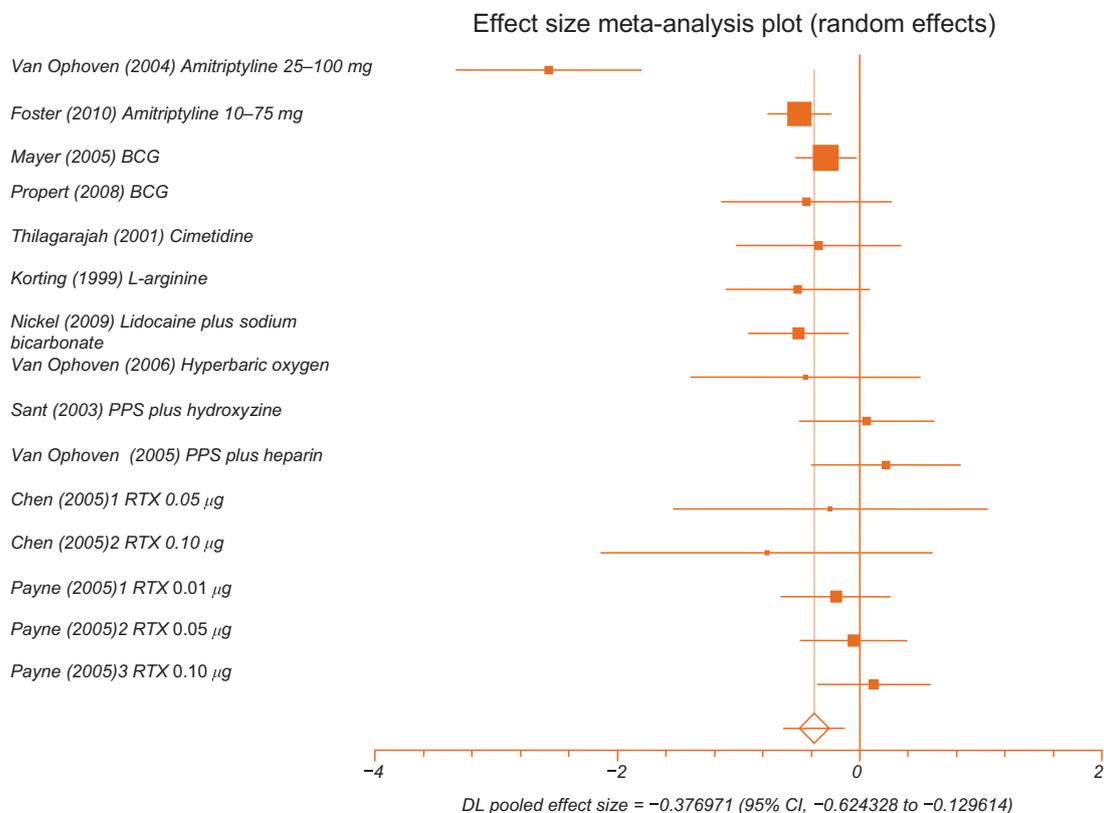
BCG = bacillus Calmette-Guérin; BoNT/A = botulinum toxin serotype A; CI = confidence interval; PPS = pentosan polysulfate sodium; RTX = resiniferatoxin.

periurethral injection versus placebo, intravesical PPS versus placebo, intravesical chondroitin sulphate versus placebo, L-arginine (1.5 g/d) versus placebo, lidocaine plus sodium bicarbonate versus placebo, cimetidine versus placebo, antibiotics versus placebo, and BCG versus placebo [16–19,28–31,33,34,39,41,43]. Only one study with no extractable data reported a positive effect for intravesical PPS versus placebo [24].

None of the treatments reported in the RCTs showed a simultaneous great effect size of SMD on all the four outcomes analyzed (ICSI, pain, urgency, and frequency). Only CyA (vs PPS) showed a simultaneous great effect size on three outcomes: ICSI, pain, and frequency. Treatment

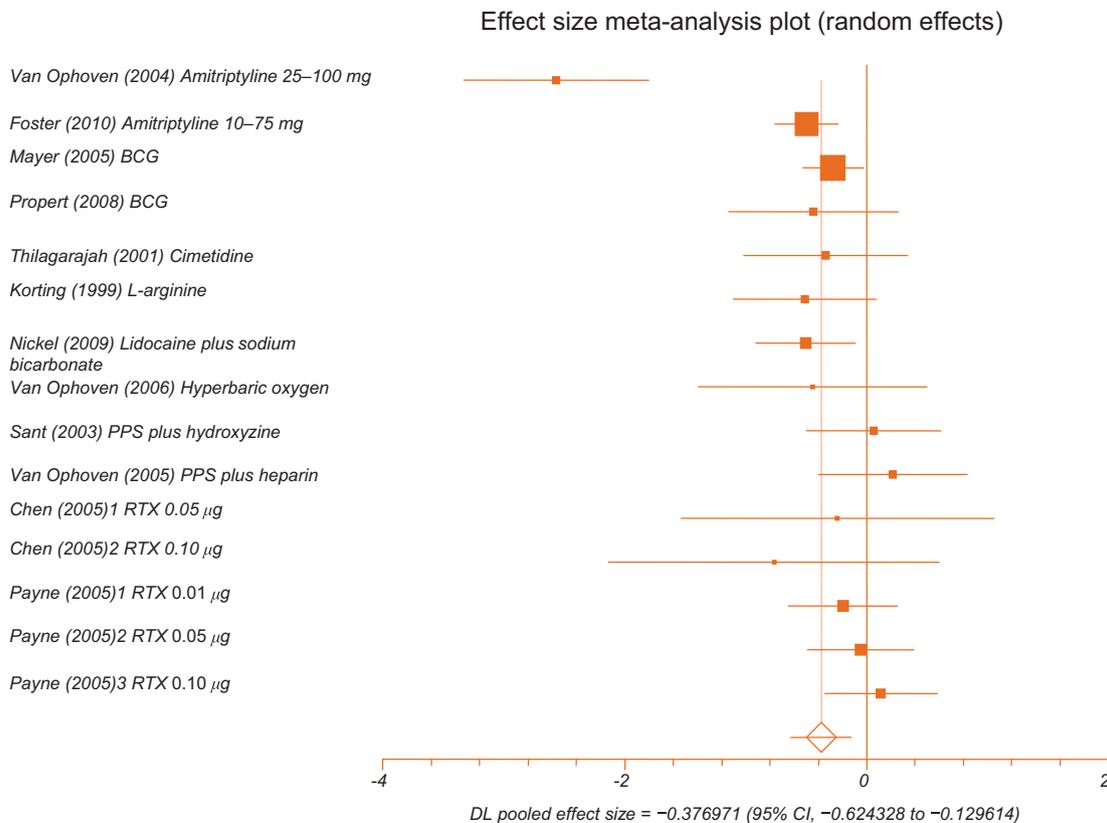
with amitriptyline (10–75 mg) showed a great effect size of SMD on ICSI and frequency; amitriptyline (25–100 mg) had a simultaneous great effect size of SMD on pain and urgency [25,27]. Hyperbaric oxygen therapy (vs normal air) showed a great effect size of SMD on ICSI and pain [37]; RTX (0.01 µM) and PPS plus heparin (vs PPS alone) showed a great effect size on pain and frequency [22,26].

Finally, when we compared the results between studies reporting the presence or absence of bladder inflammation, we were not able to find any relationship. In addition, data on the relief of bladder inflammation after treatment have never been reported.



**Fig. 3 – Urgency.**

BCG = bacillus Calmette-Guérin; CI = confidence interval; PPS = pentosan polysulfate sodium; RTX = resiniferatoxin.



**Fig. 4 – Frequency.**

BCG = bacillus Calmette-Guérin; CI = confidence interval; PPS = pentosan polysulfate sodium; RTX = resiniferatoxin.

**Table 2 – Nonrandomised controlled trials in the treatment of painful bladder syndrome/interstitial cystitis**

Treatment Study	Diagnostic criteria	No. of patients at baseline	No. of patients at follow-up	Design	Mean age, yr	Women, %	Follow-up, wk	Symptom index	Pain	Urgency	Frequency	Treatment details Side effects
Amitriptyline van Ophoven and Hertle [69]	NIDDK	94	65	Prospective	53	87	76	ICSI: –7.9 ( <i>p</i> = 0.004)	VAS (0–10 scores): –22.1 ( <i>p</i> = 0.002)	VAS (0–10 scores): –19.7 ( <i>p</i> = 0.004)	Voiding diary: –6.9 ( <i>p</i> = 0.021)	Amitriptyline: mean dose 55 mg (12.5–150) Side effects: Contributed to dropout in 86% of nonresponding patients (dry mouth, constipation, weight gain, blurred vision)
Antibiotics Zhang et al. [72]	NIDDK	11	11	Prospective	42	100	32 (median)	PUF: from 25.5 to 16.3 ( <i>p</i> < 0.01)	Not collected	Not collected	Not collected	Tetracycline: 500 mg/d (3 mo) Side effects: not reported
Bacillus Calmette-Guerin (BCG): intravesical Peters et al. [66]	NIDDK	15	14	Prospective	42	100	98	Not standardised questionnaire: 70% improvement ( <i>p</i> = 0.01)	VAS (0 = best to 5 = worst): 81% reduction ( <i>p</i> = 0.02)	Not standardised questionnaire: 71% reduction ( <i>p</i> = 0.02)	Not standardised questionnaire: 31% improvement ( <i>p</i> = 0.04)	BCG: 6-wk instillations; long-term follow-up Side effects: not reported
Propert et al. [28]	NIDDK	156	138	Prospective	48	80	34	GRA: 18% responders ICSI: (course 1) –1.0; (course 2) –1.2	Pain score (0 = best to 9 = worst): mean change in pain: (course 1) –0.8; (course 2) –1.3	Urgency score (0 = best to 9 = worst): mean change in urgency: (course 1) –0.7; (course 2) –0.5	Voiding diary frequency/24 hrs: mean change in frequency: (course 1) –1.6; (course 2) –0.0	BCG: 6 instillations (6–10 wk) Side effects: in most patients at least one effect: pain, genitourinary and gastrointestinal disorders
Aghamir et al. [67]	NIDDK	15	13	Prospective	32	100	96	ICSI: 58% improvement ( <i>p</i> = 0.001)	VAS (0–5 scores) 43% improvement ( <i>p</i> = 0.001)	VAS 28% improvement ( <i>p</i> = 0.004)	Voiding diary: 52% improvement ( <i>p</i> = 0.001)	Tice strain BCG (120 mg): 6-wk instillations Side effects: four patients (flulike syndrome in three; fatigue, malaise, and fever in one patient with dropout)
Botulinum A toxin: intravesical Smith et al. [45]	NIDDK	13	12	Prospective	52	100	12	ICSI: 71% improvement ( <i>p</i> < 0.05)	VAS: (0–10 scores): 79% improvement ( <i>p</i> < 0.01)	Not collected	Voiding diary: 44% improvement ( <i>p</i> < 0.01)	Botulinum A toxin: one single treatment, 200 U maximal dose (both Botox and Dysport) Side effects: two patients (dysuria with Botox)
Kuo [46]	Clinical and cystoscopic	10	10	Prospective	47	80	12	Not collected	VAS (0–5 scores) from 3.2 to 2.4 ( <i>p</i> = 0.003)	Not collected	Voiding diary: from 24.2 to 18.8 ( <i>p</i> = 0.025)	Botulinum A toxin: one single treatment from 100–200 U (Botox) Side effects: not reported
Giannantoni et al. [47]	Clinical and cystoscopic	14	14	Prospective	64	86	12	Not collected	VAS: (0–10 scores) from 9.3 to 6.1 ( <i>p</i> = 0.01)	Not collected	Voiding diary: from 14.2 vs 9.1 ( <i>p</i> = 0.01)	Botulinum A toxin: one single treatment with 200 U (Botox) Side effects: two patients (incomplete bladder emptying)
Giannantoni et al. [48]	Clinical and cystoscopic	15	15	Prospective	59	80	48	Not collected	VAS (0–10 scores): from 9.4 to 8.6 (5-mo follow-up) ( <i>p</i> = 0.01)	Not collected	Voiding diary: from 15.2 to 11.4 (5-mo follow-up) ( <i>p</i> = 0.01)	Botulinum A toxin: one single treatment with 200 U (Botox) Side effects: dysuria in nine patients at 1 mo and in two at 5-mo follow-up
Pinto et al. [49]	ESSIC	26	16	Prospective	48	100	96	ICSI: from 15.6 to 6.8 (3-mo follow-up) ( <i>p</i> < 0.05)	VAS (0–10 scores): from 5.8 to 1.6 ( <i>p</i> < 0.05)	Not collected	Voiding diary: from 11.4 to 4.7 (3-mo follow-up) ( <i>p</i> < 0.05)	Botulinum A toxin: two consecutive treatments with 100 U (Botox) Side effects: not reported

Giannantoni et al. [50]	Clinical and cystoscopic	13	13	Prospective	48	100	96	Not collected	VAS (0–10 scores): from 9.7 to 5.2 ( $p = 0.01$ )	Not collected	Voiding diary: from 14.8 to 7.2 ( $p = 0.01$ )	Botulinum A toxin: multiple treatments with 200 U (Botox) Side effects: dysuria in nine patients at 1 mo and in seven at 4-mo follow-up
Giannantoni et al. [51]	Clinical and cystoscopic	14	14	Prospective	57	100	12	HAM-A: from 20.6 to 7.9 ( $z = -3.11$ ; $p < 0.01$ ); HAM-D: from 18.6 to 9.7 ( $z = -3.29$ ; $p < 0.01$ ) SF-36: significant improvement ( $p < 0.05$ )	VAS (0–10 scores): from 8.8 to 4.7 ( $p < 0.01$ )	Not collected	Voiding diary: from 13.3 to 5.8 ( $p < 0.01$ )	Botulinum A toxin: one single treatment with 200 U (Botox) Side effects: dysuria in nine patients at 1 mo and in seven at 4-mo follow-up
Ramsey et al. [52]	NIDDK	11	11	Prospective	56	100	14	BFLUTS: from 132 to 105 ( $p = 0.01$ ) KHQ: from 85 to 56 ( $p = 0.03$ ) at 10 wk	BFLUTS: ( $p = 0.009$ ) at 10 wk	Not reported	Voiding diary, frequency/24 h: from 15 to 10.5 ( $p = 0.03$ )	Botulinum A toxin: one single treatment of 300 U in two patients and 200 U in nine patients Side effects: Two patients (dysuria)
Cimetidine Dasgupta et al. [73]	Clinical and cystoscopic	14	8	Prospective	51	92	48	Not collected	VAS (0–10 scores): from 7.4 to 3.3 ( $p = 0.01$ )	Not collected	Voiding diary: from 17 to 7.6 ( $p = 0.011$ )	Cimetidine: 200 mg three times per day Side effects: not reported
Cyclosporine A Forsell et al. [70]	NIDDK	11	Not reported	Prospective	7–75	91	Not reported	Not collected	Subjective analysis of pain (patient verbal comment): relief in pain in 91%	Not collected	Voiding diary, frequency/24 h: from 20.5 to 11.9 ( $p < 0.01$ )	Cyclosporine A: 2.5–5 mg/kg daily (from 3 to 6 mo) Side effects: six patients (mild hypertension, mild gingival hyperplasia, transient tremor, growth of facial hair)
Sairanen et al. [71]	NIDDK	23	4	Retrospective	59	87	360	Not collected	Subjective analysis of pain (patient verbal comment) 20/23 patients totally free of pain; 3/23 moderate improvement; 1/23 no improvement	Not collected	Voiding diary: 20.8 to 10.2 ( $p < 0.001$ )	Cyclosporine A: 3 mg/kg twice daily then 1 mg/kg as a single daily dose for at least 1 yr Side effects: seven patients (hypertension, gingival hyperplasia, induced hair growth)
Duloxetine van Ophoven and Hertle [68]	NIDDK	48	48	Prospective	49	100	8	ICSI: not significant	VAS (0–10 scores): not significant	VAS (0–10 scores): not significant	Voiding diary: not significant	Duloxetine: from 20 mg to 40 mg, with increments 1-wk intervals; dose target 40 mg twice daily for 5 wk Side effects: 17 patients (35.4%) nausea, with treatment discontinuation
Glycosaminoglycans: intravesical Steinhoff [63]	Clinical and cystoscopic	18	13	Prospective	Not reported	94	48	ICSI: from 13.1 to 7.8; 46% = good response; 15.4% = fair response; 30.8% = partial response; 7.7% = no response	Not reported	Not reported	Not reported	Chondroitin sulphate: 40 ml solution, one instillation per week for 4 wk and then once a month for 12 mo No side effects

Table 2 (Continued)

Treatment Study	Diagnostic criteria	No. of patients at baseline	No. of patients at follow-up	Design	Mean age, yr	Women, %	Follow-up, wk	Symptom index	Pain	Urgency	Frequency	Treatment details Side effects
Nordling and van Ophoven [64]	Clinical and cystoscopic	286	226	Prospective	60 (median)	91	12	Global assessment: positive assessment between 80% and 90%	VAS (0 = best, 10 = worst): from 4.8 to 2.6 ( $p < 0.0001$ )	VAS: from 6.8 to 3.4 ( $p < 0.0001$ )	Voiding diary: from 12.7 to 9.2 ( $p < 0.0001$ )	Chondroitin sulphate: one instillation per week for 4–6 wk, then one instillation per month Side effects: 23 patients (50 AEs not related to treatment) 43/50 AEs were reported as nonserious
Nickel et al. [65]	Clinical and cystoscopic	53	Not reported	Prospective	44	100	24	GRA: 8.1 (5.0) change from baseline: 6.2 ( $p < 0.001$ )	VAS (0–10 scores): 3.3 (2.5) change from baseline: 3.6 ( $p < 0.001$ )	VAS (0–10 scores): 3.5 (2.5) change from baseline: 3.9 ( $p < 0.001$ )	VAS (0–10 scores): 4.1 (2.4) change from baseline: 3.8 ( $p < 0.001$ )	Chondroitin sulphate: 20 ml solution, one instillation weekly for 6 wk and then monthly for 16 wk for a total of 10 treatments Side effects: 65 AEs, 20 related to treatment (mild genitourinary symptoms and UTIs)
Heparin: intravesical Parsons et al. [74]	NIDDK	48	16	Prospective	44 (median)	90	48	Subjective analysis of improvement: (patient verbal comment) good clinical remissions: 56% at 3 mo	VAS (0–10 scores): from 6.8 to 4.5 in responders (27/48) at 3 mo; from 6.8 to 3.3 in 15/48 patients at 12 mo ( $p < 0.01$ )	VAS (0–10 scores): from 7.1 to 4.9 in responders (27/48) at 3 mo; from 7.1 to 3.7 in 15/48 patients at 12 mo ( $p < 0.01$ )	Not collected	Heparin (10 000 U in 10 ml sterile water): one instillation three times per week for at maximum of 6 mo No side effects
Hydroxyzine: oral Theoharides and Sant [75]	Clinical and cystoscopic	140	90	Prospective	Not reported	Not reported	12	Not collected	VAS (1 = best, 10 = worst) at 3 mo: 40% reduction in symptom scores	Not reported	Not reported	Hydroxyzine: 75 mg (50 mg every night and 25 mg at midday) Side effects: sedation in most cases; increased appetite in 10%; urinary retention in two cases
L-arginine: oral Smith et al. [85]	Clinical and cystoscopic	11	10	Prospective	56	100	24	Not collected	VAS (0 = best to 10 = worst): 4.8 to 0.7 ( $p < 0.05$ )	Not collected	Voiding diary: from 13.4 to 8.1 ( $p < 0.001$ )	L-arginine: 500 mg three times per day No side effects
Leukotriene, receptor antagonist: oral Bouchelouche et al. [77]	NIDDK	10	10	Prospective	63 (median)	100	12	Not collected	VAS (0 = best to 100 = worst): from 46.8 to 19.6 ( $p = 0.006$ )	Not collected	Voiding diary, frequency/24 h: from 17.4 to 12.0 ( $p = 0.009$ )	Montelukast 10 mg daily for 3 mo No side effects
Misoprostol, immunosuppressor: oral Kelly et al. [78]	NIDDK	25	16	Prospective	64	92	36	ICSI: from 16.9 (25/25 patients) to 9 (12/25) at 9 mo ( $p < 0.01$ ) ICPI: from 13.6 (25/25) to 5.3 (12/25) at 9 mo ( $p < 0.005$ )	Interview score (from 0 = none to 5 = maximum): from 4 to 1 at 9 mo ( $p < 0.01$ )	Interview score (from 0 = none to 5 = maximum): from 3.9 to 1.4 at 9 mo ( $p < 0.01$ )	Voiding diary: from 16.9 (25/25) to 9 (12/25 patients) at 9 mo ( $p < 0.01$ )	Misoprostol: 600 µg daily for 3 mo Side effects: 16 patients (64%): abdominal cramps and diarrhoea; dropout in 9
Neuromodulation Comiter [59]	NIDDK	25	17	Prospective	47	96	56	ICSI: improved from 16.5 to 6.8 ( $p < 0.01$ ) ICPI: decreased from 14.5 to 5.4 ( $p < 0.01$ )	VAS ((0 = best to 10 = worst): from 5.8 to 1.6 points ( $p < 0.01$ )	Not collected	Voiding diary: from 17.1 to 8.7 ( $p < 0.01$ )	Permanent sacral nerve stimulation implant No side effects

Zabihi et al. [60]	IC database study	30	23	Prospective	46	70	60	ICSI: improved from 17.6 to 11.4 ( $p = 0.005$ ) ICPI: decreased from 15.1 to 9.4 ( $p = 0.007$ ) UDI-6: improved by 26% ( $p = 0.05$ ) SF-36: no statistical difference GRA: at least 50% improvement in 44/78 patients (67%)	VAS (not reported scores): improved by 40% ( $p = 0.04$ )	ICSI: from 4.6 to 3.3 ( $p < 0.05$ )	ICSI: from 3.9 to 2.3 ( $p < 0.05$ )	Bilateral S2–S4 sacral neuromodulation Side effects: four infections (17%)
Gajewski and Al-Zahrani [61]	ESSIC	78	78	Retrospective	42	90	244	Not collected	Not collected	Not collected	Not collected	Permanent sacral nerve stimulation implant Side effects: surgical revision in half of patients due to altered stimulation and pain (25%) at the site of implanted generator
Powell and Kreder [62]	Clinical and cystoscopic	39	22	Retrospective	54	82	240	Not collected	Subjective analysis of pain (patient verbal comment) 64.7% cured, 35.3% same	Subjective analysis of urgency: (patient verbal comment): 9.1% cured, 68.2% improved, 22.7% same	Subjective analysis of frequency (patient verbal comment): 13.6% cured, 63.6% improved, 22.7% same	Permanent sacral nerve stimulation implant Concomitant use of medications Side effects: infection, malfunction, and destruction of the device, troublesome foot movement in four cases
Nifedipine, immunosuppressor: oral Fleischmann et al. [79]	NIDDK	10	9	Prospective	28–51	100	16	Frequency, urgency, nocturia, dysuria, and suprapubic pain on a scale of 0–2: 50% decrease in symptom scores in 50% of patients. Three patients completely cured	VAS (0–10 scores): from 6.6 to 2	Not reported	Not reported	Nifedipine: single daily dose (30 mg) escalated to 60 mg daily when insufficient relief of symptoms Side effects: in five patients: headaches, dizziness, constipation
Pentosan polysulphate: oral Hanno [53]	Clinical and cystoscopic	2809	128	Prospective	47	90	240	Not standardised questionnaire	VAS (1 = best to 10 = worst): from 6.9 to 4.6 (for treatment duration of 17 mo) 50% positive responders from 0 to 5 mo	VAS (1 = best to 3 = worst): from 2.3 to 1.6 (for treatment duration of 11 mo) Positive response in 47% of patients from 0 to 5 mo	Voiding diary, frequency/24 h: up to 17 mo treatment: from 14.2 to 12.4 (in patients with 8–24 voids/d); similar trend in patients with >24 voids/d	Oral PPS 100 mg three times daily Side effects < 4%: alopecia in 3.91%
Jepsen et al. [54]	Clinical and cystoscopic	97	11	Prospective	45	95	464	ICDB: not significant	ICDB: not significant	ICDB: not significant	ICDB: not significant	Oral PPS: 100 mg three times daily Duration of treatment 12.3 mo Side effects: in 16 patients Comparison between early and late treatment Secondary analysis: oral PPS 300 mg/d Side effects: not reported
Nickel et al. [57]	Clinical and cystoscopic	128	36	Retrospective	45	91	32	ICSI and ICPI significantly better in early treatment ( $p = 0.0472$ )	Not reported	Not reported	Not reported	Association between response to PPS and patient questionnaire-based treatment Secondary analysis: oral PPS 300 mg/d Side effects: not reported
Sand et al. [56]	Clinical and cystoscopic	128	Not reported	Retrospective	45	91	32	ICSI: $\geq 30\%$ reduction in patient responders (49/128 patients) (42%) ( $p < 0.0001$ )	Not reported	Not reported	Not reported	LP8: 80 mg/40 ml distilled water once weekly Oral PPS: 100 mg three times daily for 4 wk Side effects: in two patients of LP8 group: mild pain in the bladder
Chuang et al. [55]	Clinical and cystoscopic	24	24	Prospective; comparison 1:1 with intravesical liposomes	47	Not reported	8	ICSI statistically significant decrease in total scores with both treatments	Statistically significant decrease in pain with both treatments	Statistically significant decrease in urgency with both treatments	Statistically significant decrease in frequency with both treatments	LP8: 80 mg/40 ml distilled water once weekly Oral PPS: 100 mg three times daily for 4 wk Side effects: in two patients of LP8 group: mild pain in the bladder

Table 2 (Continued)

Treatment Study	Diagnostic criteria	No. of patients at baseline	No. of patients at follow-up	Design	Mean age, yr	Women, %	Follow-up, wk	Symptom index	Pain	Urgency	Frequency	Treatment details Side effects
Al-Zahrani and Gajewski [58]	ESSIC	271	178	Retrospective	45	90	88	GRA: 50% improvement in 147 patients (54.2%); group 2: degree of improvement was higher but not significant ( $p = 0.09$ )	Evaluation with good and poor outcome; group 1 ( $p = 0.35$ ); group 2: ( $p = 0.99$ )	Evaluation with good and poor outcome; group 1 ( $p = 0.10$ ); group 2: ( $p = 0.73$ )	Evaluation with good and poor outcome; group 1 ( $p = 0.18$ ); group 2: ( $p = 0.15$ )	PPS: dose not reported Evaluation of the long-term efficacy and tolerability of PPS; group 1: PPS < 12 mo; group 2: PPS > 12 mo Side effects with PPS discontinuation. Stomach upset: 8.5% of patients; headache in 2.2%, hair loss in 1.1%, hypersensitivity in 1.1%, and increase in liver enzymes in 0.7%
Physiotherapy Weiss [80]	Clinical and cystoscopic	52	46	Prospective	26–80	60	78	Symptom score on pain and voiding (0 = best to 4 = worst) Marked/moderate improvement: 70% ICSI: from 8.9 to 6.9 ( $p = 0.015$ )	Not collected	Not collected	Not collected	Two massages weekly for 5 wk No side effects
Oyama et al. [81]	IC database study	21	13	Prospective	42	100	18	ICSI: from 8.9 to 6.9 ( $p = 0.015$ )	VAS: from 5.4 to 3.5 ( $p = 0.005$ )	VAS: from 4.6 to 3.0 ( $p = 0.001$ )	Not collected	18 treatments for a mean time of in 19.7 mo No side effects
Quercetin: oral Katske et al. (2001) [82]	Clinical and cystoscopic	22	20	Prospective	53	81	4	ICSI: from 11.9 to 4.5 ( $p = 0.000001$ )	Not collected	Not collected	Not collected	Quercetin: 500 mg twice a day for 4 wk Side effects: not reported
Resiniferatoxin (RTX): intravesical Peng and Kuo [83]	Clinical and cystoscopic	13	12	Prospective	50	77	12	Not standardised questionnaire: from 4.2 to 2.8 ( $p = 0.008$ )	Pain scale (1 = best to 5 = worst): from $2.3 \pm 1.4$ to $0.9 \pm 0.9$ ( $p = 0.003$ )	Not reported	IPSS: from 13.6 to 10.4 ( $p = 0.05$ )	Resiniferatoxin: RTX 10 nM in 30 ml saline, once weekly for 4 wk No side effects
Suplatast tosilate, immunosuppressor: oral Ueda et al. [84]	NIDDK	14	14	Prospective	44	100	48	ICSI: from 12.5 to 3.9	Not collected	Not collected	Not collected	Suplatast: 300 mg/d orally Side effects: not reported

NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; ICSI = Interstitial Cystitis Symptom Index; VAS = visual analogue scale; PUF = pelvic pain and urgency/frequency questionnaire; GRA = global response assessment; ESSIC = European Society for the Study of Interstitial Cystitis HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; BFLUTS = Bristol Female Lower Urinary Tract Symptom; UTI = urinary tract infection; UDI-6 = Urogenital Distress Inventory; ICDB = Interstitial Cystitis Data Base; ICPI = International Cystitis Problem Index; PPS = pentosan polysulphate sodium; RTX = resiniferatoxin; AE = adverse event.

**Table 3 – Surgical treatment for painful bladder syndrome/interstitial cystitis**

Study	Diagnostic criteria	No. of patients	Design	Mean age, yr	Women, %	Follow-up, wk	Symptom outcomes				Treatment details and side effects
							Symptom index	Pain	Urgency	Frequency	
Surgical treatment											
Hughes et al. [90]	Clinical and cystoscopic	32	Retrospective	58	91	252	Not collected	20/32 patients cured 7/32 patients improved	Not collected	Not collected	Different types of substitution cystoplasty Side effects: Pyelonephritis in four cases and renal calculi in two cases with supratrigonal cystectomy
Christmas et al. [93]	Clinical and cystoscopic	27	Prospective	61 (median)	85	120	Not collected	Relief of pain in 21/27 patients; persistent pain in 6/21 patients	Not collected	Voiding diary: from 15 voids/day to every 3–4 h	6/27 supratrigonal cystectomy; 21/27 subtotal cystectomy from 15 voids/day to every 3–4 h Side effects: intractable incontinence in five cases; stones in two cases; hydronephrosis in one case
Peeker et al. [88]	NIDDK	13	Retrospective	59	77	240	Not collected	Relief of pain: 10/10 patients	Not collected	Not reported	Supratrigonal cystectomy and ileocystoplasty (10/13 patients with ulcer IC) Side effects: intestinal obstruction in one case and intermittent catheterisation in three cases in group with classic IC
Rofeim et al. [94]	Clinical and cystoscopic	24	Prospective	63	92	92	Not collected	VAS: from 9.1 to 1.2 ( $p < 0.003$ )	VAS: from 8.2 to 1.9 ( $p < 0.003$ )	Mean voiding interval from 30 to 120 min	Nd:YAG laser ablation of Hunner ulcers Side effects: relapse in 11 patients; 6 required retreatment
van Ophoven et al. [86]	NIDDK	18	Retrospective	56	100	228	ICSI: from 32.6 to 9.9 ( $p \leq 0.005$ )	Pain improvement: 18 patients Complete pain relief: 2 patients	Improvement ( $p \leq 0.005$ )	Voiding diary 24 h: from 31.4 to 8.3 ( $p \leq 0.005$ )	Trigone-preserving orthotopic substitution: ileocecal augmentation in 10 patients; ileal substitute in 8 patients Side effects: not reported
Chakravanti et al. [87]	Clinical and cystoscopic	11	Retrospective	56	91	412	Not collected	Nonstandardised interview: abolished in 11 patients (100%)	Nonstandardised Interview: abolished in 10 patients (90%)	Voiding diary: from 17 to 6 ( $p \leq 0.0001$ )	Trigone-preserving orthotopic substitution caecocystoplasty Side effects: intermittent catheterisation in two cases; recurrent trigonal pain in two cases with consequent cystectomy
Elzawahri et al. [92]	Clinical and cystoscopic	11	Prospective	45	91	160	Not collected	Pelvic pain abolished in 10/11 patients (90%)	Not collected	Not collected	Conversion from augmented bladder or continent urinary diversion pouch to ileal conduit Side effects ureteral obstruction I two cases with consequent reimplantation
Kochakarn et al. [91]	NIDDK	35	Prospective	46	100	112	SF-36: Physical health score: from 55.7 to 82.6 ( $p < 0.001$ ) Mental health score: from 50.7 to 75.7 ( $p < 0.001$ )	VAS: from 9.8 to 1.8 ( $p < 0.001$ )	Not collected	Not collected	Cystectomy and bladder substitution by ileal neobladder Side effects neobladder stone (1 case); dyspareunia in 12 cases
Rössberger et al. [89]	NIDDK	47	Retrospective	Not reported	81	356	Not collected	Not reported	Not collected	Voiding diary (10/19 evaluable patients): decrease in voiding frequency ( $p = 0.0051$ )	Different types of reconstructive surgery Side effects: intermittent catheterisation in 13 cases; high rate of reoperations in continent diversion

NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; IC = interstitial cystitis; Nd:YAG = neodymium:yttrium-aluminum-garnet (laser); VAS = visual analogue scale; SF-36 = Short Form 36 (health survey).

Table 4 – Multimodal therapy for painful bladder syndrome/interstitial cystitis

Study	Diagnostic criteria	No. of patients at baseline	No. of patients at follow-up	Design	Age, yr, mean	Women, %	Follow-up, wk	Symptom Outcomes				Details of the studies and side effects
								Symptom Index	Pain	Urgency	Frequency	
Gabapentin, amitriptyline, nonsteroidal anti-inflammatory drug Lee et al. [95]	Clinical and cystoscopic	38	38	Prospective	56	71	24	ICSI: from 11.7 to 4.4, 3.8, and 4 (from baseline to 1, 3, and 6 mo after treatment, respectively; $p < 0.05$ )	VAS (10 = worst to 0 = best): from 6.7 to 1.8, 1.5, and 1.7 (from baseline to 1, 3, and 6 mo after treatment, respectively; $p < 0.05$ )	Not reported	Not reported	600 mg etodolac micronized, 5 mg amitriptyline, 300 mg gabapentin at bedtime. If not symptom-free after 2 wk, increase to 20 mg amitriptyline and 600 mg gabapentin, and thereafter to 75 mg and 900 mg, respectively Side effects: dry mouth in five patients, dizziness in three patients
Heparin, alkaline lidocaine Parsons [96]	NIDDK	82 (group 1 = 47; group 2 = 35)	75 (group 1 = 47; group 2 = 28)	Prospective	35	Not reported	20 min for group 1, 2 wk for group 2	PORIS: Relief in pain and urgency in 75% of patients in group 1 and in 94% of patients in group 2 ( $p < 0.01$ ) within 20 min of single instillation. Group 1: 50% relief after 48 h; group 2: relief in 16/20 patients (80%) at 2 wk	PORIS: Relief in pain in 75% of patients in group 1 and in 94% of patients in group 2 ( $p < 0.01$ ) within 20 min of single instillation	PORIS: Relief in urgency in 75% of patients in group 1 and in 94% of patients in group 2 ( $p < 0.01$ ) within 20 min of single instillation	Not collected	40,000 U heparin solution, 8 ml 1% lidocaine (group 1) or 2% lidocaine (group 2) and 3 ml 8.4% sodium bicarbonate intravesically. Group 2: additional instillations of the 2% lidocaine solution, 3 treatments per week for 2 wk No side effects
Hyaluronic acid, hydrodistension, intravesical heparin Shao et al. [97]	NIDDK	47	44	Prospective	55 (median)	100	36	Not collected	VAS (0 = worst; 10 = best): HA Group: from 7.1 to 3.4, 4.9, and 6.1 (at 3, 6, and 9 mo, respectively; $p < 0.001$ , $p < 0.001$ , $p < 0.01$ ). Heparin group: from 7.2 to 3.9, 6.5, and 7.1 (at 3, 6, and 9 mo, respectively; $p < 0.001$ , $p < 0.01$ , $p > 0.05$ ). Hydrodistension group: from 7.1 to 6.6 and 7.5 (at 3 and 6 mo, respectively; $p$ not significant)	Not collected	Voiding diary 24 h: HA group: from 19.3 to 11.1, 14.6, and 17.5 (at 3, 6, and 9 mo, respectively; $p < 0.001$ , $p < 0.001$ , $p < 0.01$ ). Heparin group: from 19.7 to 12.1, 18.3, and 19.7 (at 3, 6, and 9 mo, respectively; $p < 0.001$ , $p < 0.01$ , $p > 0.05$ ) Hydrodistension group: from 18.5 to 18.4 and 19.7 (at 3 and 6 mo, respectively; $p$ not significant)	Hydrodistension: Twice for 8 min under 100 cm H <sub>2</sub> O pressure in all patients. HA: After hydrodistension, 20 patients received intravesically 40 mg of HA, weekly in the first month and then monthly in the following months. Intravesical heparin: After hydrodistension, 16 patients used 12 500 U with 100 mg lidocaine weekly in the first month and then monthly in the following months No side effects
Doxepin, piroxicam Wammack et al. [98]	NIDDK	37	32	Prospective	39	100	12	Not collected	VAS (from 10 = worst to 1 = best): from 6.4 to 2.1 and 5 (during and after treatment, respectively)	Urgency (present or absent): 17/19 patients subjective improvement	Voiding diary 24 h: from 17.6 to 11.1 and 15.9 (during and after treatment, respectively)	Doxepin: from 25 mg to 75 mg daily at bedtime for 8 wk Piroxicam: 40 mg daily at bedtime for 8 wk Doxepin and piroxicam were administered together Side effects: Weight gain, dry mouth, gastric pain, and drowsiness in 14 patients; severe gastric pain in 1 patient and intolerable drowsiness in 3 patients, inducing discontinuation

Behavioural, pharmacologic (Macrofantin, hydroxyzine, Urised) and endoscopic therapies												
Hanley et al. [99]	IC data base study	25	18	Prospective	36	100	40	2 mo after hydrodistention: ICSI from 8.5 to 7 At the end of follow-up, data are available in 7 patients: ICSI from 8.5 to 6.7; $p < 0.001$	Not reported	Not reported	Not reported	Behavioural therapy: diet recommendations, fluid restriction to 64 oz/d, progressive times voiding and Kegel exercises Oral therapy: Macrofantin 100 mg daily, hydroxyzine 10–20 mg daily, Urised <sup>*</sup> four tablets daily, PPS 100 mg three times per day if patients started this drug 6 mo prior the first visit. Endoscopic treatment: at a minimum of 2 wk after behavioural/pharmacologic therapy: hydrodistention three times at bladder capacity Side effects: gastrointestinal irritation (one patient with Urised, one patient with Macrofantin); dizziness in one patient with hydroxyzine
Cystoprotek <sup>**</sup> Theoharides and Sant [100]	NIDDK	37	37	Prospective	39	100	24	ICSI: from 16.3 to 6.9 ( $p < 0.05$ ). ICPI: from 13.1 to 5.4 ( $p < 0.05$ ). Global assessment (0 = least, 10 = worst): from 9 to 4.3 ( $p < 0.05$ )	Not reported	Not reported	Not reported	Cystoprotek: six tablets daily for 6 mo Side effects: stomach irritation in nine patients
Hydrocortisone and heparin intravesical; oral antimuscarinic drugs; intramuscular injection of triamcinolone Taneja and Jawade [101]	NIDDK	26	26	Prospective	52	88	72	Not collected	Relief in pain: complete in 73%, satisfactory in 19%, inadequate in 8%	Not collected	24-h voiding diary: from 23.8 to 10.6	Intravesical hydrocortisone (200 mg) and heparin (25 000 IU) in saline solution for 6 wk. When no relief, intramuscular injection of triamcinolone 40 mg weekly for 6 wk. Oral antimuscarinic drugs: oxybutynin hydrochloride (5 mg twice a day) or tolterodine (4 mg once a day) were continued throughout the follow-up period. No side effects

ICSI = Interstitial Cystitis Symptoms Index; VAS = visual analogue scale; NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; ICPI = Interstitial Cystitis Problem Index; PORIS: Patient Overall Rating of Improvement of Symptoms; HA = hyaluronic acid; IC = interstitial cystitis; PPS = pentosan polysulphate sodium.

Note: Sairanen 2007 (cyclosporine A plus PPS), Sant 2003 (pentosan polysulphate plus oral hydroxyzine), van Ophoven 2005 (pentosan polysulphate and subcutaneous low-dose heparin), Kuo 2009 (botulinum toxin A plus hydrodistention) are reported in Table 1.

<sup>\*</sup> Urised: methenamine, methylene blue, phenyl salicylate, benzoic acid, atropine sulphate, and hyoscyamine.

<sup>\*\*</sup> Cystoprotek: glucosamine sulphate, chondroitin sulphate, sodium hyaluronate, quercetin dehydrate, and olive kernel extract.

### 3.2. Treatment efficacy in nonrandomised controlled trials

Table 2 gives the details of 41 nRCTs. Results on a single agent were evaluated in all 41 nRCTs. Six studies were retrospective; 35 were prospective. The 41 trials spanned the years 1991–2011, reporting on a total of 4855 adult patients at baseline. A total of 1418 patients completed the studies; three studies did not report this information. The number of patients included ranged from 10 to 2809, and mean ages ranged from 32 to 64 yr. Sixteen nRCTs used the NIDDK research criteria for diagnosing PBS/IC; the ESSIC criteria were used in three studies (Table 2). Length of follow-up ranged from 4 to 464 wk (mean: 73.79 wk). The most frequently adopted treatments were botulinum A toxin intravesical injections in eight prospective studies [45–52], oral PPS in six studies (three retrospective and three prospective) [53–58], neuromodulation in two studies [59–62], and intravesical glycosaminoglycans and intravesical BCG in three studies, respectively [63–66,28,67]. All but one nRCT reported significant or good efficacy in at least one of the four considered outcomes. Van Ophoven and Hertle did not document any effect on ICSI, pain, urgency, and frequency when using oral duloxetine from 20 mg to 40 mg with increments at 1-wk intervals, with a dose target of 40 mg twice daily for 5 wk [68]. With regard to amitriptyline, in one study the significant improvements obtained in the four analyzed outcomes were accompanied by side effects that induced discontinuation in 25% of patients after a 6-wk follow-up [69]. CyA has been used in two studies with a small number of patients, and it had a therapeutic effect that was maintained in the long term [70,71]. Many other different agents or treatment modalities were adopted in the selected nRCTs [72–85].

When we compared the results between studies reporting the presence or absence of bladder inflammation, we were not able to find any relationship. In addition, data on the relief of bladder inflammation after treatment have never been reported.

### 3.3. Surgical treatment

Table 3 shows the details of nine studies reporting on surgical treatment of patients with PBS/IC. Five studies were retrospective; four were prospective [86–94]. The nine studies spanned the years 1995–2007, reporting on a total of 218 adult patients who underwent different kinds of reconstructive surgery. In one study, neodymium: yttrium-aluminum-garnet laser ablation of Hunner ulcers was performed [94]. The number of patients included ranged from 11 to 47, and mean ages from 45 to 63 yr. Four studies used the NIDDK research criteria for diagnosing PBS/IC (Table 3). Length of the follow-up ranged from 92 to 412 wk, with a mean of 219.1 wk. A standardised questionnaire to evaluate symptoms was used in only two studies [86,91]. Improvement in pain was observed in 2–100% of patients, but in most studies the assessment was performed with a nonstandardised interview.

### 3.4. Multimodal therapy

To date, seven prospective studies have been identified among multimodal approaches to treat PBS/IC (Table 4). Other studies using multimodal therapies have been reported among the RCTs [16,19,20,22,25]. Five studies used the NIDDK research criteria for diagnosing IC and one the IC database study criteria (Table 4). The studies spanned the years 2002–2010 and included 292 adult patients. Length of follow-up ranged from 2 to 72 wk. Different combination of agents and treatment modalities were used, including antidepressants; nonsteroidal anti-inflammatory drugs; behavioural and oral plus intravesical therapies, including heparin; anaesthetics; and endoscopic surgical procedures. A standardised questionnaire and visual analogue scale (VAS) scores for the evaluation of symptoms were used in four and three studies, respectively [95–100]. An improvement in pain was reported in seven studies, and frequency amelioration was collected and reported in three. Only one study reported a high rate (75.6%) of side effects with the combination of a tricyclic antidepressant and a cyclo-oxygenase inhibitor, with a treatment discontinuation rate of 10.8% [98].

### 3.5. Side effects

Table 1 lists the side effects from RCTs. Some of the studies did not describe side effects or the discontinuation rate due to side effects. Higher rates of side effects were described for oral amitriptyline (dry mouth, dizziness, gastrointestinal problems in 79–88% of cases vs 21–72% of patients treated with placebo) [25,27]. Antibiotic therapy also induced nausea and vomiting, diarrhoea, headache, dizziness, and rash in about 80% of patients compared with 40% of patients in the placebo group [41]. Side effects related to oral PPS were variably reported and ranged from 1% to 80% [19,21,22,36,40]; intravesical chondroitin sulphate induced at least one side effect in 76.9% [31]. With regard to intravesical BCG, irritative symptoms were noted in about 50% of patients [18,28,29,43]. Most patients treated with intravesical RTX reported pain during instillation [17,26,38].

Side effects were mild to moderate for CyA in 30 patients in the CyA arm (increased blood pressure and serum creatinine) and in 18 in the PPS arm (gastrointestinal disturbances, headache, fatigue, and gross haematuria in one). The dropout rate at 6 mo was relevant (25% of patients in the CyA arm and 12.5% in the PPS arm) [20]. The use of CyA is considered a fifth-line treatment in the AUA Guidelines for the Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome [3]. The side effects reported in the nRCTs are reported in Table 2, 3, and 4.

## 4. Conclusions

We found that only 9 of the 29 eligible RCTs presented with extractable data on the four assessed outcomes: change in ICSI questionnaire, pain, urgency, and frequency [19,25–29,33,34,37]. Meta-analysis of these studies shows that only CyA

**Table 5 – Levels of evidence applied according to the European Association of Urology for agents and/or treatment modalities of painful bladder syndrome/interstitial cystitis in randomised controlled studies**

Treatment	Level of evidence	Grade of recommendation	Comments
Amitriptyline	1b	A	Great effect size of SMD on ICSI and pain
Intravesical BCG	1b	A	Small effect size of SMD on ICSI and pain
BoNT/A plus intravesical hydrodistention	1b	A	Medium effect size of SMD on ICSI Small effect size of SMD on pain
Intravesical chondroitin sulphate	1b	A	Small effect size of SMD on ICSI and pain
Cyclosporine A	1b	A	Great effect size of SMD on ICSI, pain and frequency
PPS plus hydroxyzine	1b	A	Small effect size of SMD on ICSI and pain
L-arginine	1b	A	Small effect size of SMD on ICSI; medium effect size of SMD in pain
Intravesical lidocaine plus sodium bicarbonate	1b	A	Small effect size of SMD on ICSI and pain
Hyperbaric oxygen	1b	A	Great effect size of SMD on ICSI and pain
Oral PPS	1b	C	Data not available; the effects are reported as positive
PPS plus subcutaneous heparin	1b	A	Great effect size of SMD on pain
Sacral neuromodulation	1b	C	Great effect size of SMD on ICSI. Other effects not reported

SMD = standardised mean difference; ICSI = Interstitial Cystitis Symptom Index; BCG = bacillus Calmette-Guérin; BoNT/A = botulinum toxin serotype A; PPS = pentosan polysulphate sodium.

1.5 mg/kg twice daily for 6 mo versus PPS (a high-quality study according to the Jadad score) showed a simultaneous great effect size on three outcomes (ICSI, pain, and frequency), although the discontinuation rate at 6 mo due to side effects was relevant in the CyA arm [20]. For amitriptyline, increasing doses once daily from 25 mg to 100 mg for 4 mo versus placebo [27], a great effect size was reported for pain and urgency. The same drug with different dosages and times of administration in a high-quality study (increasing doses once daily from 10 to 75 mg for 12 wk) with the addition of behavioural modification versus placebo plus behavioural modification showed a great effect size in ICSI and frequency as observed in the subanalysis [25]. The study did not show intent-to-treat significance, perhaps because in these treatment-naïve patients the behavioural management obscured the effect of the drug [25].

Some differences existed between clinical characteristics of patients and outcomes assessed between the study of van Ophoven et al. [27] and that of Foster et al. [25]. The study of van Ophoven et al. [27] included patients who met the symptoms criteria of NIDDK for IC and who had received previous conservative medical treatment. The study of Foster and coworkers [25] included naïve patients (no prior significant treatment for PBS/IC) affected by bladder pain/discomfort and urinary frequency of  $\geq 3$  on a separate 0–10 Likert scale. Perhaps the results from these two studies on amitriptyline indicate that higher doses of the drug and longer administration times could induce improvements in different outcomes, although the rate of side effects was relevant. With regard to RCTs on PPS, we were able to find four high-quality studies even if the level of evidence was 1b and the grade of recommendations ranged from A to C [19,24,36,44]. Contradictory results were reported in studies evaluating the efficacy of intravesical RTX. RTX 0.001  $\mu\text{M}$  intravesically delivered produced a great effect size in pain and frequency [38], whereas RTX 0.10  $\mu\text{M}$  showed a great effect size in urgency. Worthy of note was a small effect size due to RTX on all four of the parameters

observed in the multicentre study performed by Payne and coworkers, which is the only high-quality RCT on RTX [26]. Due to these results, the AUA guidelines on the diagnosis and treatment of PBS/IC stated that intravesical instillation of RTX should not be considered for treatment due to insignificant differences between treatment and placebo groups or between different dosages used [3]. With regard to the results of intravesical BCG, RCTs showed only a limited efficacy in the evaluated outcomes. One of these RCTs was a high-quality study [29]. In addition, when also considering the potential and serious adverse effects of BCG, as shown in urothelial cancer patients treated with intravesical BCG, we agree with the AUA guidelines on the diagnosis and treatment of PBS/IC that suggest only using BCG for investigational purposes [3].

No RCT reported a great effect size in all the four considered outcomes. The remaining RCTs showed sporadic significant changes in only one of the four considered parameters. In general, meta-analysis of RCTs showed a great heterogeneity in the applied methodologies, clinical outcomes assessed, and in the obtained results in different studies, factors that cannot be completely adjusted by adopting a random-effects model. Because the heterogeneity tests were highly significant ( $I^2 > 70\%$ ;  $p < 0.0001$ ) in overall analyses, random-effects models were preferred to fixed-effects models. The Begg and Egger tests did not show significant publication bias [12,13]. Table 5 shows the level of evidence and grades of recommendations for each individual agent/treatment modalities shown in RCTs according to the analysis applied.

Regarding the results from nRCTs, the heterogeneity in drugs and treatment modalities, clinical outcomes, and obtained results is obviously much more evident, and performing a meta-analysis was not possible or adequate. When considering the reasons for the high rate of dropout in these studies, at least three different aspects can be identified: presence of intolerable side effects, lack of efficacy, and the retrospective nature of the study. In some

cases the reason for dropout was not specified. The most frequently adopted treatment in many publications was oral PPS (three retrospective and two prospective studies) [45–52]. Due to the high number of patients included and the length of follow-up (240 mo), Hanno's study deserves particular mention [53]. Oral PPS 100 mg three times daily showed about a 50% positive response in pain and urgency, as assessed with a VAS scale. This is the study with the longest follow-up in the treatment of PBS/IC patients with oral PPS [53]. It appeared that the use of botulinum A toxin intravesical injections as a treatment for PBS/IC is increasing (eight prospective studies). This does not reflect what happens in everyday clinical practice, and the neurotoxin is considered a second-line treatment for the disease with a level of evidence 3 [102].

All prospective studies about intradetrusorial BoNT/A injections reported a significant decrease in pain as assessed by VAS and frequency. Unfortunately, only three of these studies evaluated symptoms with a standardised questionnaire [45,49,50]. It is not clear if trigone injection with BoNT/A produces additional effects, although it is possible to argue that the dense innervation located in the trigone may benefit from BoNT/A injections. Ramsay et al. did not specify the injected sites into the bladder [52]. Kuo et al. did not find therapeutic improvements between patients with or without trigone injections [46], but Pinto et al. obtained significant clinical improvement by injecting only the trigone [49]. Good results were observed by Giannantoni and coworkers, who injected the trigone into the lateral and posterior walls of the bladder [50]. Due to the nonrandomised characteristics of these studies and the previously mentioned high heterogeneity, it is not possible to come to a definitive conclusion about the efficacy of each individual treatment in the nRCTs. Thus the attributed levels of evidence ranged from 2a to 3 and the grades of recommendations from B to C. The critical analysis of the results is really difficult when examining studies related to surgical treatment of PBS/IC. It was evident that surgical treatment was offered in patients with refractory PBS/IC as the last chance for improvement. A strong limit was represented by the extreme heterogeneity in the surgical approaches that were offered to patients; thus any comparison among different studies was not possible. It is interesting to note that all the studies on multimodal therapy adopted the rationale to target more than one of the key components of PBS/IC, that is, urothelium disease, neural inflammation, allergies, and the resulting pain. Despite the small number of these studies, the adopted rationale probably represents a turning point in attempting to achieve consistent and long-lasting success in the treatment of the disease.

The meta-analysis performed here in the evaluation of RCTs and the evaluation of all nRCTs revealed a great heterogeneity in methodology, symptoms assessment, duration of treatment, and follow-up. This likely reflects a lack of understanding of the pathophysiology of the disease. The inability to propose definitive conclusions from the results coming from most of the proposed treatments nevertheless can stimulate efforts to improve the quality of studies needed to optimize medical care for PBS/IC.

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*Study concept and design:* Giannantoni

*Acquisition of data:* Giannantoni, Proietti.

*Analysis and interpretation of data:* Bini.

*Drafting of the manuscript:* Giannantoni, Proietti, Dmochowski, Hanno, Nickel, Wyndaele.

*Critical revision of the manuscript for important intellectual content:* Dmochowski, Hanno, Nickel, Wyndaele, Giannantoni.

*Statistical analysis:* Bini.

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