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Interventions for treating people with symptoms of bladder pain syndrome: a network meta-analysis (Review)

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[Intervention Review]

Interventions for treating people with symptoms of bladder pain syndrome: a network meta-analysis

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ABSTRACT

Background

Bladder pain syndrome (BPS), which includes the condition of interstitial cystitis, is a poorly understood clinical condition for which patients present with varying symptoms. Management of BPS is challenging for both patients and practitioners. At present, there is no universally accepted diagnosis and diverse causes have been proposed. This is reflected in wide-ranging treatment options, used alone or in combination, with limited evidence. A network meta-analysis (NMA) simultaneously comparing multiple treatments may help to determine the best treatment options for patients with BPS.

Objectives

To conduct a network meta-analysis to assess the effects of interventions for treating people with symptoms of bladder pain syndrome (BPS).

Search methods

We searched the Cochrane Incontinence Specialised Register, which contains trials identified from the Cochrane Central Register of Controlled Trials (CENTRAL, in the Cochrane Library), MEDLINE, MEDLINE In-Process, MEDLINE Epub Ahead of Print, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and handsearched journals and conference proceedings (searched 11 May 2018) and the reference lists of relevant articles. We conducted a further search on 5 June 2019, which yielded four small studies that were screened for eligibility but were not incorporated into the review.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs of interventions for treating adults with BPS. All types of interventions (including conservative, pharmacological and surgical) were eligible.

Data collection and analysis

We assessed the risk of bias of included studies using Cochrane's 'Risk of bias' tool. Primary outcomes were the number of people cured or improved, pain, frequency and nocturia. For each outcome, random-effects NMA models were fitted using WinBUGS 1.4. We monitored median odds ratios (ORs) for binary outcomes and mean differences (MDs) for continuous outcomes with 95% credible intervals (CrIs). We

compared results of the NMA with direct evidence from pairwise meta-analysis of head-to-head trials. We used the CINeMA tool to assess the certainty of evidence for selected treatment categories.

Main results

We included 81 RCTs involving 4674 people with a median of 38 participants (range 10 to 369) per RCT. Most trials compared treatment against control; few trials compared two active treatments. There were 65 different active treatments, and some comparisons were informed by direct evidence from only one trial. To simplify, treatments were grouped into 31 treatment categories by mode of action. Most studies were judged to have unclear or high risk of bias for most domains, particularly for selection and detection bias. Overall, the NMA suggested that six (proportion cured/improved), one (pain), one (frequency) and zero (nocturia) treatment categories were effective compared with control, but there was great uncertainty around estimates of effect.

Due to the large number of intervention comparisons in this review, we focus on three interventions: antidepressants, pentosan polysulfate (PPS) and neuromuscular blockade. We selected these interventions on the basis that they are given 'strong recommendations' in the EAU Guidelines for management of BPS (EAU Guidelines 2019).

We found very low-certainty evidence suggesting that antidepressants were associated with greater likelihood of cure or improvement compared with control (OR 5.91, 95% CrI 1.12 to 37.56), but it was uncertain whether they reduced pain (MD -1.27, 95% CrI -3.25 to 0.71; low-certainty evidence), daytime frequency (MD -2.41, 95% CrI -6.85 to 2.05; very low-certainty evidence) or nocturia (MD 0.01, 95% CrI -2.53 to 2.50; very low-certainty evidence).

There was no evidence that PPS had improved cure/improvement rates (OR 0.14, 95% CrI 0.40 to 3.35; very low-certainty evidence) or reduced pain (MD 0.42, 95% CrI -1.04 to 1.91; low-certainty evidence), frequency (MD -0.37, 95% CrI -5.00 to 3.44; very low-certainty evidence) or nocturia (MD -1.20, 95% CrI -3.62 to 1.28; very low-certainty evidence).

There was evidence that neuromuscular blockade resulted in greater cure or improvement (OR 5.80, 95% CrI 2.08 to 18.30) but no evidence that it improved pain (MD -0.33, 95% CrI -1.71 to 1.03), frequency (MD -0.91, 95% CrI -3.24, 1.29) or nocturia (MD -0.04, 95% CrI -1.35 to 1.27). The certainty of this evidence was always very low.

Authors' conclusions

We are uncertain whether some treatments may be effective in treating patients with BPS because the certainty of evidence was generally low or very low. Data were available for a relatively large number of trials, but most had small sample sizes and effects of treatments often could not be estimated with precision. An NMA was successfully conducted, but limited numbers of small trials for each treatment category hampered our ability to fully exploit the advantages of this analysis. Larger, more focused trials are needed to improve the current evidence base.

PLAIN LANGUAGE SUMMARY

Treatments for people with bladder pain syndrome

What is bladder pain syndrome?

Bladder pain syndrome (BPS; also called painful bladder syndrome or interstitial cystitis) is a long-term painful condition that affects the bladder. ‘Syndrome’ refers to a collection of symptoms. In BPS, these symptoms include: intense pain in the pelvis (felt below the bellybutton); sudden strong urges to urinate; needing to urinate more often than usual; and waking up several times during the night to urinate.

BPS is more common in women. We do not know what causes it or how to cure it. Symptoms sometimes come and go in phases. BPS can significantly affect lifestyle, work, emotional health and relationships.

Treatments for BPS

Lifestyle changes are usually tried first, then medicines and supportive therapies. Surgery may be needed as a last resort.

Medicines used include pentosan polysulfate sodium – which may help to restore the inner surface of the bladder – anti-inflammatories, antidepressants and antihistamines. Medicines that block the connection between nerves and muscles can be injected into the bladder muscle to try to relax it (‘neuromuscular blockade’). Supportive therapies and treatments include behavioural therapy, physiotherapy, bladder re-training, psychological therapy and transcutaneous electrical nerve stimulation (TENS).

Review question

In this Cochrane Review, we wanted to find out which treatments work best to treat BPS.

What did we do?

We searched for studies that looked at any type of treatment for BPS. We looked for randomised controlled studies, in which the treatment people receive is randomly decided, because these studies usually give the most reliable evidence about treatments.

Search date

We included evidence published up to 11 May 2018. We conducted a further search on 5 June 2019, which yielded four small studies that were screened for eligibility but were not incorporated into the review.

What we found

We found 81 studies involving 4674 people with BPS. The biggest study included 369 people, and the smallest study included 10 people. Most studies lasted around three months; only six studies lasted 12 months or longer. Twenty-four studies were funded by pharmaceutical companies.

We found 65 treatments for BPS, which we grouped into 31 categories based on how the treatments worked. In most studies, a treatment for BPS was compared with a placebo (or dummy) treatment. We compared all treatments with each other using a mathematical method called network meta-analysis.

What are the results of our review?

After 12 months, antidepressants or neuromuscular blockade (and some other treatments) may improve symptoms of BPS more than placebo, but we are not certain about this result. We did not find enough evidence to know if pentosan polysulfate sodium improves symptoms.

We are uncertain whether 12 months of treatment with antidepressants, neuromuscular blockade or pentosan polysulfate sodium reduced pain (as measured on a scale); the number of times people had to urinate during the day; or the number of times people had to get up to urinate during the night.

Our confidence in the results

We are uncertain about our results because we did not find enough reliable evidence. Although we obtained results from 81 studies, most of these studies were small and did not include enough people for us to be certain of their results. Some of the studies (30%) were conducted by pharmaceutical companies, and this may have affected how the studies were designed, conducted and reported. Our results may change when results from more, and larger, studies become available.

Conclusions

We did not find enough reliable evidence about how well medicines, behavioural therapy, physiotherapy and neuromuscular blockade worked to treat all, or any, of the symptoms of BPS.

Summary of findings 1. Interventions for treating people with symptoms of bladder pain syndrome

Interventions for treating people with symptoms of bladder pain syndrome

Patient or population: people with bladder pain syndrome

Settings: hospital setting

Intervention: antidepressants, pentosan polysulfate (PPS), neuromuscular blockade

Comparison: control treatment

Outcomes	Effects and 95% credible intervals (NMA) and confidence intervals (pairwise) in the effects. Main comparator is control treatment				Comments
	Risk with control treatment*	Risk with antidepressants**	Risk with PPS**	Risk with neuromuscular blockade**	
Cure or improvement: median odds ratio (95% credible interval)	26.2% (303 to 1156)	**OR 5.91** (1.12 to 37.56) ⊕⊖⊖⊖ **Very low** [a]	**OR 1.14** (0.40 to 3.35) ⊕⊖⊖⊖ **Very low** [b]	**OR 5.80** (2.08 to 18.30) ⊕⊖⊖⊖ **Very low** [c]	Follow-up: 12 months or nearest time point available to 12 months
Pain score: mean differences vs control (95% credible interval)	Mean pain score at follow-up ranged across control groups from 2.6 to 9.4	Mean pain score in the intervention groups was **1.27 lower** (3.25 lower to 0.71 higher) ⊕⊕⊖⊖ **Low** [d]	Mean pain score in the intervention groups was **0.42 higher** (1.04 lower to 1.91 higher) ⊕⊖⊖⊖ **Very low** [e]	Mean pain score in the intervention groups was **0.33 lower** (1.71 lower to 1.03 higher) ⊕⊖⊖⊖ **Very low** [c]	Scale ranged from 0 to 10. Less pain indicated by lower values MCID = 2.5 points Follow-up: 12 months or nearest time point available to 12 months
Daytime frequency (number of daytime voids): mean differences vs control (95% credible interval)	Mean daytime frequency ranged across control groups from 8.2 to 14.8	Mean number of daytime voids in the intervention groups was **2.41 lower** (6.85 lower to 2.05 higher) ⊕⊖⊖⊖ **Very low** [f]	Mean number of daytime voids in the intervention groups was **0.37 lower** (5.00 lower to 3.44 higher) ⊕⊖⊖⊖ **Very low** [d]	Mean number of daytime voids in the intervention groups was **0.91 lower** (3.24 lower to 1.29 higher) ⊕⊖⊖⊖ **Very low** [g]	Lower scores indicate better outcome MCID = 2 points Follow-up: 12 months or nearest time point available to 12 months

Nocturia (number of nighttime voids): mean differences vs control (95% credible interval)	Mean nocturia ranged across control groups from 1.0 to 5.8	Mean number of nighttime voids in the intervention groups was **0.01 higher** (2.53 lower to 2.50 higher) ⊕⊖⊖⊖ **Very low** [h]	Mean number of nighttime voids in the intervention groups was **1.20 lower** (3.62 lower to 1.28 higher) ⊕⊖⊖⊖ **Very low** [i]	Mean number of nighttime voids in the intervention groups was **0.04 lower** (1.35 lower to 1.27 higher) ⊕⊖⊖⊖ **Very low** [e]	Lower scores indicate better outcome MCID = 1 point Follow-up: 12 months or nearest time point available to 12 months

* **The risk in the control group** (and its 95% confidence interval) is based on a meta-analysis of proportions from the studies included in this review for this group.

** **Risks in the antidepressant, PPS and neuromuscular blockade groups** (and their 95% credible interval) are based on the assumed risk in the control group and the relative effects of the interventions (and their 95% credible interval).

Note: In GRADE assessments, 'within-study bias' was determined using the following domains from the 'risk of bias' assessments: sequence generation, allocation concealment and blinding of outcome assessor. Studies were classified as 'low risk of bias' if all key domains were judged to be at low risk, 'unclear risk of bias' if one or more key domains were judged to be at unclear risk, and 'high risk of bias' if one or more key domains were judged to be at high risk. We conducted GRADE assessments using the CINeMA 2017 web application.

MCID: minimal clinically important difference; **NMA:** network meta-analysis; **OR:** odds ratio; **PPS:** pentosan polysulfate.

GRADE Working Group grades of evidence.

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded due to within-study bias, heterogeneity and incoherence, based on 2 studies.
[b]Downgraded due to within-study bias and imprecision, based on 6 studies.
[c]Downgraded due to within-study bias and heterogeneity, based on 6 studies.
[d]Downgraded due to within-study bias and imprecision, based on 2 studies.
[e]Downgraded due to within-study bias and heterogeneity, based on 4 studies.
[f]Downgraded due to within-study bias, imprecision and heterogeneity, based on 1 study.
[g]Downgraded due to within-study bias, imprecision and heterogeneity, based on 5 studies.
[h]Downgraded due to within-study bias and imprecision, based on 1 study.
[i]Downgraded due to within-study bias and heterogeneity, based on 2 studies.

BACKGROUND

Description of the condition

Bladder pain syndrome (BPS), which includes the condition of interstitial cystitis, is a chronic condition that most often affects women and is characterised by pain in the bladder and/or pelvis and other urinary symptoms, such as urgency and frequency (Hanno 2017). The causes of BPS remain poorly understood, and no single causative trigger or validated diagnostic markers have been identified. Thus, diagnosis primarily relies on reported symptoms and the exclusion of any other identifiable causes (Hanno 2017).

During a major international meeting in 1987, and later in 1990, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) developed diagnostic criteria for interstitial cystitis based on objective cystoscopic and urodynamic evaluation (NIDDK 2017). Such evaluation involves putting the patient under local or general anaesthesia and catheterising the urinary bladder, and so is associated with substantial risks and costs. The NIDDK criteria have helped inform the selection of homogeneous patient populations for research purposes but have proven too strict for use in routine clinical practice (Hanno 1999). Consequently, the International Continence Society (ICS) proposed a broader term - 'painful bladder syndrome' (Abrams 2002). The European Society for Study of Interstitial Cystitis/Bladder Pain Syndrome (ESSIC) used the term, 'bladder pain syndrome (BPS)', defined as "chronic pelvic pain, pressure or discomfort of greater than six months duration perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or urinary frequency. Confusable diseases as the cause of the symptoms must be excluded" (van de Merwe 2008). This definition was accepted by the International Consultation on Incontinence in 2010 (Hanno 2010). As patients tend to refer to it as interstitial cystitis, the name 'interstitial cystitis' may be used in parallel with BPS (e.g. 'IC/BPS'). In this Cochrane Review, we will refer to the condition as BPS, although we will also consider some older literature using the original terminology.

Lack of a universally accepted clinical diagnosis of BPS makes epidemiological studies of the condition problematic. Prevalence estimates vary widely depending on diagnostic criteria and how prevalence estimates were derived (i.e. self-report, physician diagnoses and/or symptom-based surveys). One estimate is that BPS is experienced by 100 to 200 per 100,000 women, with a male prevalence of 10% to 20% of the estimate for females (Hanno 2017), although it is accepted that BPS is more common than is suggested by empirical studies (Hanno 2017). BPS may negatively impact quality of life and the psychological state of people with the condition, with some experiencing depression, anxiety, distress and sexual dysfunction (Cox 2016).

Although not consistently present (particularly in non-ulcerative BPS), the main pathological feature of BPS is inflammation of the bladder. This leads to vasodilation, enhanced vascular permeability and degradation of the mucosal glycosaminoglycan coating of the urothelium. When inflammation is present, it can spread to deeper tissues of the bladder, and, in some cases, Hunner's lesions may appear in the bladder wall. This is often referred to as ulcerative BPS. It is thought that this abnormal inflammation of the bladder underlies the symptoms of pain (Grover 2011; Logadottir 2014).

To date, no definitive consensus has been reached on how or why BPS develops.

Description of the intervention

Treatment options for BPS are varied (Hanno 2017). Current clinical guidelines emphasise that an individualised treatment plan is likely to lead to better patient outcomes (Cox 2016). Usually, the initial treatment of BPS comprises patient education and support, dietary manipulation, stress reduction, non-prescription analgesics and pelvic floor relaxation techniques. When the conservative approach fails, or symptoms are severe and conservative management is unlikely to succeed, pharmacological interventions including analgesics, antidepressants, antibiotics and immune modulators may be used orally or intravesically (directly into the bladder). As a last approach, surgery, including botulinum toxin A injections or removal of the bladder, may be considered (Hanno 2017). Some evidence indicates that BPS with Hunner's lesions may have a different clinical response to certain treatment as compared with non-lesion disease; however, this has not yet been formalised (Hanno 2017).

How the intervention might work

Conservative interventions including dietary and lifestyle changes, behavioural modifications (e.g. patient education, bladder retraining) and psychological therapies (e.g. stress management techniques) can be beneficial in reducing the symptoms associated with BPS. Women with BPS may also have pelvic floor dysfunction, and physical therapy techniques such as pelvic floor muscle training and soft tissue massage can be effective in helping to relax the pelvic floor muscles.

Pharmacological treatments address the many theories of pathogenesis, including the following.

- Analgesics, such as non-steroidal anti-inflammatory drugs (NSAIDs), target the main symptom of pain.
- Antidepressants are often used to manage pain in chronic conditions, including BPS.
- Antibiotics are known to decrease the markers of bladder inflammation, thus reducing pain.
- Immune modulators, such as bacillus Calmette-Guerin (BCG), are believed to work immunologically, on the basis of an autoimmune cause for interstitial cystitis.
- Steroids are known to have an anti-inflammatory effect.

Surgery should be considered only when all other treatments have failed (Hanno 2017). People should be informed of all aspects of surgery and should understand the consequences and potential side effects of these interventions. Surgical interventions can work in the following ways.

- Botulinum toxin A injections inhibit the release of chemical transmitters from nerve fibres and the urothelium.
- A total cystectomy (removal of the bladder) can be performed for extreme cases. This approach also requires subsequent urinary diversion to expel urine from the body.

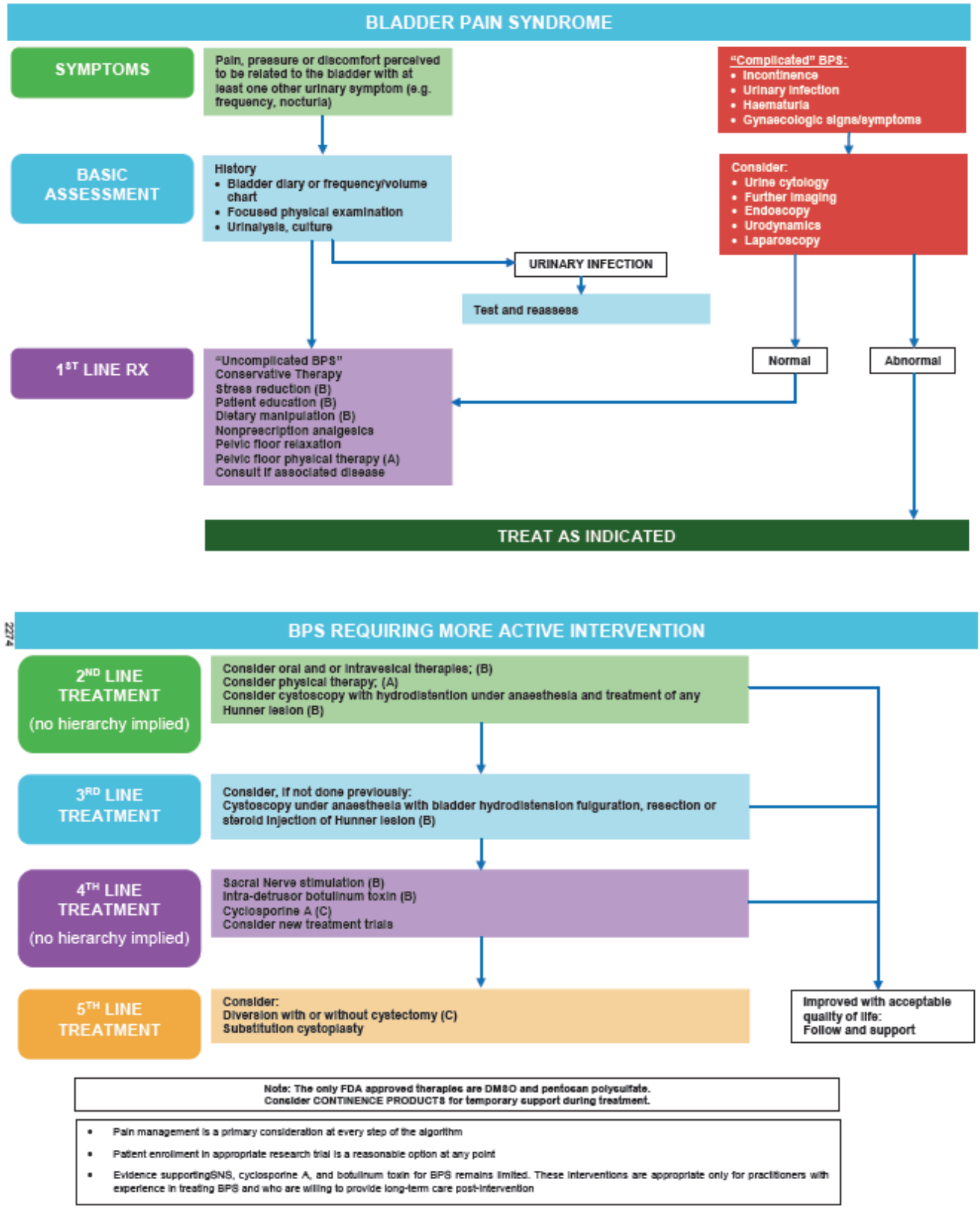
Some therapies for treating BPS are emerging. These include:

- hyperbaric oxygen, which involves breathing pure oxygen in a pressurised chamber;

- monoclonal antibodies, which inhibit nerve growth factors and act as potential analgesics;
- cannabinoids, which could help relieve the symptoms of BPS; and
- intravesical liposomes, which could potentially protect against inflammation.

The algorithm for diagnosis and treatment proposed at the Sixth International Consultation on Incontinence in 2016 is presented in Figure 1 (Hanno 2017).

Figure 1. Algorithm for diagnosis and treatment: 2016 International Consultation on Incontinence. Taken from Hanno 2017, and reproduced with permission from Abrams 2017.



Why it is important to do this review

BPS is a condition with an unknown cause. More information is needed about the effects and safety of available treatment options and therapies. Currently, several small trials are assessing a wide range of treatment options, but the number of large trials comparing one treatment versus another is limited (there is one existing Cochrane Review on intravesical treatments for BPS (Dawson 2007)). A Cochrane Review increasing coverage to all clinical interventions by any route of administration, including both direct and indirect comparisons, will help to provide valuable information to inform clinical practice. A systematic review using network meta-analysis (NMA) is the most appropriate method in this clinical context, as it can simultaneously incorporate evidence for the effectiveness of many different treatments within a single analysis.

OBJECTIVES

To conduct a network meta-analysis to assess the effects of interventions for treating people with symptoms of bladder pain syndrome (BPS).

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel-group and cross-over randomised controlled trials (RCTs) and quasi-RCTs (e.g. alternate allocation) of interventions for treating BPS.

Types of participants

Allowing for the many terminologies that have been used for this condition, we included trials in which adults were specified as having BPS, interstitial cystitis or painful bladder syndrome. We accepted the classification of diagnoses as defined by trial investigators, and we regarded as eligible a clinical diagnosis of BPS that did or did not meet NIDDK criteria (NIDDK 2017). We excluded studies of adults with urethral syndrome.

Types of interventions

We included trials of any intervention that aimed to cure or improve symptoms of BPS, covering both emerging and more traditional modes of treatment. All types of interventions were eligible, including conservative, pharmacological and surgical therapies.

Conservative therapies include behavioural therapies (e.g. bladder training), psychological therapies (e.g. stress management techniques), complementary therapies (e.g. acupuncture) and physical therapy (e.g. pelvic floor muscle training, non-invasive electrical stimulation). We considered pharmacological treatments regardless of their routes of administration (which are likely to be oral, subcutaneous, intramuscular, intravenous or intravesical). Examples of relevant interventions are shown in Table 1.

Valid comparators were placebo, no treatment and another intervention.

We excluded trials:

- comparing two or more regimens of the same treatment (e.g. varying doses of pentosan polysulfate); or
- comparing two or more treatments with the same mechanism or mode of action (e.g. sacral nerve stimulation versus pudendal nerve stimulation, both of which are neuromodulation).

Types of outcome measures

We used the following definitions of outcomes. If a particular outcome was reported by using different definitions across different studies, then, depending on the quantity of data available, we decided either to restrict inclusion to the primary (or most common) definition or to include multiple definitions selected according to the hierarchies proposed below. In the event that a study reported any other measure not included in our proposed list, we added this measure to the bottom of the hierarchy and extracted the data.

Primary outcomes

- Proportion of participants whose symptoms were cured or improved: self-reported measures are preferred, such as the Global Response Assessment. We used objective measures (e.g. number of participants who experienced pain score reduction) as a proxy if self-reported measures were unavailable. We used the number cured if this was reported. If cure was not reported, we used the number improved, as defined by trial investigators
- Pain score: we used the following hierarchy to select one outcome measure per study: visual analogue scale (VAS); numerical rating scale (NRS); McGill Pain Questionnaire (Melzack 1975; Melzack 1987); Short Form Health Survey (SF-36)/RAND-36 (if a score for the pain-specific item is available) (Hays 1993; McHorney 1993; Ware 1992); and the number of participants with pain reduction
- Daytime frequency (number of voids): we considered the following terms to be equivalent to daytime frequency: frequency; daily frequency; frequency per day; and daytime frequency. We excluded 24-hour frequency
- Nocturia (number of nighttime voids)

Secondary outcomes

- Subjective symptom measures (combining frequency, nocturia and pain): we used the following hierarchy to select one outcome measure per study: O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) (O'Leary 1997); Pelvic Pain and Urgency/Frequency Questionnaire (PUF) (Parsons 2002); University of Wisconsin Interstitial Cystitis Scale (UW-IC Scale) (Goin 1998); and King's Health Questionnaire (KHQ), Part III (Kelleher 1997)
- Quality of life (including symptom bother): we used the following hierarchy to select one outcome measure per study: O'Leary-Sant Interstitial Cystitis Problem Index (ICPI) (O'Leary 1997); Pelvic Pain and Urgency/Frequency Questionnaire (PUF), bother score (Parsons 2002); King's Health Questionnaire (KHQ) (Kelleher 1997); Short Form Health Survey (SF)-36 and SF-12, Mental component (McHorney 1993; Ware 1992; Ware 1996); and SF-36 and SF-12, Physical component (McHorney 1993; Ware 1992; Ware 1996)
- Functional bladder capacity: this is defined using the following terms for the purpose of this review: functional bladder capacity; functional bladder volume; bladder capacity; maximum bladder capacity; and maximum tolerable bladder capacity. We excluded volume at first or strong desire to void, (mean) voided volume, (maximum) cystometric bladder capacity and urodynamic capacity

- Adverse events: the category of adverse events was accepted as reported by study authors

Timing of outcome assessment

The primary time point for outcome assessment is 12 months or the nearest time point available to 12 months.

Main outcomes for 'Summary of findings' tables

We included the following outcomes in our 'Summary of findings' table, in order of priority.

- Proportion of participants whose symptoms were cured or improved.
- Pain score (VAS (0 to 10)).
- Daytime frequency.
- Nocturia.

We used minimal clinically important difference (MCID) to rate the certainty of evidence for the primary outcomes in the 'Summary of findings' table. As there is no agreed MCID in the literature for BPS, we considered MCID to be as follows based on expert opinion: for cure or improvement, risk reduction of 25% (odds ratio (OR) 0.8 to 1.25); for pain, 2.5 points; for daytime frequency, 2 points; and for nocturia, 1 point.

Search methods for identification of studies

We did not impose any language or other limitations on any of the searches described below.

Electronic searches

We performed searches that drew on the search strategy developed for Cochrane Incontinence. We identified relevant trials from the Cochrane Incontinence Specialised Register. For details of the search methods used to build the Specialised Register, please see the Group's webpages, where details of the Register's development (from inception) and the most recent searches performed to populate the Register can be found. To summarise, the Register contains trials identified from the Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library; MEDLINE; MEDLINE In-Process; MEDLINE Epub Ahead of Print; ClinicalTrials.gov; WHO ICTRP; and the UK Clinical Research Network Portfolio (now replaced by Be Part of Research), and from handsearching of journals and conference proceedings. Many of the trials in the Cochrane Incontinence Specialised Register are also contained in CENTRAL.

The terms that we used to search the Cochrane Incontinence Specialised Register are given in Appendix 1.

The most recent search of the Cochrane Incontinence Specialised Register was fully incorporated into this review on 11 May 2018. A further search was conducted on 5 June 2019, which was screened for eligibility but was not incorporated into the review.

Searching other resources

We identified relevant studies from an existing Cochrane Review on intravesical treatments for BPS (date of last search: 30 May 2006) (Dawson 2007). We also screened the reference lists of the included studies for other relevant trials.

Data collection and analysis

Selection of studies

One review author (SW) established the selection of studies from the relevant Cochrane Review on intravesical treatments for BPS (Dawson 2007), which a second review author (MI) checked. Two review authors (JO and AF) independently screened the titles and abstracts of all citations identified by the literature searches. The same two review authors evaluated full-text copies of all potentially relevant reports. We resolved any discrepancies or inconsistencies by recourse to a third review author (SW, MI, NS or MB).

We obtained translations of eligible studies when resources allowed, including any available translated information obtained by Dawson 2007. If translations were not obtained, we added these studies to Studies awaiting classification and discussed the implications of any missing information under Overall completeness and applicability of evidence.

Data extraction and management

We exported study characteristics and outcome data of individual studies from the relevant Cochrane Review, and one review author (MI or YAD) checked them against individual trial reports (Dawson 2007). From additional studies identified by updated literature searches, one review author (MI or YAD) performed data extraction using a pre-piloted data form, which another review author (MI or YAD) checked. We resolved any discrepancies or inconsistencies by recourse to a third review author (SW, NS or MB).

We collected information on study design and setting, participant characteristics (including disease diagnosis), study eligibility criteria, details of the intervention(s) given, outcomes assessed and the source of study funding for each included study. When multiple publications of the same study were identified, we extracted the most complete data across all known publications.

For binary outcomes, we extracted the total number of participants in each treatment arm and the number with the event. For continuous outcomes, we extracted mean scores (i.e. mean scores at follow-up or mean change scores from baseline) for each arm along with standard deviation (SD) and the number of participants. If both final scores and change scores were available, we used final scores in the analysis.

Assessment of risk of bias in included studies

We used the original risk of bias assessments made by review authors of the relevant Cochrane Review (Dawson 2007). In that review, judgements were made for the following criteria.

- Adequacy of randomisation and description of allocated groups before treatment and blinding to allocation.
- Adherence to prescribed treatment once allocated.
- Adequacy of follow-up and accounting for participants excluded/withdrawing from trial.
- Analysis of participants based on allocated treatment group and adequacy of presented data.

Each study was judged to be at 'low', 'high' or 'unclear' risk of bias.

Two review authors (JO and AF) independently updated these assessments using Cochrane's 'Risk of bias' tool (Higgins

2011a), resolving any discrepancies by discussion. The updated assessments addressed the following domains.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessor (detection bias).
- Incomplete outcome data (attrition bias).
- Free of selective reporting (reporting bias).
- Other sources of bias.

Assessment of two domains, detection bias and attrition bias, was modified further and these domains were assessed on an outcome-specific basis. One review author (MI) performed these assessments, which were checked by another review author (SW).

For detection bias, we grouped outcomes into subjective and objective outcomes. We defined the following as subjective outcomes.

- Proportion of participants whose symptoms were cured or improved.
- Pain score.
- Daytime frequency.
- Nocturia.
- Subjective symptom measures (combining frequency, nocturia and pain).
- Quality of life (QoL) (including symptom bother).
- Adverse events.

We defined functional bladder capacity as an objective outcome.

For attrition bias, we assessed individual outcomes separately.

Measures of treatment effect

For binary outcomes, we used odds ratios (ORs) as the measure of treatment effect. For continuous outcomes, we used mean differences (MDs) in final scores or in change scores.

We re-scaled visual analogue scale (VAS) pain scores so that zero represented no pain and 10 maximum pain.

Unit of analysis issues

We included only patient randomised trials in this review, and the unit of analysis was the individual participant.

For cross-over trials, we intended to use data from paired analyses when available. In cross-over studies, when paired analyses were not reported, we used data from the first trial period if these were presented separately, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions*, Section 16.4.5 (Higgins 2011b). We excluded cross-over studies from the analysis if only data for the first and second periods combined were available.

If two or more arms of a multi-arm trial belonged to the same treatment category, we combined data using standard pooling formulae (Higgins 2011b).

Dealing with missing data

We employed a number of approaches to calculate or estimate SDs when these were not reported. The standard methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* were preferred (Higgins 2011c). If standard errors (SEs) were reported, we derived the SD using the appropriate standard formula, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions*, Section 7.7.3.2 (Higgins 2011b). If necessary, we calculated SDs from a 90% or 95% confidence interval (CI) for a mean difference or from the P value for a t-test (Higgins 2011b), or we imputed the SD using the average of other studies in the review.

Assessment of heterogeneity

We assessed the presence of statistical heterogeneity by visually inspecting forest plots for pairwise meta-analyses and by calculating the I^2 statistic (Higgins 2003). I^2 values above 50% were considered to represent important heterogeneity. For network meta-analyses, we also investigated consistency between direct and indirect evidence (see Data synthesis).

Assessment of reporting biases

If there had been more than 10 trials per comparison in an outcome, we had planned to examine funnel plots to assess reporting bias.

Data synthesis

We divided interventions into treatment categories, each of which was further classified as a conservative, pharmacological or surgical intervention. The total number of treatment categories that could be included in each analysis depended on the number of studies that provided usable data for the outcomes of interest. If considered clinically appropriate (e.g. if treatment B is considered a routine therapy or procedure), we 'cancelled' treatments (e.g. a trial of A + B versus B become A versus control). If this was not considered appropriate, we used a combination of therapies as a single treatment category (e.g. "chondroitin sulfate plus hyaluronic acid"). We combined different doses of the same treatment as a single category, provided this was considered clinically appropriate.

We performed two approaches to meta-analysis. The primary method was network meta-analysis, but we also conducted standard pairwise meta-analyses and compared the results with those from the network meta-analysis.

Network meta-analysis

Network meta-analysis is an analytical approach that allows a large number of treatments to be evaluated within a single analysis, and allows the effect size between any two treatments to be estimated using evidence from the entire network. If we found a large number of treatment combinations, we planned to report only the effects of each active treatment versus control.

We followed the recommendations in the National Institute for Health and Care Excellence Decision Support Unit Technical Support Documents 2 (NICE DSU TSD 2) (Dias 2016). Network meta-analysis models were fitted using WinBUGS 1.4 and were used to conduct synthesis of trial data (Lunn 2000). We used a binomial likelihood for binary outcomes and the normal likelihood for continuous outcomes. We used random-effects models due

to expected heterogeneity between treatments and outcome measures. Three chains were used and parameters were fitted using vague normal prior distributions.

For binary outcomes, we used Programme 1(c) from the NICE DSU TSD 2 (Dias 2016). We monitored ORs for all treatments in the network against control and presented results using 95% credible intervals (CrI). ORs greater than 1 were associated with a favourable effect of treatment versus control. We monitored only effects of active treatments versus control. Treatments were described as effective if 95% CrIs from the NMA did not contain 1 (binary outcome) or 0 (continuous outcomes).

For continuous outcomes, the effect size was the mean difference (MD) between groups. We monitored only contrasts between active treatments and control. For each outcome, high scores represent poorer patient outcomes than lower scores. Therefore, effect sizes less than zero will mean that treatment is favoured over control. We used a shared parameter model (Programme 8(a) from the NICE DSU TSD 2) to simultaneously incorporate two data formats (Dias 2016).

- Final score arm-based data.
- Contrast-based differences in change from baseline.

For the network meta-analysis, there is an additional assumption of transitivity, also known as consistency or coherence, which assumes that included participants should be eligible to be randomised to any treatment within the network. Violations of this assumption can be investigated by examining the consistency between direct and indirect evidence when there are closed loops in the network that allow this. We intended to use the methods described in the NICE DSU TSD 4 to compare closed loops within the network (Dias 2014), and we used CINeMA software as the primary way to examine direct and indirect evidence (CINeMA 2017).

We produced network diagrams for each outcome using the *networkplot* command in Stata (Stata 2017). Lines between treatment categories mean that direct evidence exists between a pair of treatments. The thickness of the line is proportionate to the number of included studies.

When data allowed, we planned to undertake network meta-analyses for all outcomes specified in the review. For cross-over trials that provided usable data, we used data from the first period only if they did not provide information to approximate a paired analysis.

Pairwise meta-analyses

We compared results of the network meta-analysis with direct evidence from head-to-head trials using standard Cochrane methods. For each outcome, we performed a separate pairwise meta-analysis for each treatment category versus control. We conducted meta-analyses using the *metan* command in Stata (Stata 2017). We did not conduct meta-analyses between pairs of active treatments. The number of trials contributing to the pairwise meta-analyses may be smaller than the number included in the corresponding network meta-analysis because only trials with a control group were included.

For binary outcomes, we pooled ORs for each treatment versus control. We used the Mantel-Haenszel approach to meta-analysis using random-effects models in Stata as the primary analysis (Stata 2017). For continuous outcomes, the effect size was the mean difference between treatment and control. As for network meta-analyses, we used a mixture of change score and final score data within the same analysis (see the *Cochrane Handbook for Systematic Reviews of Interventions,* Section 9.4.5.2; Deeks 2011). We combined studies using the inverse variance weighted approach and presented results using 95% confidence intervals (CIs).

Subgroup analysis and investigation of heterogeneity

We did not conduct subgroup analyses.

Sensitivity analysis

We did not conduct sensitivity analyses.

Summarising findings and assessing certainty of the evidence

We assessed the overall certainty (quality) of evidence for the primary outcomes using the GRADE approach (Guyatt 2008; Guyatt 2011; Schünemann 2011). We applied the GRADE approach modified for network meta-analysis (Salanti 2014), using the CINeMA 2017 web application. We rated the certainty of each outcome as 'high', 'moderate', 'low' or 'very low', taking into account six criteria: within-study bias (study limitations), across-studies bias (e.g. publication bias), indirectness, imprecision, heterogeneity and incoherence (among direct, indirect and mixed evidence).

Two review authors (MI and NS) worked together to conduct the GRADE assessment, reaching consensus for how each outcome should be rated. We followed the guidance provided in the latest draft version of the *Cochrane Handbook for Systematic Reviews of Interventions,* in the chapter on network meta-analysis, to develop our own 'Summary of findings' table (Chaimani 2017).

Due to the large number of intervention comparisons in this review, we present one 'Summary of findings' table with three interventions: antidepressants (including amitriptyline), pentosan polysulfate and neuromuscular blockade (injection of botulinum toxin type A). We selected these interventions on the basis that they are given 'strong recommendations' in the EAU Guidelines for management of BPS (EAU Guidelines 2019).

RESULTS

Description of studies

Results of the search

The initial search of the list of included studies of an existing Cochrane Review yielded 12 reports of nine studies that were eligible for this current review (Dawson 2007).

The literature search produced 431 records in total, which were screened. The full text of 160 articles was obtained for further assessment, of which 129 reports of 81 studies were included and the available data fully incorporated into this review. Sixteen reports of 14 studies did not meet the eligibility criteria and were excluded, the reasons for which are given in the Characteristics of excluded studies table. Additionally, we identified 15 reports of 13 ongoing studies; the details of these can be found in the Characteristics of ongoing studies table.

The further updated literature search (conducted on 5 June 2019) identified 45 records, which were screened. Of these, 15 reports of 14 studies were eligible for inclusion in this review (five reports of four new studies; three additional reports of three already included studies; and seven study registrations of seven ongoing studies). All four new studies were small (ranging from 15 to 42 participants) (Aboyan 2018; Bosch 2018; Cervigni 2018; Oh-Oka 2017). Only one of these studies covered one of the comparisons included in our NMA (hyaluronic acid alone compared with hyaluronic acid in combination with chondroitin sulphate) (Aboyan 2018). Due to resource constraints, these were not fully incorporated into the review, but brief details of each can be viewed in the Characteristics of studies awaiting classification table.

The flow of literature through the assessment process is shown in the PRISMA diagram (Figure 2).

Figure 2. PRISMA study flow diagram.

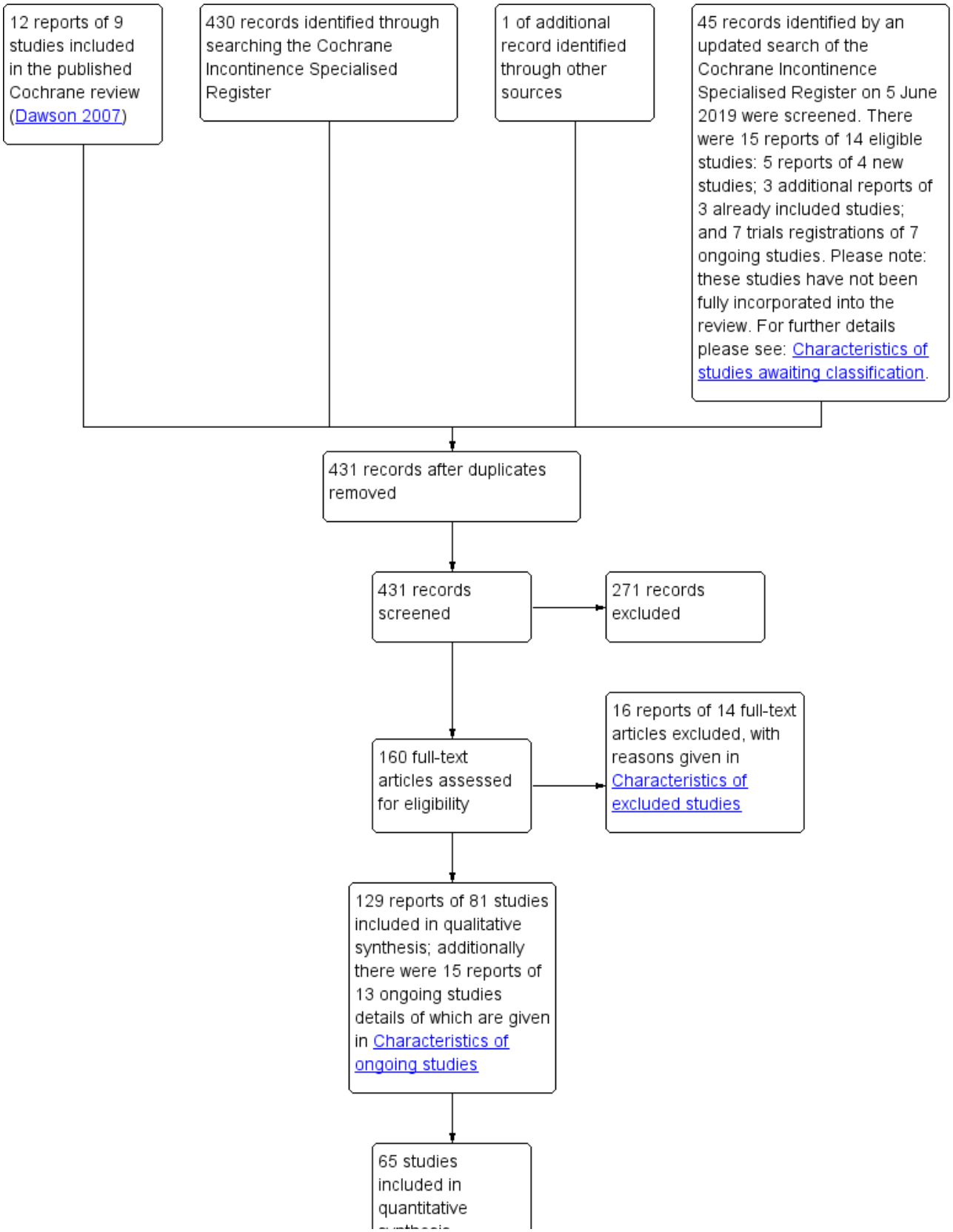
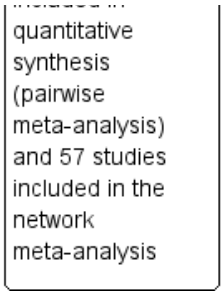


Figure 2. (Continued)



Included studies

The 81 RCTs identified by the literature searches were published between 1988 and 2017 (Carty 2017; Chuang 2017; Nomiya 2017; Perez-Marrero 1988; Wang 2017a). Of these, 61 (75%) were available as full-text publications (Bade 1997; Barbalias 2000; Bosch 2014; Carrico 2008; Cartledge 2000; Carty 2017; Cervigni 2014; Chen 2005; Chen 2014; Chuang 2017; Davis 2008; De Ridder 2013; El-Hefnawy 2015; Evans 2011; FitzGerald 2009; FitzGerald 2012; Foster 2010; Geirsson 1993; Gottsch 2011; Gulpinar 2015; Ham 2012; Hsieh 2012; Irani 2004; Kanter 2016; Korting 1999; Kuo 2009; Kuo 2016; Lazzeri 1996; Lazzeri 2000; Leadership 201 Trial 2016; Lee 2014; Lu 2015; Manning 2014; Matsumoto 2013; Mayer 2005; Mulholland 1990; Nguan 2005; Nickel 2009; Nickel 2010; Nickel 2012a; Nickel 2012b; Nickel 2015; Nickel 2016; O'Reilly 2004; Parsons 2012; Payne 2005; Payne 2014; Peeker 2000; Perez-Marrero 1988; Peters 1997; Sairanen 2005; Sairanen 2009; Sant 2003; Souza 2012; Thilagarajah 2001; van Ophoven 2004; van Ophoven 2006; Wang 2017a; Warren 2000; Yang 2011; Zakaria 2016), and the remaining 20 (25%) were available as conference abstracts only (Ahmadnia 2011; Dimitrakov 2001; Gulpinar 2013; Hanno 2015; Herati 2011; Ismail 2016; Kasyan 2012; Kim 2012; Kim 2015; Lee 2016; Mirkin 2012; Mirkin 2015; Moldwin 2015; Nomiya 2017; Oliver 2013; Pinto 2016; Shirvan 2015; Singh 2003; Taha 2007; Yassin 2011).

The Characteristics of included studies tables provide further details of the included studies.

Design

Six of the identified studies were randomised cross-over trials (Cartledge 2000; Geirsson 1993; Nguan 2005; Parsons 2012; Peeker 2000; Perez-Marrero 1988). The other 75 studies were parallel RCTs.

Sample size

The included studies enrolled a total of 4674 participants. A majority of studies had a small sample size, but 34 studies (42%) included 50 or more participants (Carty 2017; Cervigni 2014; Chuang 2017; Evans 2011; FitzGerald 2012; Foster 2010; Gulpinar 2013; Hanno 2015; Hsieh 2012; Korting 1999; Kuo 2009; Kuo 2016; Leadership 201 Trial 2016; Lee 2014; Lee 2016; Manning 2014; Mayer 2005; Mirkin 2015; Moldwin 2015; Mulholland 1990; Nickel 2009; Nickel 2010; Nickel 2012a; Nickel 2012b; Nickel 2015; Nickel 2016; O'Reilly 2004; Payne 2005; Sairanen 2005; Sairanen 2009; Sant 2003; van Ophoven 2004; Warren 2000; Yang 2011). Sample sizes ranged from 10 in Oliver 2013 to 369 in Nickel 2015, with a median size of 38.

Setting

Of the included studies, 29 studies (36%) were conducted in several centres (multi-centre) (Cervigni 2014; Chen 2005; Chen 2014; Chuang 2017; De Ridder 2013; Evans 2011; FitzGerald 2009; FitzGerald 2012; Foster 2010; Irani 2004; Kim 2015; Kuo 2016; Leadership 201 Trial 2016; Manning 2014; Mayer 2005; Mulholland 1990; Nguan 2005; Nickel 2009; Nickel 2010; Nickel 2012a; Nickel 2012b; Nickel 2015; Parsons 2012; Payne 2005; Sairanen 2005; Sant 2003; Wang 2017a; Warren 2000; Yang 2011). Thirteen (16%) were small-scale, single-centre trials (Bade 1997; Bosch 2014; Carrico 2008; Carty 2017; Davis 2008; El-Hefnawy 2015; Gottsch 2011; Lu 2015; Payne 2014; Perez-Marrero 1988; Peters 1997; Souza 2012; van Ophoven 2004). Thirty-nine (48%) did not provide information on the number of centres involved (Ahmadnia 2011; Barbalias 2000; Cartledge 2000; Dimitrakov 2001; Geirsson 1993; Gulpinar 2013; Gulpinar 2015; Ham 2012; Hanno 2015; Herati 2011; Hsieh 2012; Ismail 2016; Kanter 2016; Kasyan 2012; Kim 2012; Korting 1999; Kuo 2009; Lazzeri 1996; Lazzeri 2000; Lee 2014; Lee 2016; Matsumoto 2013; Mirkin 2012; Mirkin 2015; Moldwin 2015; Nickel 2016; Nomiya 2017; O'Reilly 2004; Oliver 2013; Peeker 2000; Pinto 2016; Sairanen 2009; Shirvan 2015; Singh 2003; Taha 2007; Thilagarajah 2001; van Ophoven 2006; Yassin 2011; Zakaria 2016).

Included studies were conducted in various countries. The USA was the country where most studies were conducted (25 studies) (Bosch 2014; Carrico 2008; Carty 2017; Davis 2008; Evans 2011; FitzGerald 2009; FitzGerald 2012; Foster 2010; Gottsch 2011; Hanno 2015; Herati 2011; Kanter 2016; Korting 1999; Mayer 2005; Moldwin 2015; Mulholland 1990; Nickel 2012a; Oliver 2013; Parsons 2012; Payne 2005; Payne 2014; Peeker 2000; Peters 1997; Sant 2003; Warren 2000). Nineteen studies were conducted in 11 other Western countries, including Canada (Chen 2005; Nguan 2005; Perez-Marrero 1988); Australia (Manning 2014; O'Reilly 2004); Belgium (De Ridder 2013); Finland (Sairanen 2005); Germany (van Ophoven 2004; van Ophoven 2006); Greece (Barbalias 2000); Italy (Cervigni 2014; Lazzeri 1996; Lazzeri 2000); Portugal (Pinto 2016); Sweden (Geirsson 1993); the Netherlands (Bade 1997); and the UK (Cartledge 2000; Singh 2003; Thilagarajah 2001). Eighteen studies were conducted in six different Asian countries, including China (Chen 2014; Lu 2015); Japan (Matsumoto 2013; Nomiya 2017); Korea (Ham 2012; Kim 2012; Kim 2015); Taiwan (Chuang 2017; Hsieh 2012; Kuo 2009; Kuo 2016; Lee 2014; Lee 2016); Iran (Ahmadnia 2011; Irani 2004; Shirvan 2015); and Turkey (Gulpinar 2013; Gulpinar 2015). Four studies were conducted in Egypt (El-Hefnawy 2015; Taha 2007; Yassin 2011; Zakaria 2016); three in Iran (Ahmadnia 2011; Irani 2004; Shirvan 2015); and one in Brazil (Souza 2012), and three studies were conducted in Russia (Kasyan 2012; Mirkin 2012; Mirkin 2015). Seven studies involved more than one country (Leadership 201 Trial 2016; Nickel 2009; Nickel 2010; Nickel 2012b; Nickel 2015; Wang 2017a; Yang 2011). For four studies, the country in which the study was conducted is unclear (Dimitrakov 2001; Ismail 2016; Nickel 2016; Sairanen 2009).

Participants

Participants enrolled in the included studies presented with various clinical diagnoses including interstitial cystitis (IC); painful bladder syndrome (PBS); bladder pain syndrome (BPS); painful bladder disease (PBD); chronic urogenital pain (Carty 2017); severe bladder pain (Lazzeri 1996); or hypersensitive disorder and severe pain (Lazzeri 2000). One study included patients with IC/PBS, as well as patients with chronic prostatitis (CP)/chronic pelvic pain syndrome (CPPS) (not eligible for this evidence synthesis) (FitzGerald 2009).

Study participants were female in 29 studies and were predominantly (> 75%) female in 34 studies (Bosch 2014; Cartledge 2000; Chen 2005; Chuang 2017; De Ridder 2013; Evans 2011; Foster 2010; Ismail 2016; Kuo 2016; Lazzeri 1996; Matsumoto 2013; Mayer 2005; Mulholland 1990; Nickel 2009; Nickel 2010; Nickel 2012b; Nickel 2015; Nickel 2016; Nomiya 2017; Oliver 2013; Payne 2005; Payne 2014; Peeker 2000; Perez-Marrero 1988; Sairanen 2005; Sairanen 2009; Sant 2003; Souza 2012; Thilagarajah 2001; van Ophoven 2004; Wang 2017a; Warren 2000; Yang 2011; Yassin 2011). Two studies included slightly more women than men (51% to 63%) (FitzGerald 2009; Lazzeri 2000), and one study included only men (Zakaria 2016). The other 15 studies did not report participants' gender.

The reported mean or median age of participants in each study lay between 30 and 44 years in 12 studies (Carrico 2008; Cartledge 2000; Chen 2014; Davis 2008; El-Hefnawy 2015; FitzGerald 2009; FitzGerald 2012; Foster 2010; Geirsson 1993; Lazzeri 2000; Mirkin 2012; Thilagarajah 2001); between 45 and 64 years in 45 studies (Bade 1997; Barbalias 2000; Bosch 2014; Carty 2017; Cervigni 2014; Chen 2005; Chuang 2017; Gottsch 2011; Gulpinar 2013; Gulpinar 2015; Ham 2012; Hsieh 2012; Irani 2004; Kanter 2016; Kim 2012; Kim 2015; Korting 1999; Kuo 2016; Lazzeri 1996; Leadership 201 Trial 2016; Lee 2014; Lu 2015; Manning 2014; Mayer 2005; Mulholland 1990; Nickel 2009; Nickel 2010; Nickel 2012a; Nickel 2012b; Nickel 2015; Nickel 2016; Payne 2005; Payne 2014; Peeker 2000; Perez-Marrero 1988; Peters 1997; Pinto 2016; Sairanen 2005; Sairanen 2009; Sant 2003; Souza 2012; van Ophoven 2004; Wang 2017a; Warren 2000; Yang 2011); and 65 years or older in four studies (Matsumoto 2013; Nomiya 2017; Oliver 2013; van Ophoven 2006). Mean or median age of participants was not reported in the remaining 20 studies.

Study funding sources

Twenty-four included studies (30%) were sponsored by pharmaceutical companies that manufactured the products being studied (Bosch 2014; Cervigni 2014; Chuang 2017; Davis 2008; De Ridder 2013; Evans 2011; Leadership 201 Trial 2016; Mirkin 2012; Moldwin 2015; Mulholland 1990; Nickel 2009; Nickel 2010; Nickel 2012a; Nickel 2012b; Nickel 2015; Nickel 2016; Parsons 2012; Payne 2005; Payne 2014; Peeker 2000; Peters 1997; Pinto 2016; van Ophoven 2004; Wang 2017a), and 19 included studies (23%) were independent or were publicly funded (e.g. from research councils, government, individual hospitals) (Carrico 2008; Chen 2014; Dimitrakov 2001; Geirsson 1993; Herati 2011; Kanter 2016; Kim 2012; Kuo 2016; Lee 2014; Matsumoto 2013; Mayer 2005; Nguan 2005; Nomiya 2017; Sairanen 2005; Sant 2003; Taha 2007; van Ophoven 2006; Warren 2000; Yang 2011). Four studies (5%) stated that no research funding was received (Kasyan 2012; Lee 2016; Oliver 2013; Yassin 2011). The other 34 studies (42%) did not specify the source of funding (Ahmadnia 2011; Bade 1997; Barbalias 2000; Cartledge 2000; Carty 2017; Chen 2005; El-Hefnawy 2015; FitzGerald 2009; FitzGerald 2012; Foster 2010; Gottsch 2011; Gulpinar 2013; Gulpinar 2015; Ham 2012; Hanno 2015; Hsieh 2012; Irani 2004; Ismail 2016; Kim 2015; Korting 1999; Kuo 2009; Lazzeri 1996; Lazzeri 2000; Lu 2015; Manning 2014; Mirkin 2015; O'Reilly 2004; Perez-Marrero 1988; Sairanen 2009; Shirvan 2015; Singh 2003; Souza 2012; Thilagarajah 2001; Zakaria 2016).

Interventions

The included studies assessed 65 different active treatments, given alone or in combination. We grouped these treatments into treatment categories by mode of action, based on treatment descriptions for BPS from the 6th ICI wherever possible (Hanno 2017). The analysis included 31 active treatment categories, which are shown in Table 2. No studies were identified using our search strategies for the interventions listed in Table 3. A majority of the treatment categories in the analysis were pharmacological therapies, and a relatively small number of treatment categories were related to conservative therapies and surgical interventions.

For trials that compared two or more varieties of the same treatment against control, trial arms comparing the same treatment were combined. For example, Chen 2005 comparing resiniferatoxin (RTX) 0.05 microMol/L, RTX 0.1 microMol/L and placebo, and Payne 2005 comparing RTX 0.01 microMol/L, RTX 0.05 microMol/L, RTX 0.10 microMol/L and control, were both analysed as 'RTX (calcium channel agonist) versus control'; and Chuang 2017 comparing liposomal-formulated onabotulinumtoxinA (lipotoxin), onabotulinumtoxinA in normal saline and normal saline was analysed as 'onabotulinumtoxinA (neuromuscular blockade) versus control'. One trial comprising four intervention groups using a factorial design (antihistamines, PPS, PPS + antihistamines and control) was analysed as a four-intervention arm trial (Sant 2003).

Outcomes

No common single outcome was assessed by all included trials. Outcomes that were conceptually similar such as pain were measured by different scales or tools, and a clear definition often was not provided. Continuous outcomes (e.g. pain, daytime frequency, nocturia) were reported as mean scores at last follow-up or as mean changes from baseline. Considerable efforts were made to standardise the reported outcomes to incorporate them into the analysis. A sizeable number of studies provided no usable outcome data.

Length of follow-up

A majority of studies provided short follow-up. Only six studies (7%) had follow-up of 12 months or longer (Irani 2004; Kuo 2009; Lu 2015; Mayer 2005; Peters 1997; Taha 2007). Follow-up time ranged from 0 months in Mirkin 2012, Nickel 2009 and Souza 2012 to 27 months in Peters 1997, with a median of three months.

Excluded studies

Sixteen reports of 14 studies were excluded after full-text screening. For example, we excluded studies that enrolled participants with urethral syndrome (Choa 1983; Costantini 2003), as well as studies that compared different regimens of the same treatment (Lai 2013; Lubeck 2001; Nickel 2005; Peters 2007). Further details are provided in the Characteristics of excluded studies table.

Risk of bias in included studies

Summaries of 'Risk of bias' judgements for the included studies are presented in Figure 3 and Figure 4.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

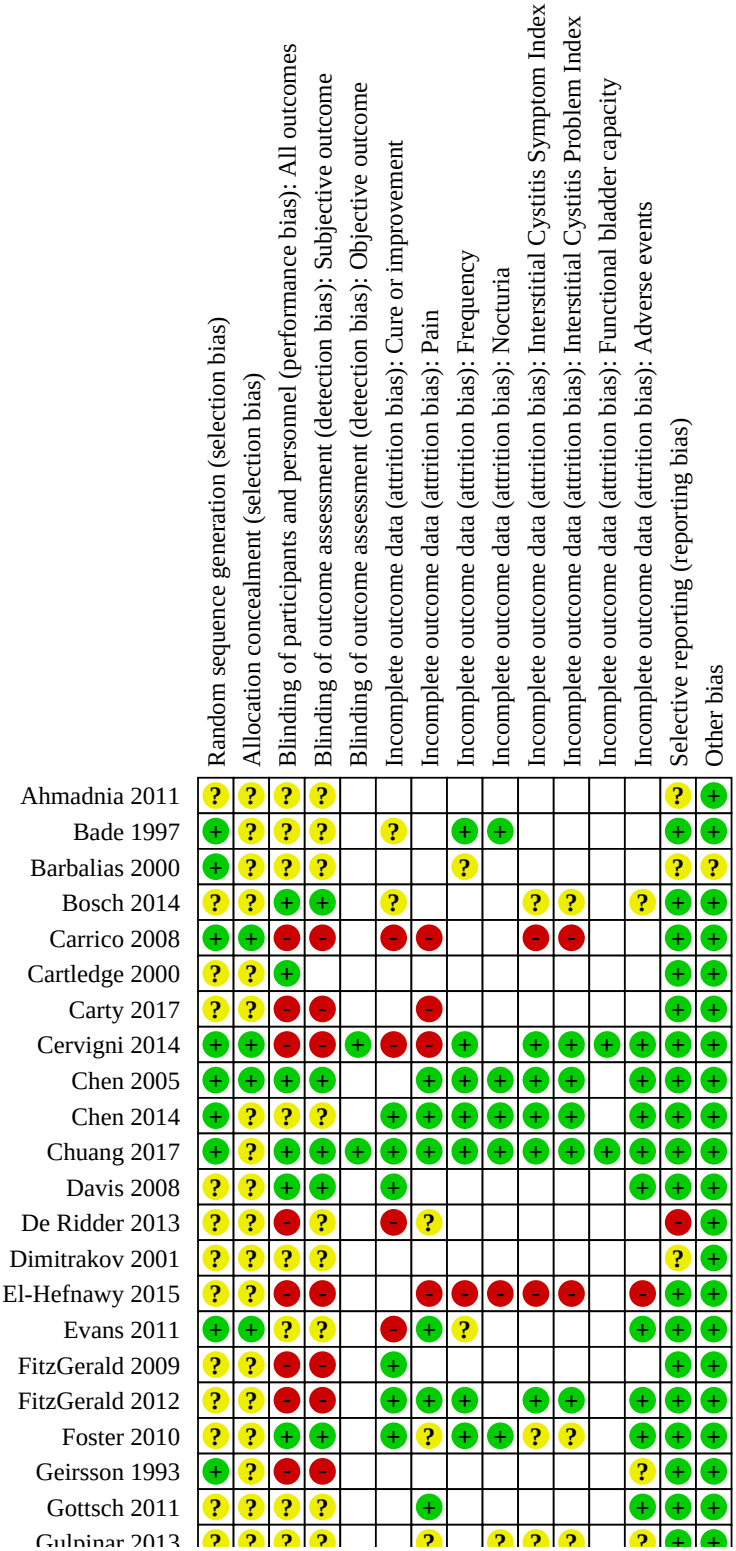


Figure 3. (Continued)

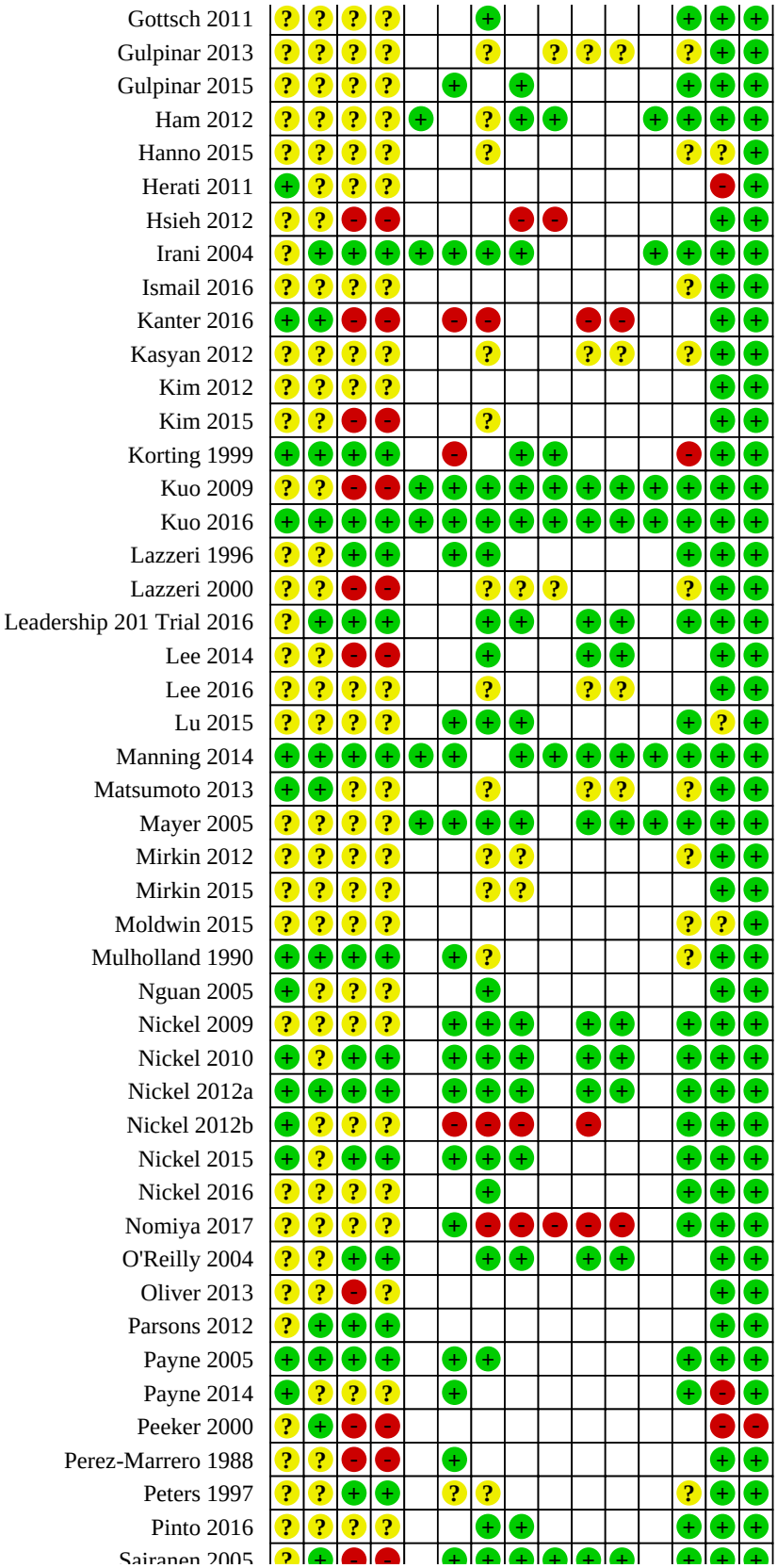


Figure 3. (Continued)

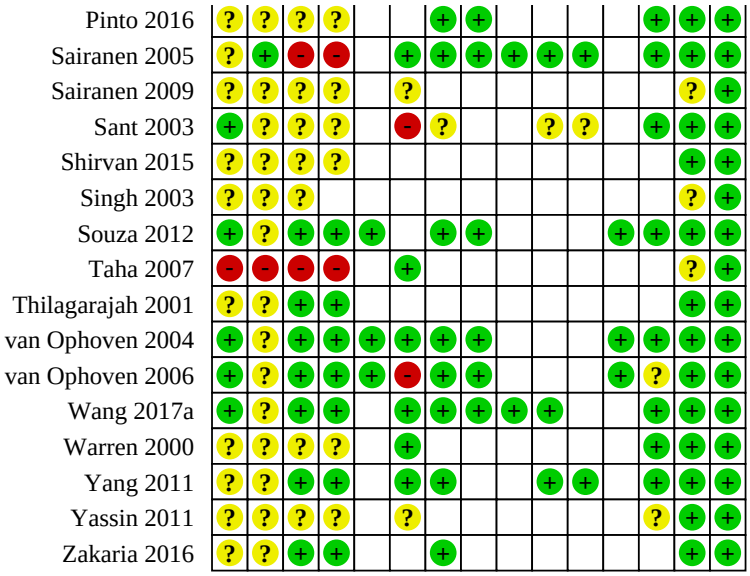
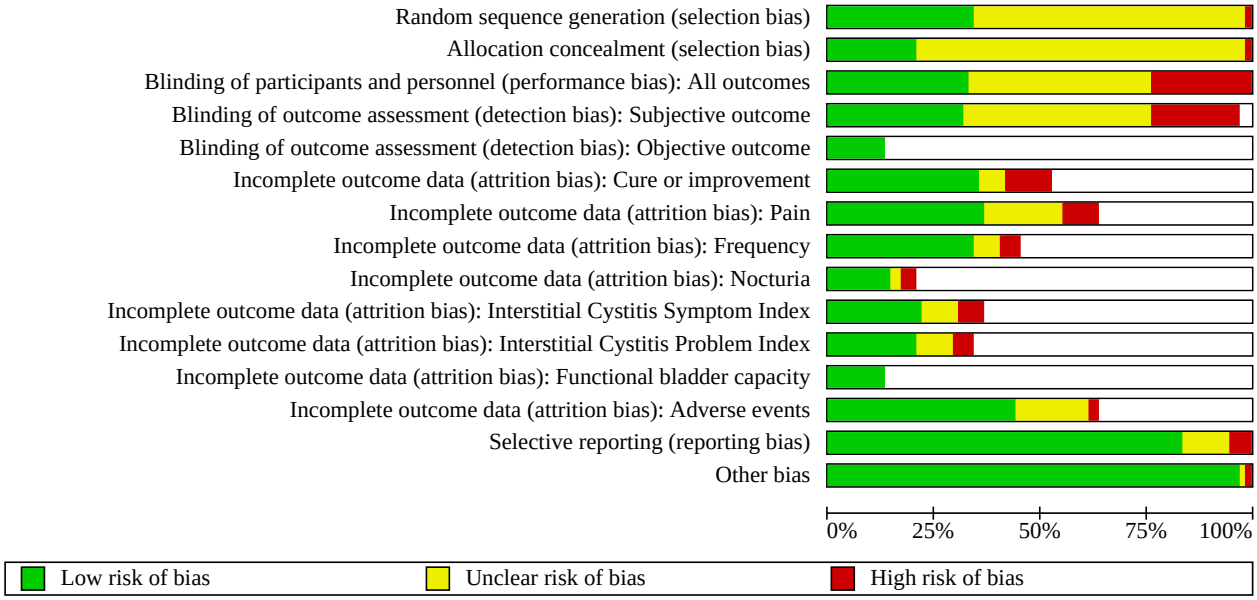


Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Twelve studies (15%) were considered to have adequate random sequence generation and appropriate allocation concealment, indicating an overall low risk of selection bias (Carrico 2008; Cervigni 2014; Chen 2005; Evans 2011; Kanter 2016; Korting 1999; Kuo 2016; Manning 2014; Matsumoto 2013; Mulholland 1990; Nickel 2012a; Payne 2005). Seventeen studies (21%) had adequate random sequence generation but it was unclear whether they assured allocation concealment (Bade 1997; Barbalias 2000; Chen 2014; Chuang 2017; Davis 2008; Geirsson 1993; Herati 2011; Nguan 2005; Nickel 2010; Nickel 2012b; Nickel 2015; Payne 2014; Sant 2003; Souza 2012; van Ophoven 2004; van Ophoven 2006; Wang 2017a), and five studies (6%) had adequate allocation concealment but it was unclear how the random sequence was generated (Irani 2004; Leadership 201 Trial 2016; Parsons 2012; Peeker 2000; Sairanen 2005). In one study that used alternate allocation, both random sequence generation and allocation concealment were considered inadequate, indicating an overall high risk of selection bias (Taha 2007). The other 46 studies (57%) did not provide sufficient information on which to assess the risk of selection bias.

Blinding

Performance bias

Twenty-seven studies (33%), most of which were placebo- or sham-controlled trials, reported adequate methods for blinding participants and personnel to treatment allocation and were considered to have low risk of performance bias (Bosch 2014; Cartledge 2000; Chen 2005; Chuang 2017; Davis 2008; Foster 2010; Irani 2004; Korting 1999; Kuo 2016; Lazzeri 1996; Leadership 201 Trial 2016; Manning 2014; Mulholland 1990; Nickel 2010; Nickel 2012a; Nickel 2015; O'Reilly 2004; Parsons 2012; Payne 2005; Peters 1997; Souza 2012; Thilagarajah 2001; van Ophoven 2004; van Ophoven 2006; Wang 2017a; Yang 2011; Zakaria 2016).

In 19 studies (23%), it was assumed that blinding of both patients and personnel was not done and the risk of performance bias was considered to be high. These included 13 studies using behavioural, physical or surgical interventions when blinding was not feasible due to the nature of the interventions (Carrico 2008; Carty 2017; El-Hefnawy 2015; FitzGerald 2009; FitzGerald 2012; Geirsson 1993; Hsieh 2012; Kanter 2016; Kim 2015; Kuo 2009; Lee 2014; Oliver 2013; Taha 2007). The other six studies reported some noticeable difference between the intervention and the comparator, such as the garlic-like taste or an odour of dimethyl sulfoxide (DMSO) on the participant's breath (Cervigni 2014; Peeker 2000; Perez-Marrero 1988); a light warm or burning sensation after instillation of resiniferatoxin solution (Lazzeri 2000); the use of vials of different sizes (De Ridder 2013); or the use of an ‘open-label’ study design (Lazzeri 2000).

In the remaining 35 studies (43%), blinding was not mentioned, or the term 'blinding' was mentioned (e.g. ‘double-blind study’) but the method used for blinding was not described (e.g. placebo was unspecified). We judged these studies to be at unclear risk of bias.

Detection bias

For blinding subjective outcome assessment, 26 studies (32%) reported adequate methods for blinding assessors of subjective outcomes and were judged to be at low risk of bias (Bosch 2014; Chen 2005; Chuang 2017; Davis 2008; Foster 2010; Irani 2004; Korting 1999; Kuo 2016; Lazzeri 1996; Leadership 201 Trial 2016; Manning 2014; Mulholland 1990; Nickel 2010; Nickel 2012a; Nickel 2015; O'Reilly 2004; Parsons 2012; Payne 2005; Peters 1997; Souza 2012; Thilagarajah 2001; van Ophoven 2004; van Ophoven 2006; Wang 2017a; Yang 2011; Zakaria 2016). Seventeen studies were judged to be at high risk because the participants either were not or could not be blinded to the intervention (Carrico 2008; Carty 2017; Cervigni 2014; El-Hefnawy 2015; FitzGerald 2009; FitzGerald 2012; Geirsson 1993; Hsieh 2012; Kanter 2016; Kim 2015; Kuo 2009; Lazzeri 2000; Lee 2014; Peeker 2000; Perez-Marrero 1988; Sairanen 2005; Taha 2007). The risk of detection bias was unclear in the remaining 36 studies (44%) as the blinding of study participants was not explicitly stated. Risk of bias was not applicable in two studies that did not report any usable subjective outcome data (Cartledge 2000; Singh 2003).

For blinding objective outcome assessment, we assessed 11 studies (14%) that reported functional bladder capacity as being at low risk of bias, as bladder capacity was measured in terms of urine volume (mL) and therefore was unlikely to be affected by lack of blinding (Cervigni 2014; Chuang 2017; Ham 2012; Irani 2004; Kuo 2009; Kuo 2016; Manning 2014; Mayer 2005; Souza 2012; van Ophoven 2004; van Ophoven 2006). Risk of bias was not applicable in the remaining 70 studies (86%), which did not report this outcome.

Incomplete outcome data

We assessed the risk of attrition bias based on differential dropout rates. We judged that there was high risk of attrition bias when the number of participants lost at follow-up differed between treatment groups by 10% or more.

For the outcome of cure or improvement, as reported in 43 studies (53%), risk of attrition bias was considered to be low in 29 studies (36%) (Chen 2014; Chuang 2017; Davis 2008; FitzGerald 2009; FitzGerald 2012; Foster 2010; Gulpinar 2015; Irani 2004; Kuo 2009; Kuo 2016; Lazzeri 1996; Lu 2015; Manning 2014; Mayer 2005; Mulholland 1990; Nickel 2009; Nickel 2010; Nickel 2012a; Nickel 2015; Nomiya 2017; Payne 2005; Payne 2014; Perez-Marrero 1988; Sairanen 2005; Taha 2007; van Ophoven 2004; Wang 2017a; Warren 2000; Yang 2011); high in nine studies (%) (Carrico 2008; Cervigni 2014; De Ridder 2013; Evans 2011; Kanter 2016; Korting 1999; Nickel 2012b; Sant 2003; van Ophoven 2006); and unclear in five studies (6%) (Bade 1997; Bosch 2014; Peters 1997; Sairanen 2009; Yassin 2011).

For the outcome of pain, as reported in 51 studies (63%), risk of attrition bias was considered to be low in 30 studies (11%) (Chen 2005; Chen 2014; Chuang 2017; Evans 2011; FitzGerald 2012; Gottsch 2011; Ham 2012; Irani 2004; Kuo 2009; Kuo 2016; Lazzeri 1996; Leadership 201 Trial 2016; Lee 2014; Lu 2015; Mayer 2005; Nguan 2005; Nickel 2009; Nickel 2010; Nickel 2012a; Nickel 2015; Nickel 2016; O'Reilly 2004; Payne 2005; Pinto 2016; Sairanen 2005; Souza 2012; van Ophoven 2004; van Ophoven 2006; Wang 2017a; Yang 2011); high in seven studies (9%) (Carrico 2008; Carty 2017; Cervigni 2014; El-Hefnawy 2015; Kanter 2016; Nickel 2012b; Nomiya 2017); and unclear in 14 studies (17%) (De Ridder 2013; Foster 2010; Gulpinar 2013; Hanno 2015; Kasyan 2012; Kim 2015; Lazzeri 2000; Lee 2016; Matsumoto 2013; Mirkin 2012; Mirkin 2015; Mulholland 1990; Peters 1997; Sant 2003).

For the outcome of daytime frequency, as reported in 40 studies (49%), risk of attrition bias was considered to be low in 29 studies (36%) (Bade 1997; Cervigni 2014; Chen 2005; Chen 2014; Chuang 2017; Evans 2011; FitzGerald 2012; Foster 2010; Gulpinar 2015; Ham 2012; Irani 2004; Korting 1999; Kuo 2009; Kuo 2016; Leadership 201 Trial 2016; Lu 2015; Manning 2014; Mayer 2005; Nickel 2009; Nickel 2010; Nickel 2012a; Nickel 2015; O'Reilly 2004; Pinto 2016; Sairanen 2005; Souza 2012; van Ophoven 2004; van Ophoven 2006; Wang 2017a); high in four studies (5%) (El-Hefnawy 2015; Hsieh 2012; Nickel 2012b; Nomiya 2017); and unclear in seven studies (9%) (Barbalias 2000; Gulpinar 2013; Lazzeri 2000; Matsumoto 2013; Mirkin 2012; Mirkin 2015; Sant 2003).

For the outcome of nocturia, as reported in 18 studies (22%), risk of attrition bias was considered to be low in 13 studies (16%) (Bade 1997; Chen 2005; Chen 2014; Chuang 2017; Foster 2010; Ham 2012; Korting 1999; Kuo 2009; Kuo 2016; Lu 2015; Manning 2014; Sairanen 2005; Wang 2017a); high in three studies (4%) (El-Hefnawy 2015; Hsieh 2012; Nomiya 2017); and unclear in two studies (2%) (Gulpinar 2013; Lazzeri 2000).

For the outcome of ICSI, as reported in 31 studies (38%), risk of attrition bias was considered to be low in 18 studies (22%) (Cervigni 2014; Chen 2005; Chen 2014; Chuang 2017; FitzGerald 2012; Kuo

2009; Kuo 2016; Leadership 201 Trial 2016; Lee 2014; Manning 2014; Mayer 2005; Nickel 2009; Nickel 2010; Nickel 2012a; O'Reilly 2004; Sairanen 2005; Wang 2017a; Yang 2011); high in five studies (6%) (Carrico 2008; El-Hefnawy 2015; Kanter 2016; Nickel 2012b; Nomiya 2017); and unclear in eight studies (10%) (Bosch 2014; De Ridder 2013; Foster 2010; Gulpinar 2013; Kasyan 2012; Lee 2016; Matsumoto 2013; Sant 2003).

For the outcome of ICPI, as reported in 28 studies (35%), risk of attrition bias was considered to be low in 17 studies (21%) (Cervigni 2014; Chen 2005; Chen 2014; Chuang 2017; FitzGerald 2012; Kuo 2009; Kuo 2016; Leadership 201 Trial 2016; Lee 2014; Manning 2014; Mayer 2005; Nickel 2009; Nickel 2010; Nickel 2012a; O'Reilly 2004; Sairanen 2005; Yang 2011); high in four studies (5%) (Carrico 2008; El-Hefnawy 2015; Kanter 2016; Nomiya 2017); and unclear in seven studies (9%) (Bosch 2014; Foster 2010; Gulpinar 2013; Kasyan 2012; Lee 2016; Matsumoto 2013; Sant 2003).

For the outcome of functional bladder capacity, as reported in 11 studies (14%), risk of attrition bias was considered to be low in all 11 studies (Cervigni 2014; Chuang 2017; Ham 2012; Irani 2004; Kuo 2009; Kuo 2016; Manning 2014; Mayer 2005; Souza 2012; van Ophoven 2004; van Ophoven 2006).

For the outcome of adverse events, as reported in 52 studies (64%), risk of attrition bias was considered to be low in 35 studies (43%) (Cervigni 2014; Chen 2005; Chen 2014; Chuang 2017; Davis 2008; Evans 2011; FitzGerald 2012; Foster 2010; Gottsch 2011; Gulpinar 2015; Ham 2012; Irani 2004; Kuo 2009; Kuo 2016; Lazzeri 1996; Leadership 201 Trial 2016; Lu 2015; Manning 2014; Mayer 2005; Nickel 2009; Nickel 2010; Nickel 2012a; Nickel 2012b; Nickel 2015; Nickel 2016; Nomiya 2017; Payne 2014; Pinto 2016; Sairanen 2005; Sant 2003; Souza 2012; van Ophoven 2004; Wang 2017a; Warren 2000; Yang 2011); high in two studies (2%) (El-Hefnawy 2015; Korting 1999); and unclear in 15 studies (19%) (Bosch 2014; Dimitrakov 2001; Geirsson 1993; Gulpinar 2013; Hanno 2015; Ismail 2016; Kasyan 2012; Lazzeri 2000; Matsumoto 2013; Mirkin 2012; Moldwin 2015; Mulholland 1990; Peters 1997; van Ophoven 2006; Yassin 2011).

Selective reporting

We considered that there was low risk of reporting bias when the results of all outcomes specified in the methods were reported. Studies were considered at high risk of bias when outcomes specified in the methods were missing or were partially reported in the results, or when outcomes not specified in the methods were reported in the results. Risk of reporting bias was considered to be high in five studies (6%) (due to limited information available) (Barbalias 2000; De Ridder 2013; Herati 2011; Payne 2014; Peeker 2000); unclear in eight studies (10%) (Ahmadnia 2011; Dimitrakov 2001; Hanno 2015; Lu 2015; Moldwin 2015; Sairanen 2009; Singh 2003; Taha 2007); and low in the remaining 68 studies (84%).

Other potential sources of bias

In one cross-over study (Peeker 2000), participants were randomly allocated to a treatment, and if they did not improve, they were crossed over to the other treatment. The analysis was conducted at the end of the study period; therefore, treatment effects in this study could have been estimated after most (if not all) of the participants had received both treatments. As such, we judged this study to be at high risk of other bias. No other potential sources of bias were identified in the other studies.

Effects of interventions

See: **Summary of findings 1** Interventions for treating people with symptoms of bladder pain syndrome

We included 81 randomised controlled trials (RCTs) with a total of 4674 participants and a median of 38 participants (range 10 to 369). Most trials compared treatment against control; few trials compared two active treatments. There were 65 different active treatments, and some comparisons were informed by direct evidence from only one trial.

Data from one study could not be included in the statistical analyses as participants with interstitial cystitis (IC)/painful bladder syndrome (PBS) were a subgroup of the study population (including chronic prostatitis (CP)/chronic pelvic pain syndrome (CPPS)), but randomisation was not stratified according to clinical diagnosis (FitzGerald 2009).

For some outcomes, certain treatments were not part of a connected network and therefore could not be evaluated against control within the network meta-analysis (NMA). This occurred, for example, when a pair of active treatments were included only in a particular head-to-head trial but not in any other trials in the review.

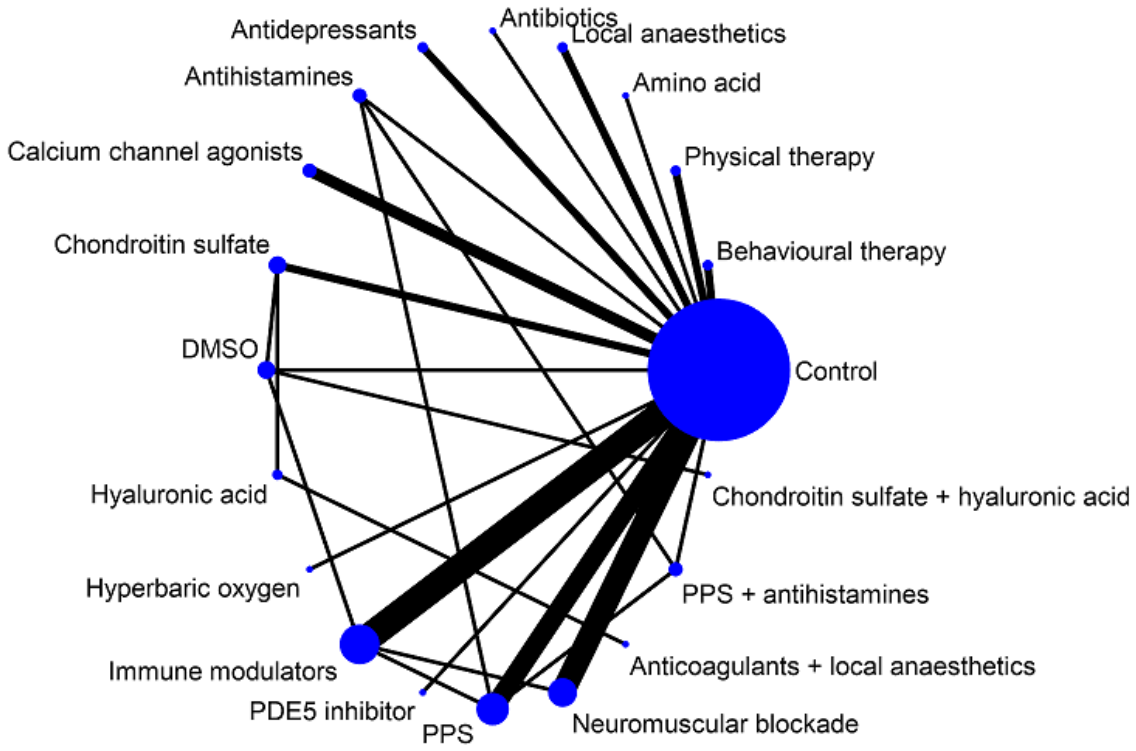
As reported in the Methods, we present one 'Summary of findings' table with three interventions: antidepressants (including amitriptyline), pentosan polysulfate and neuromuscular blockade (injection of botulinum toxin type A). GRADE ratings for the other interventions can be found in Table 4, Table 5, Table 6 and Table 7.

Primary outcomes

Proportion of participants whose symptoms were cured or improved

Figure 5 shows the network diagram with the number of trials assessing each pair of treatments in the network for the proportion of participants cured or improved. A majority of trials compared an active treatment versus control. All trials were contained within a connected network; therefore an NMA was conducted.

Figure 5. Network diagram for the proportion of participants whose symptoms were cured or improved. The thickness of each line is proportionate to the number of included studies.

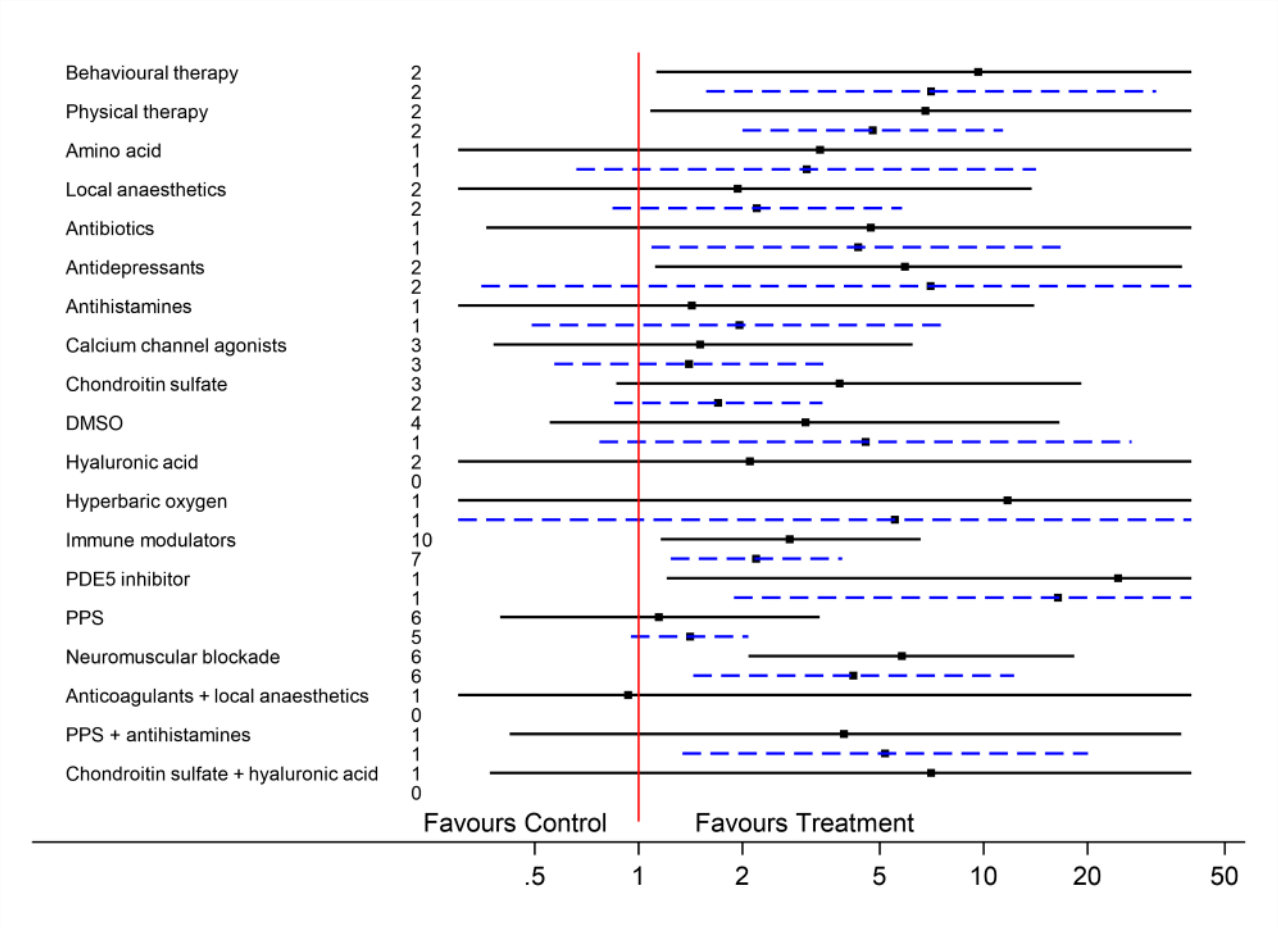


Forty-three trials with usable data for the cure outcome were identified, forming a network of 20 treatment categories: control, two types of conservative therapy, 13 types of pharmacological treatments, one surgical intervention and three combination therapies of two different pharmacological interventions. Most trials had two treatment arms, but one trial included four treatment arms (Sant 2003). Trials were generally small; only five trials provided data for over 100 participants.

After the initial NMA models were run in WinBUGS, the diagnostic plots suggested that results for hyperbaric oxygen (HBO) were unstable and the model failed to converge. This treatment was assessed in only one trial in which three participants in the HBO group were cured or improved compared with none in the control group (van Ophoven 2006). As such, the lack of convergence is likely to be related to the zero cell count. For this trial, we followed the advice of the National Institute for Health and Care Excellence Decision Support Unit Technical Support Documents 2 (NICE DSU TSD 2) and added 1 to the denominator and 0.5 to the numerator in each group (Dias 2016). No adjustment was necessary for the other trial that had a zero cell count, as this was one of several studies that compared neuromuscular blockade with control (Payne 2014). The results for all other treatments showed good convergence.

Figure 6 and Table 4 show results of the final NMA for each of the 19 active treatment categories versus control. Median odds ratios (ORs) from the NMA were above 1 for 18 treatment categories, indicating favourable cure rates versus control, but the 95% credible intervals (CrIs) were wide, reflecting the small number and size of available trials. Very low-certainty evidence suggests that the following treatment categories were effective versus control: behavioural therapy (OR 9.42, 95% CrI 1.01 to 110.83), physical therapy (OR 6.78, 95% CrI 1.08 to 46.85), antidepressants (OR 5.91, 95% CrI 1.12 to 37.56), immune modulators (OR 2.74, 95% CrI 1.16 to 6.57), phosphodiesterase-5 (PDE5) inhibitors (OR 24.53, 95% CrI 1.21 to 1255.14) and neuromuscular blockade (OR 5.80, 95% CrI 2.08 to 18.30).

Figure 6. Meta-analysis results for proportion of participants whose symptoms were cured or improved. For each treatment category, the unbroken horizontal line represents the odds ratio (95% CrI) versus control from the network meta-analysis, and the dotted line represents the odds ratio (95% CI) versus control from the pairwise meta-analysis (if applicable). The number of studies included in each analysis is also shown. Intervals less than 0.3 and greater than 40 have been truncated.



A comparison of results of the network and pairwise meta-analyses is provided in Figure 6 and Table 4. The results were generally consistent, although in both sets of analyses, there was a wide range of uncertainty about the true effects of treatment. The pairwise results suggested benefits for two additional treatments: antibiotics and pentosan polysulfate (PPS) plus antihistamines (Table 6; Figure 4).

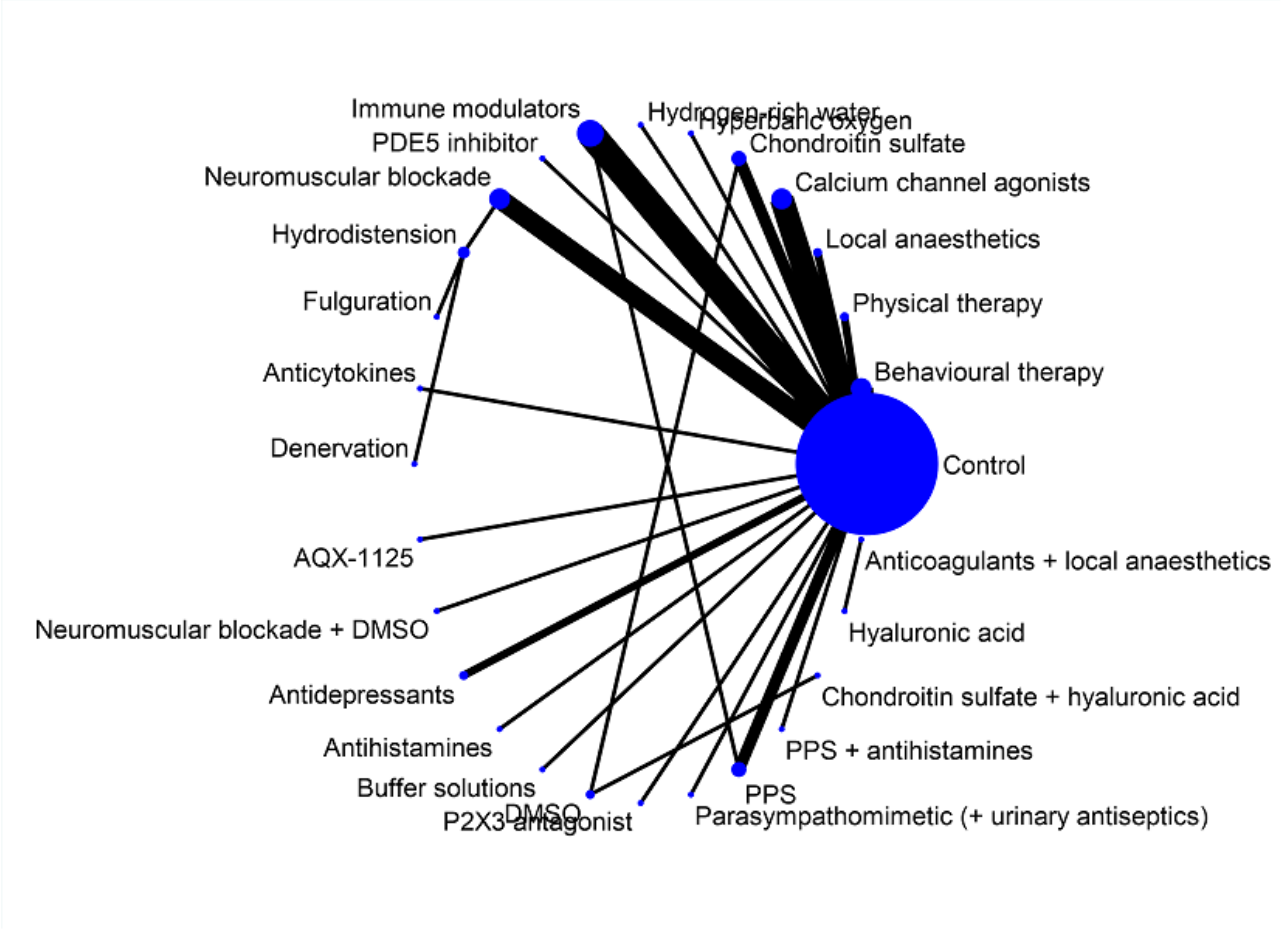
We assessed the heterogeneity and consistency assumptions of the NMA. Three of the nine pairwise comparisons containing more than one study were associated with an I^2 statistic greater than 50%, suggesting important heterogeneity. There were relatively few closed loops within the network by which to assess the consistency assumption, but a global test based on a random-effects design-by-treatment interaction model in CINeMA suggested evidence of inconsistency (P = 0.02) that was primarily associated with the results for chondroitin sulfate versus control. Overall, however, results of the NMA and the pairwise meta-analysis seemed to be consistent, considering the wide CrIs and confidence intervals (CIs).

Pain score

We were able to include a variety of continuous pain scales in the analyses. Scores were re-scaled so that 0 represented no pain and 10 the worst possible pain. No categorical measures of pain were included in the analyses.

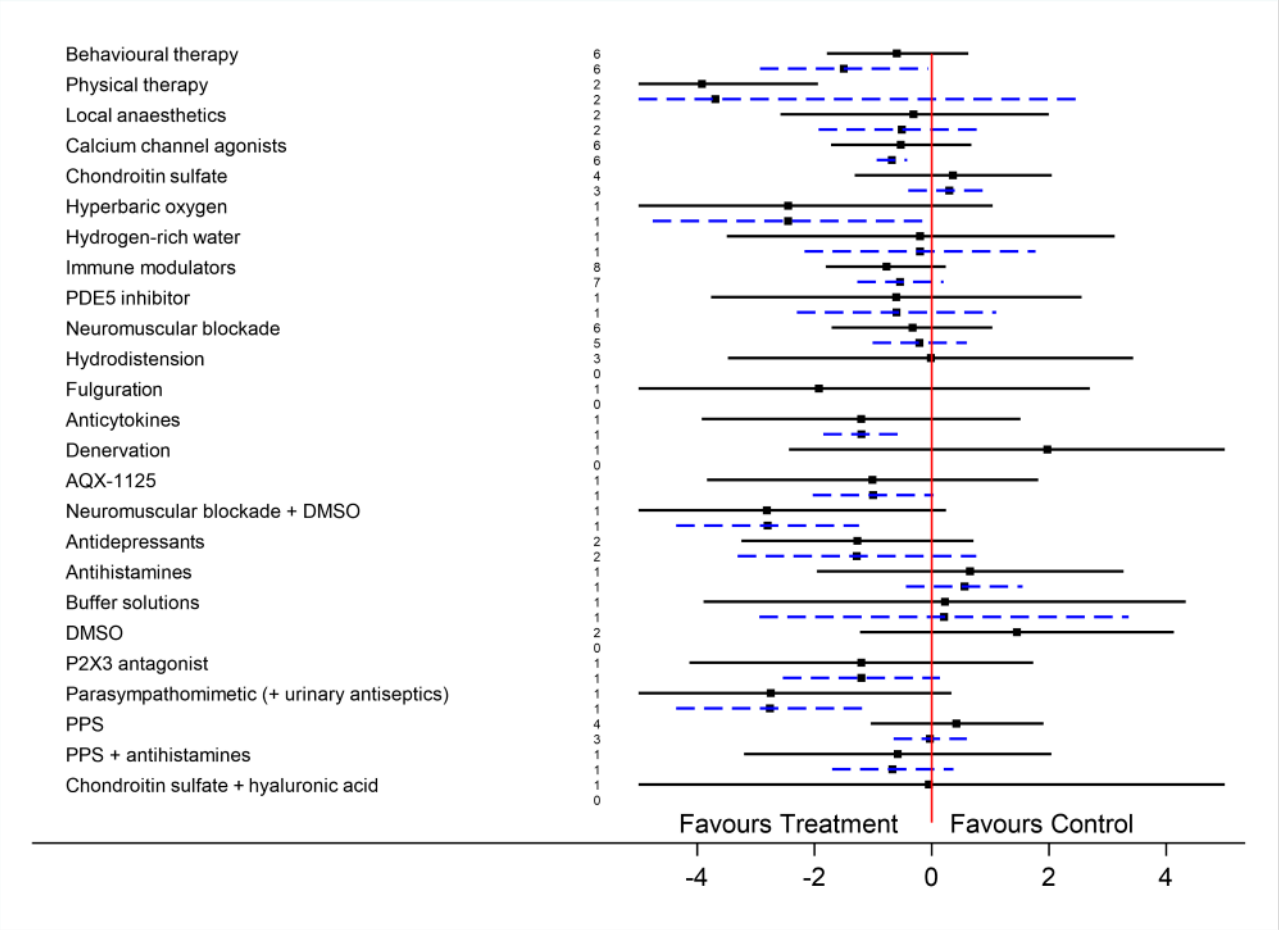
Figure 7 shows the network diagram for the pain outcome. Most comparisons in the network were against control. One trial comparing hyaluronic acid with anticoagulants plus local anaesthetics was disconnected from the rest of the network and therefore could not be included in the NMA (Lu 2015). Of the 51 studies comprising 25 active treatment categories that could be included, 28 had final score data for pain. For the remaining 23 studies, change score data had to be used.

Figure 7. Network diagram for pain score. The thickness of each line is proportionate to the number of included studies.



Results for the NMA are shown in Figure 8 and Table 5. Moderate-certainty evidence shows that physical therapy reduced pain compared with control by around 4 points on a 0 to 10 scale (mean difference (MD) -3.92, 95% CI -5.80 to -1.94). However, this comparison contained two studies with very heterogeneous results. One study showed an extreme effect, with mean (standard deviation (SD)) pain scores of 2.6 (0.13) and 9.4 (0.21) in the treatment and control groups, respectively, at four months' follow-up (Zakaria 2016). The other study showed a more modest effect (mean pain scores of 3.8 and 4.3, respectively) (FitzGerald 2012). Due to this heterogeneity, caution should be applied when interpreting these results. There is no clear evidence that any other treatment categories were effective.

Figure 8. Meta-analysis results for pain score. For each treatment category, the unbroken horizontal line represents the mean difference (95% CrI) in VAS (0-10) versus control from the network meta-analysis, and the dotted line represents the mean difference (95% CI) versus control from the pairwise meta-analysis (if applicable). The number of studies included in each analysis is also shown.

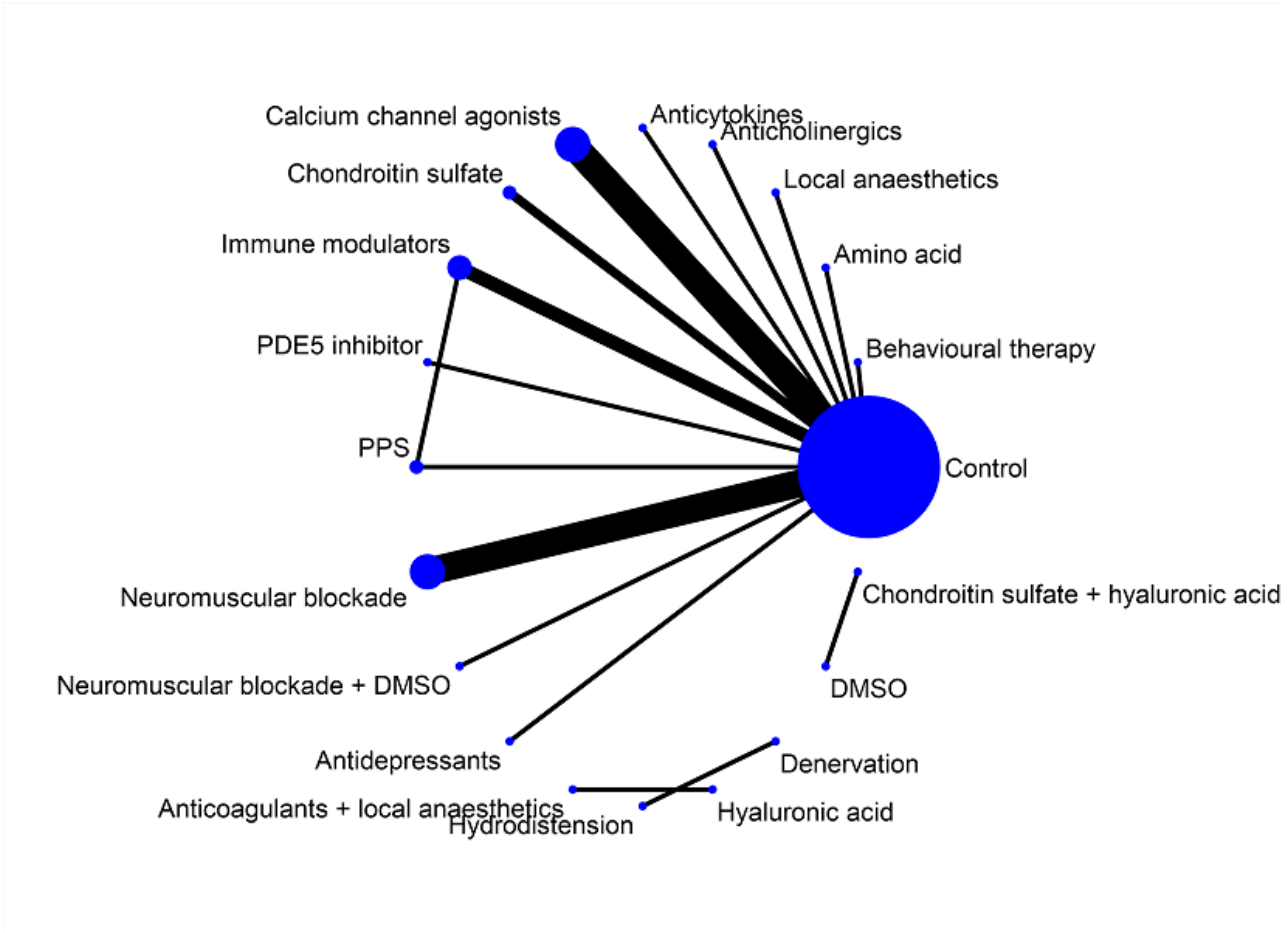


The pairwise meta-analyses generally provided similar effect sizes to the NMA, but CIs tended to be narrower (Figure 8; Table 5). There was important heterogeneity (I^2 > 50%) for four of nine pairwise comparisons with at least two studies. There were no concerns about the consistency of the NMA itself (P value for interaction = 0.18), but it was difficult to assess this assumption as there was only a small number of closed loops within the network, which meant that few comparisons between direct and indirect effect estimates could be made (the primary way that consistency in an NMA can be addressed).

Daytime frequency (number of voids)

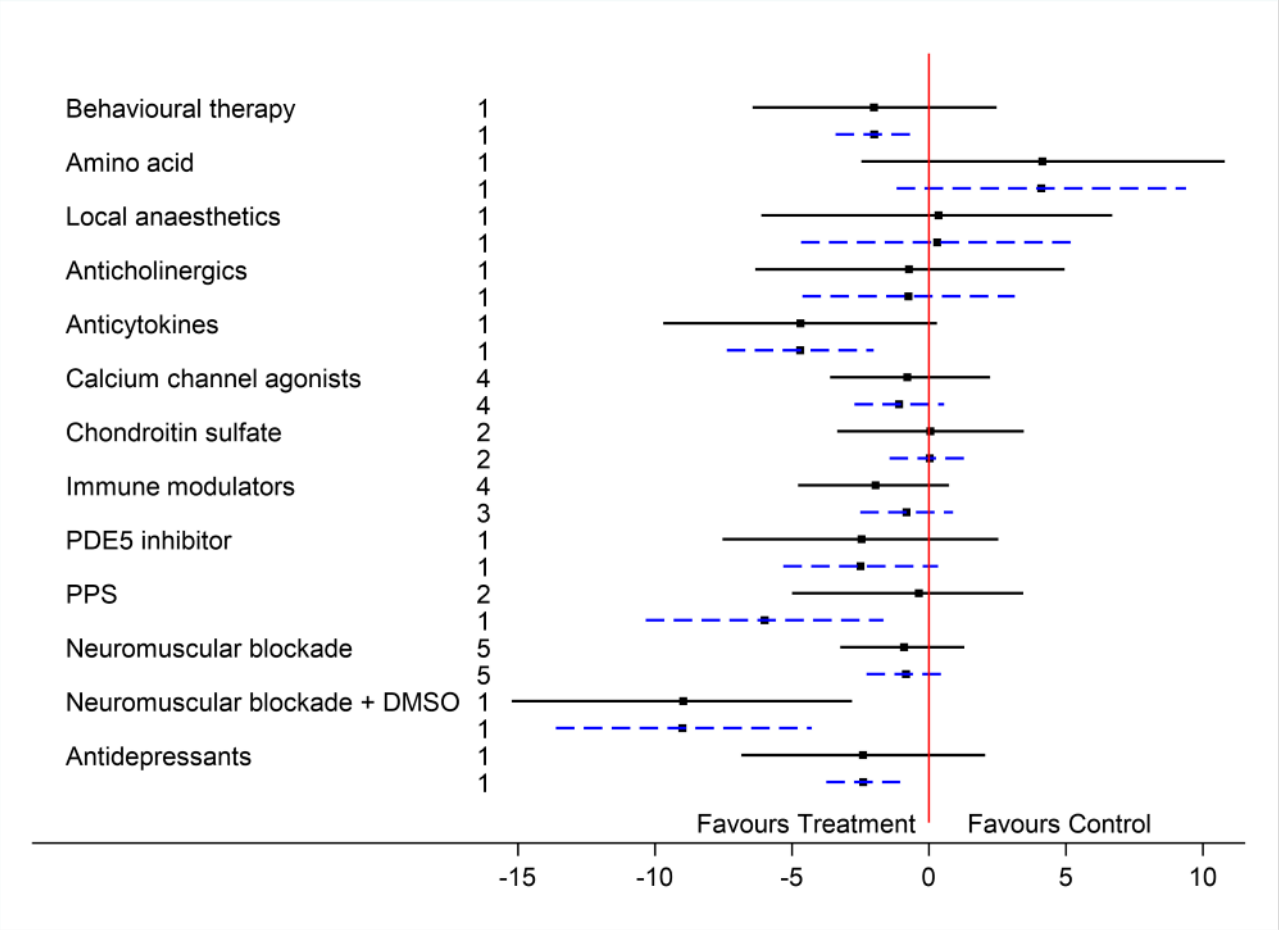
The network diagram for the frequency outcome is shown in Figure 9. Fourteen treatment categories are included in this network, but 23 of the 27 trials compared a single treatment against control, resulting in a network that was nearly completely "star-shaped", which meant that there were few closed loops within the network, which makes it difficult to assess consistency in results of the NMA. Six treatments could not be included as they are not connected to the rest of the network. These include denervation and hydrodistension (compared only in El-Hefnawy 2015); dimethyl sulfoxide (DMSO) and chondroitin sulfate plus hyaluronic acid (compared only in Cervigni 2014); and hyaluronic acid and anticoagulants plus local anaesthetics (compared only in Lu 2015). Eighteen studies in the network contributed final score data, and six studies contributed change score data.

Figure 9. Network diagram for daytime frequency (number of daytime voids). The thickness of each line is proportionate to the number of included studies.



The NMA results are presented in Figure 10 and Table 6. These yielded moderate-certainty evidence that the combination of neuromuscular blockade plus DMSO was associated with a reduction of around nine voids per day compared with control (MD -8.97, 95% CrI -15.23 to -2.81).

Figure 10. Meta-analysis results for daytime frequency (number of daytime voids). For each treatment category, the unbroken horizontal line represents the mean difference (95% CrI) in number of daytime voids versus control from the network meta-analysis, and the dotted line represents the mean difference (95% CI) versus control from the pairwise meta-analysis (if applicable). The number of studies included in each analysis is also shown.

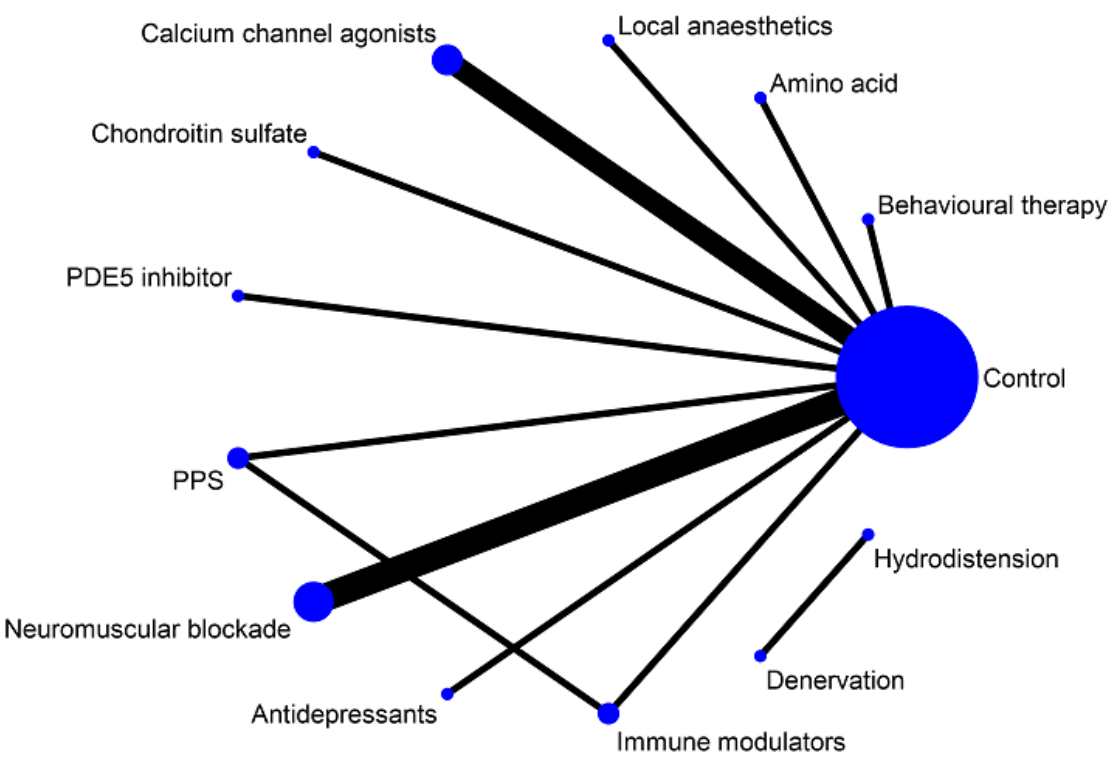


The pairwise meta-analyses generally yielded similar results but also suggested benefits for four additional treatment categories (behavioural therapy, anticytokines, PPS and antidepressants) (Figure 10; Table 6). There was evidence of heterogeneity (I^2 > 50%) for one of the four pairwise comparisons with at least two studies. There were some concerns about consistency within the only closed loop within the network involving immune modulators, PPS and control (P value for interaction = 0.007).

Nocturia (number of nighttime voids)

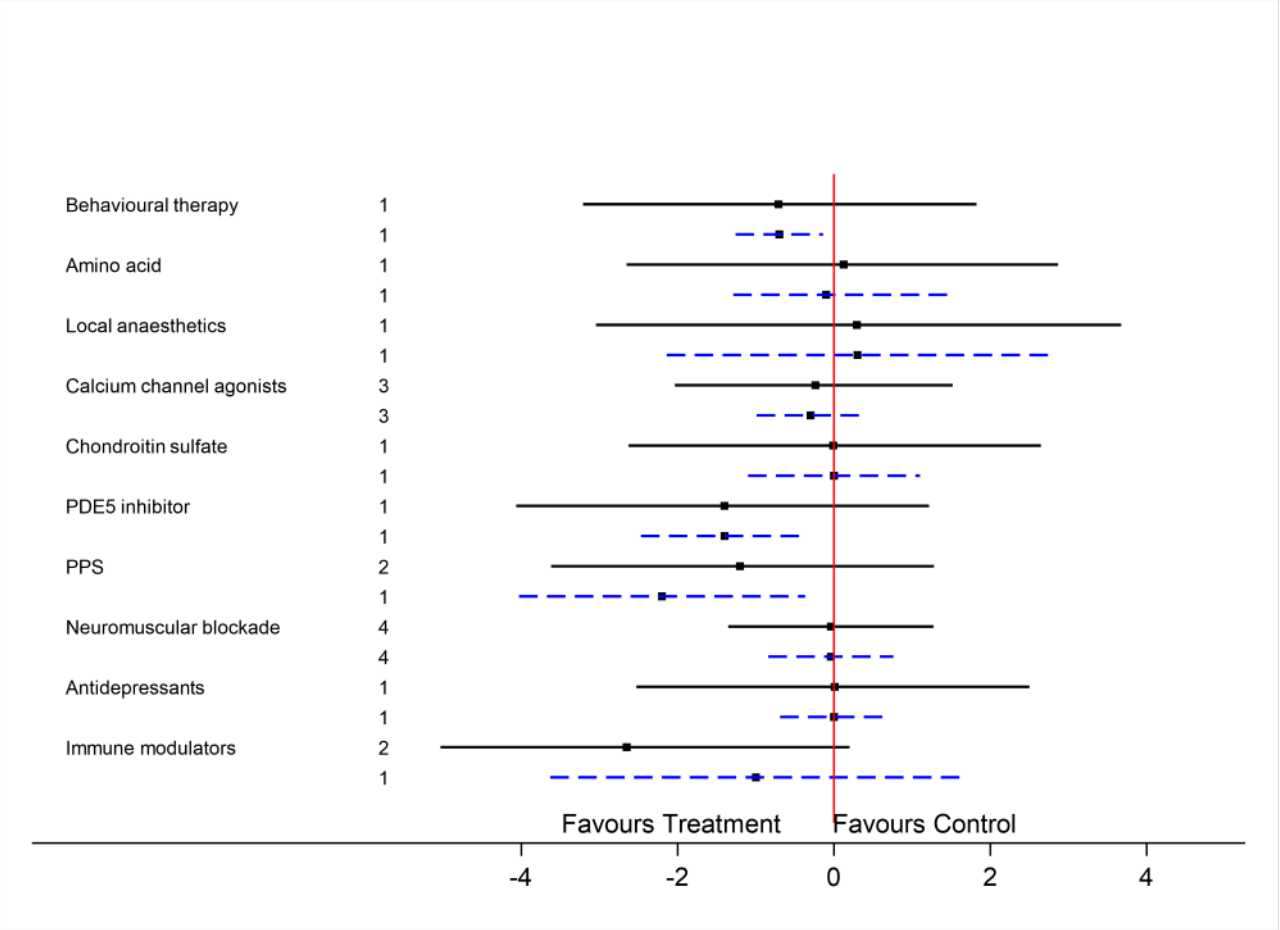
Figure 11 shows the network diagram for nocturia. Again, there were relatively few closed loops, resulting in a network that was almost star-shaped, with all treatments compared only with control, except for one comparison of PPS and immune modulators. Once again, the denervation and hydrodistension treatment categories could not be included, as they were not connected to the rest of the network (El-Hefnawy 2015). Thirteen studies in the network contributed final score data, and three studies contributed change score data.

Figure 11. Network diagram for nocturia (number of nighttime voids). The thickness of each line is proportionate to the number of included studies.



The NMA results did not yield any treatment categories with a 95% CrI excluding zero, so there was no clear evidence that any treatments were beneficial in reducing nocturia (Figure 12; Table 7). The advantage of an NMA in this situation may not be particularly large due to the star-shaped network. However, the corresponding pairwise meta-analyses suggested favourable results for behavioural therapy, PDE5 inhibitors and PPS (Figure 12; Table 7). One of the two comparisons with at least two studies was associated with important heterogeneity ($I^2 > 50\%$). There was again only a single closed loop within the network, but there were no concerns about inconsistency (P value for interaction = 0.10).

Figure 12. Meta-analysis results for nocturia (number of nighttime voids). For each treatment category, the unbroken horizontal line represents the mean difference (95% CrI) in number of nighttime voids versus control from the network meta-analysis, and the dotted line represents the mean difference (95% CI) versus control from the pairwise meta-analysis (if applicable). The number of studies included in each analysis is also shown.



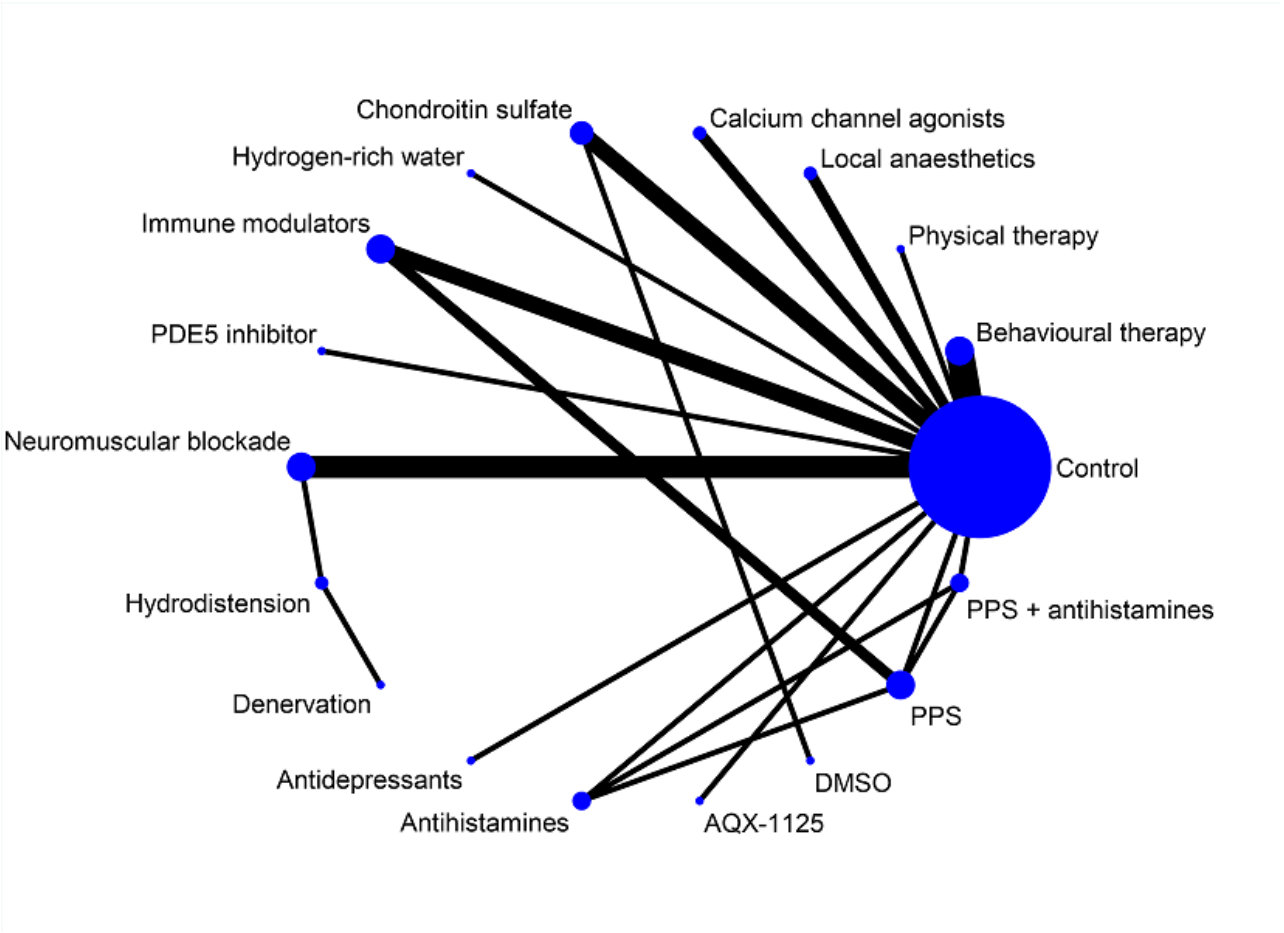
Secondary outcomes

Subjective symptom measures (combining frequency, nocturia and pain)

Although studies reported symptoms in a variety of ways, we included only data for the Interstitial Cystitis Symptom Index (ICSI) subscale because this was the most commonly reported subjective measure across trials. On the ICSI subscale, 0 represented the lowest possible and 20 the highest possible severity of symptoms. We did not include studies that reported the ICSI and Interstitial Cystitis Problem Index (ICPI) Scales combined.

The network diagram for the ICSI outcome is shown in Figure 13. Compared with other outcomes, the number of connections between treatments was relatively high, although most treatments were compared to control. Eighteen studies contributed final score data, and 12 studies (including Sant 2003, a four-arm trial) contributed change score data. Evidence from the NMA suggests that PDE5 inhibitors reduced symptoms by around 6 points on a 0 to 20 scale (MD -6.02, 95% CrI -9.05 to -2.93) (Table 8).

Figure 13. Network diagram for subjective symptom measures (combining frequency, nocturia and pain) - ICSI. The thickness of each line is proportionate to the number of included studies.



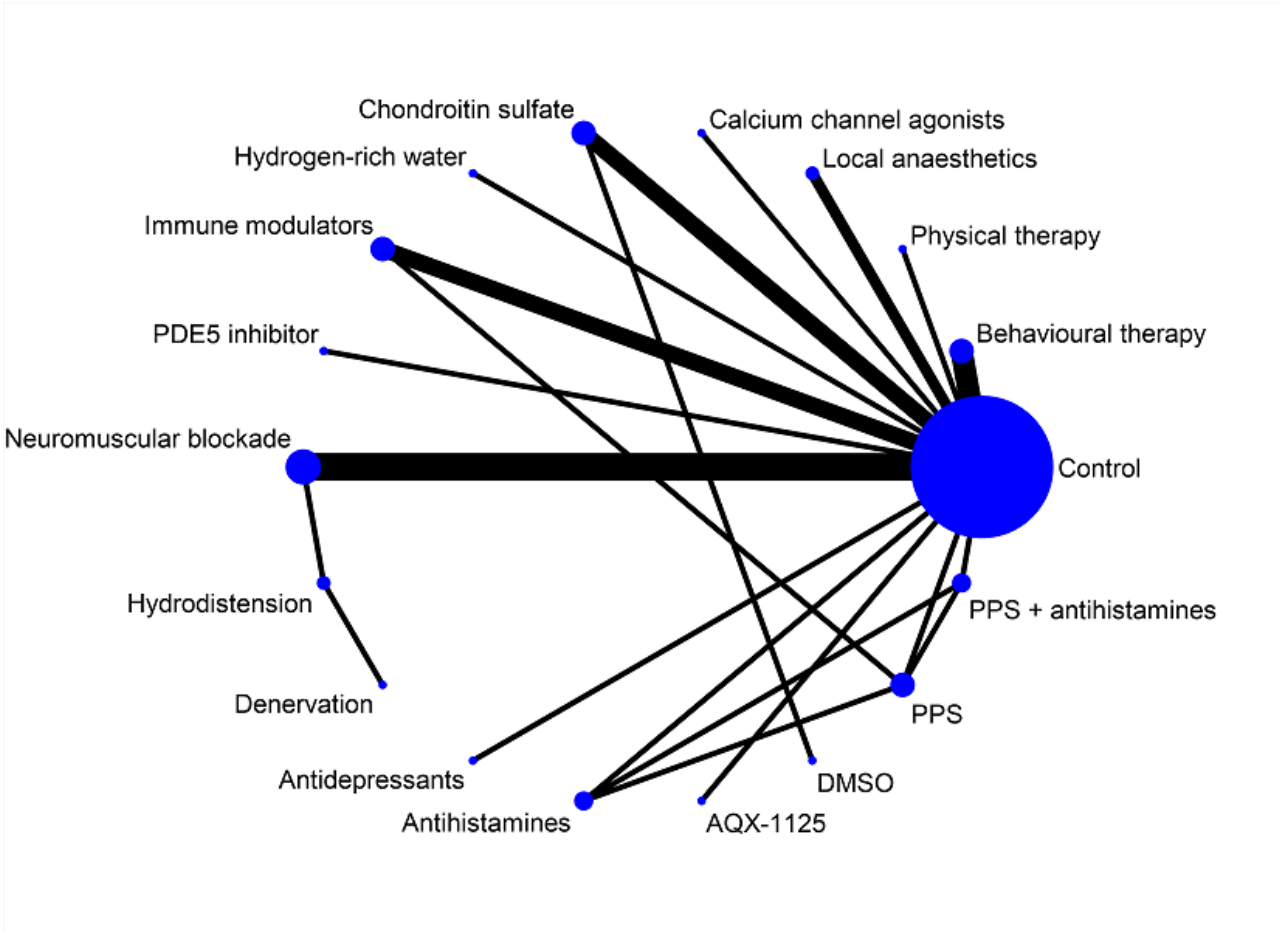
The pairwise meta-analyses also suggested benefits for antidepressants and for AQX-1125 (Table 8).

Quality of life (including symptom bother)

We included only studies that had reported the ICPI subscale because it was the most commonly reported quality of life measure across trials. In ICPI, scores of 0 represented the highest possible quality of life and scores of 16 the lowest possible quality of life.

The network diagram for the ICPI diagram was the same as that for ICSI but with a slightly reduced number of trials involved (Figure 14). Eighteen studies contributed final score data, and 10 studies contributed change score data.

Figure 14. Network diagram for quality of life - ICSI. The thickness of each line is proportionate to the number of included studies.



There was no clear evidence from the NMA suggesting that any treatment category was effective in reducing quality of life as measured by this scale (Table 9). The corresponding pairwise meta-analyses suggested benefits for four additional treatments: local anaesthetics; PDE5 inhibitors; antidepressants; and AQX-1125.

Functional bladder capacity (descriptive statistics)

Limited data were available for the outcome of functional bladder capacity, and no meta-analyses were performed because of variation in the way this outcome was reported across studies (Table 10). In general, differences in mean between groups, or changes in mean from baseline in each group, appear small and were in the range of 30 mL or less. Although not empirically tested, it has been suggested that an increase in bladder capacity of 30 mL may not be clinically relevant (Hanno 2017). A slightly larger difference between groups (from about 40 to 60 mL in terms of MD) was observed in one trial comparing immune modulator (bacillus Calmette-Guérin (BCG)) and control (Irani 2004), as well as in two further trials comparing neuromuscular blockade versus control (Kuo 2009; Manning 2014), but reported P values (0.165, 0.05 and 0.27, respectively) indicate that there is no evidence of a difference between treatment groups.

Adverse events

Table 11 shows the number of participants experiencing at least one adverse event. Classifications and definitions of adverse events were described as reported by trial investigators and were not directly comparable across studies. In many cases, trial authors grouped adverse events under the broad categories of 'adverse events' or 'serious adverse events' without specifying the types of events. Due to variation in the way in which adverse events were reported, we were unable to conduct meta-analyses.

Although a large number of participants experienced one or more adverse event in most trials, these events were reported to be primarily mild to moderate in severity, and the treatments under study were reported to be reasonably well tolerated, with similar percentages of participants between groups experiencing undesirable effects.

Some trials reported relatively more adverse events with intervention than with control. Warren 2000 reported that adverse events occurred in 80% (20 out of 25) of participants taking antibiotics compared with 40% (10 of 25) taking placebo, with nausea and/or vomiting the most common event category. This led to discontinuation of 10 courses of antibiotics due to perceived adverse events, compared with two in the placebo group (reported P value of 0.018). van Ophoven 2004 reported a higher incidence

of anticholinergic side effects, particularly mouth dryness, in the group taking an antidepressant (amitriptyline) compared with the placebo group (92% (22 of 24) versus 21% (5 of 24)), although the reported events were not considered by trialists to be severe (grade 3 or higher). Kuo 2016 reported significantly more adverse events in the group that received botulinum toxin A compared with the control group (dysuria was the most common adverse event), although these adverse events were judged to be manageable and acceptable. In Sairanen 2005, there were more adverse events in the immune modulator (cyclosporin A) group than in the PPS group (94% (30 of 32) versus 56% (18 of 32)), but withdrawals were reported to be similar in both study arms. In five trials comparing calcium channel agonists (e.g. capsaicin, resiniferatoxin) versus control, pain during instillation was commonly reported among participants in the intervention group (Chen 2005; Ham 2012; Lazzeri 1996; Lazzeri 2000; Payne 2005).

The number of participants experiencing serious adverse events is shown in Table 12. Definitions of serious adverse events were those reported by trial investigators. Overall, serious adverse events appear uncommon (≤ 3% within the study group). In trials where a greater number of serious adverse events were reported (possibly due to different definitions used), overall event rates appear similar between study arms.

For example, in one trial comparing immune modulators (BCG) and placebo (Mayer 2005), rates of 'severe' events (defined as grade 3 on the Common Toxicity Criteria) were 50% (64 of 129) in the treatment group and 48% (63 of 132) in the placebo group. This study also reported a total of 32 'serious' adverse events in 21 participants, although the number in each group was not reported. Two of these were associated with the study drug (BCG hypersensitivity reaction in one patient in the BCG group, and prostatitis and urinary tract infection (UTI) in one patient in the placebo group).

Nickel 2009 reported that 'severe' adverse events were experienced by 8% (4 of 50) and 10% (5 of 52) of participants receiving local anaesthetic (PSD597, intravesical alkalised lidocaine) and placebo, respectively. The most common event was bladder pain, which usually resolved within a day of instillation.

Evans 2011 reported 'serious' adverse events in 7% (2 of 29) of participants treated with immune modulator and in 20% (4 of 20) of those who received placebo. Events associated with immune modulator treatment included 'vertigo' and 'drug exposure during pregnancy', and 'cholelithiasis', 'ovarian mass', 'urosepsis/urinary tract infection' and 'transient ischaemic attack' were associated with placebo.

DISCUSSION

Summary of main results

Results of the network meta-analysis (NMA) suggest that the following treatment categories appear effective versus control for treatment of bladder pain syndrome (BPS), although a degree of caution is required in interpreting these results because of the small number of studies and the wide credible intervals.

Primary outcomes (level of certainty)

- Proportion cured or improved: behavioural therapy (very low), physical therapy (very low), antidepressants (very low), immune modulators (very low), phosphodiesterase-5 (PDE5) inhibitors (very low) and neuromuscular blockade (very low)
- Pain: physical therapy (moderate)
- Frequency: neuromuscular blockade plus dimethyl sulfoxide (DMSO) (moderate)
- Nocturia: no evidence from the NMA that any treatment category was effective

Secondary outcomes

- Interstitial Cystitis Symptom Index (ICSI): PDE5 inhibitors
- Interstitial Cystitis Problem Index (ICPI): no evidence from the NMA that any treatment category was effective

Because relatively few trials compared two non-control treatments, the benefit of using an NMA approach for some outcomes may have been relatively small, and this method may have produced results that were more conservative than the corresponding pairwise meta-analysis results. The results of these were generally consistent with the NMA, but as confidence intervals (CIs) tended to be slightly narrower, a wider range of treatments had CIs that excluded the null effect.

For the proportion of participants who were cured or improved, the point estimate for the odds ratios (ORs) for treatment versus control was generally above two, suggesting large effects that could perhaps be considered clinically important. However, credible intervals (CrIs) were very wide, reflecting that only a small number of studies were available for each comparison, and that sample sizes for included studies were generally small. For most treatments, the CrI also included values that were within the range specified as unlikely to be clinically important for our review (0.8 to 1.25). Similar findings were observed for continuous outcomes.

A descriptive analysis based on limited available data for assessment of functional bladder capacity suggests a relatively small difference between study arms. This difference is unlikely to be clinically relevant.

In general, treatments under investigation were reported to be reasonably well tolerated, and adverse events were usually reported to be mild or moderate in severity. Serious adverse events appear relatively uncommon for all interventions under investigation. As information on adverse events is limited, and given that adverse events were reported in various ways, we could not meta-analyse results or assess certainty of the evidence.

Overall completeness and applicability of evidence

This review included 81 randomised controlled trials (RCTs) involving a total of 4674 participants. A majority of studies were parallel-arm trials with a small sample size (median 38) and short follow-up (median three months). Six studies were cross-over RCTs. The included studies evaluated 31 active treatment categories (grouped by mode of action). The most commonly evaluated treatment categories were immune modulators (e.g. bacille Calmette-Guérin (BCG), tanezumab) in 15 studies (Bosch 2014; Dimitrakov 2001; Evans 2011; Irani 2004; Mayer 2005; Nickel 2016; Oliver 2013; Peeker 2000; Peters 1997; Sairanen 2005; Sairanen 2009; Shirvan 2015; Taha 2007; Wang 2017a; Yang 2011); neuromuscular blockade in 13 studies (e.g. onabotulinumtoxinA) (Ahmadnia 2011; Chuang 2017; Gottsch 2011; Ismail 2016; Kasyan 2012; Kuo 2009; Kuo 2016; Manning 2014; Mirkin 2012; Payne 2014;

Pinto 2016; Taha 2007; Yassin 2011); calcium channel agonists in seven studies (e.g. capsaicin, resiniferatoxin (RTX)) (Chen 2005; Ham 2012; Kim 2012; Lazzeri 1996; Lazzeri 2000; Nickel 2012b; Payne 2005); DMSO in six studies (Cervigni 2014; De Ridder 2013; Peeker 2000; Perez-Marrero 1988; Sairanen 2009; Singh 2003); and pentosan polysulfate (PPS) in six studies (Bade 1997; Davis 2008; Mulholland 1990; Nickel 2015; Sairanen 2005; Sant 2003). However, most treatment categories were assessed only in single trials. Study participants had various diagnoses including interstitial cystitis (IC), bladder pain syndrome (BPS), painful bladder syndrome (PBS) and painful bladder disease (PBD). It is worth noting that although there is significant overlap, these clinical diagnoses are not identical. This reflects the fact that the aetiology of BPS and validated diagnostic criteria have yet to be established.

We did not impose any language or other limitations on the literature search, which should help ensure overall completeness of the evidence. A further updated search of the Cochrane Incontinence Specialised Register was undertaken on 5 June 2019. Of the 45 records retrieved by the search, 15 reports of 14 studies appeared to meet the inclusion criteria for this evidence synthesis: five reports of four new studies; three additional reports of three already included studies; and seven trial registrations of seven ongoing studies. The four new studies were all small (ranging from 15 to 42 participants) (Aboyan 2018; Bosch 2018; Cervigni 2018; Oh-Oka 2017). Only one of these studies covered one of the comparisons included in our NMA (hyaluronic acid alone compared with hyaluronic acid in combination with chondroitin sulphate) (Aboyan 2018). Further details are given in the Characteristics of studies awaiting classification table. None of these study reports have been incorporated into the current evidence synthesis.

A strength of this work is that we have been able to assess all treatments for BPS, including many different conservative, pharmacological and surgical interventions, within a single analysis. NMA is a relatively new method that is well suited to this type of evidence synthesis, wherein a large number of trials evaluate a large number of treatments. Its key advantage is that it can incorporate both direct and indirect evidence between each pair of treatments.

Nevertheless, the limited number of small trials available for each treatment category hindered our ability to fully exploit the advantages of NMA. This was compounded by the fact that most treatments were compared with placebo or control, sometimes resulting in a so-called ‘star-shaped’ network. Consequently, CrIs tended to be wide, indicating great uncertainty in effect estimates. There were also some differences in results of the pairwise meta-analyses. These more conservative results from NMA are not unexpected when the network is mainly star-shaped and there are few connections between pairs of non-control treatments (Filippini 2013).

We did not compare pairs of active treatments directly because there were too many combinations of treatments and the degree of uncertainty was considerable. A small number of treatments could not be assessed because they were disconnected from the rest of the network. We also decided not to use the NMA to rank treatments. It was difficult to assess the consistency assumption of the NMA due to the small number of closed loops within most networks, which meant that we were generally unable to compare the evidence from direct and indirect estimates of effect to check that these were consistent.

A further methodological challenge was that definitions of treatments and reported outcomes were heterogeneous across trials. We grouped treatments into broad categories, and within these there was often variation in types of treatments and how these were delivered. Some trials evaluated two treatments delivered in combination, and incorporating these into the analyses was sometimes challenging. Finally, we included a range of therapies that may be considered either first- or second-line treatments but did not consider this in our analyses. The populations of included participants in each trial may have differed in terms of symptom severity. An assumption of the NMA is that included patients could be randomised to any of the treatments, but in practice this may not have been the case.

No common single outcome was assessed by all included trials. Outcomes that were conceptually similar were measured in different ways. For example, pain was reported as measured by different scales or assessment tools. Continuous outcomes were reported as mean scores at last follow-up or as mean changes from baseline, and very few studies reported data in both formats. Outcome definitions were often unclear or ambiguous, and standard deviations (SDs) and denominators were not always provided. Considerable additional work was required to make extracted data suitable for the statistical analyses. Despite this additional effort, a sizeable number of studies often provided no usable data.

For the small number of cross-over trials that provided usable data, we used data from the first period only, as none provided information to approximate a paired analysis. This may have introduced bias and loss of precision, but the impact is likely to be small.

Although Cochrane recommends using final scores rather than change scores for continuous outcomes, roughly half of the included studies reported only change scores. We were successful in incorporating both types in the meta-analyses, but this complicated the analysis. We were able to utilise National Institute for Health and Care Excellence Decision Support Unit (NICE DSU) programmes that allowed data as both change and final scores, as well as multi-arm trials, to be used.

Another limitation of this work is that no subgroup analyses nor sensitivity analyses were carried out. Due to the multi-factorial aetiology of BPS, which is yet to be established, heterogeneity of the trial populations was anticipated, but we were not able to identify specific sources of heterogeneity worthy of further exploration. Future updates of this review could consider subgroup analyses or network meta-regression, if possible, and could consider a sensitivity analysis to explore the effect of including studies with high risk of bias.

Clinical characteristics of study participants included BPS with Hunner's lesions (classic diagnosis of IC). However, in most of the included studies, results were not reported separately for this subgroup. Therefore, we are not in a position to comment on the applicability of findings to patients with or without Hunner's lesions, who may show different responses to treatment.

Quality of the evidence

We assessed the overall certainty (quality) of evidence for the primary outcomes using the GRADE approach as modified for

network meta-analysis (Salanti 2014), via the CINeMA 2017 web application. The overall certainty of evidence was moderate at best, and was low or very low for most outcomes. Evidence level was most often downgraded for within-study risk of bias, imprecision and heterogeneity. The quality of reporting was insufficient in most trial reports included in the review, and this may have contributed to downgrading of the certainty of evidence. However, these assessments may be conservative, as they were dependent on the choice of minimal clinically important difference (MCID) and subjective judgements in interpreting CINeMA guidance to enable GRADE assessment.

Potential biases in the review process

Although two review authors independently assessed the eligibility of published trial reports for inclusion in this review, data extraction and risk of bias assessment were carried out by one review author and were checked by another review author. The GRADE assessment of the certainty of evidence was conducted by two review authors working together, not independently, reaching consensus in discussion. This was a pragmatic decision due to resource constraints and may carry some risk of bias.

Agreements and disagreements with other studies or reviews

To the best of our knowledge, this review represents the first comprehensive assessment of published evidence for all interventions for BPS evaluated in RCTs. A narrative systematic review on interventions for BPS and IC published in 2016 identified the lack of high-level evidence in this area, as well as clinical and methodological heterogeneity in published studies (Pazin 2016), which is in line with the findings of the current review.

Recent systematic reviews of RCT evidence focused on individual interventions including PPS and onabotulinumtoxinA (Lee 2019; van Ophoven 2019). Other recent systematic reviews incorporating non-randomised evidence also focused on specific interventions such as cyclosporin A (Wang 2016); intravesical therapy (Barua 2016); intravesical hyaluronic acid with chondroitin sulfate (Pyo 2016); hydrodistension (Olson 2018); sacral modulation (El-Azab 2019; Wang 2017b); and complementary therapy (Verghese 2016). These reviews found only limited efficacy and pointed to a small evidence base and diversity in study populations, interventions and outcome measures, as well as insufficient descriptions of study methods used, which hindered further assessment to identify effective treatment options for BPS.

AUTHORS' CONCLUSIONS

Implications for practice

This review includes evidence from direct and indirect comparisons of existing treatments for BPS. These range from conservative treatments to surgical interventions. Very low-certainty evidence suggests that behavioural therapy, physical therapy, antidepressants, immune modulators, PDE5 inhibitors and neuromuscular blockade may be effective in treating some, if not all, of the symptoms of BPS. However, due to limitations of the current evidence base, it is difficult to identify treatments that are superior to others.

Until further evidence for therapies for managing and treating pelvic floor dysfunction becomes available, developing a multi-disciplinary model of care, which involves not only the clinicians who traditionally treat BPS but also other professionals (including physical therapists, psychotherapists, pain management specialists and clinicians from other specialties) when non-bladder symptoms or disorders, as well as patient support groups, are part of the clinical picture, seems to be the best way forward.

Implications for research

An attempt to harmonise definitions and measurement tools across research groups would be useful, as would the use of tools that capture patient-reported outcomes. In particular, a definition of pain and the way to measure it should be clearly reported in future studies.

It is worth noting that BPS remains an unclear and controversial condition with unknown aetiology and no accepted diagnostic markers. Future research designed to better understand this clinical condition and consequently manage patients more effectively is clearly needed. In particular, there is a need to understand the pathophysiological processes involved in BPS and how these interrelate with chronic pelvic pain syndromes, and to identify both systemic and bladder-specific biomarkers (e.g. nerve growth factors, angiogenic growth factors, cytokines chemokine profiles). Better clinical phenotyping of BPS patients would allow health professionals to tailor specific treatments to individual patients. For trials that focus on BPS patients, it would be helpful to analyse data from patients with Hunner's lesion and from those with non-lesion disease separately, as these two groups of patients may respond differently to treatment.

According to the 6th International Consultation on Incontinence (Hanno 2017), as well as the US Food and Drug Administration (FDA) Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) 2018 criteria for IC/BPS (Nickel 2018), future research should cover the following clinical areas.

- Pathology of BPS.
- Biomarker development.
- Immunology of BPS.
- Neurological aspects, with particular attention to the relationship of BPS and overactive bladder.
- The relationship of bladder pain syndrome to chronic pelvic pain syndrome (non-bacterial prostatitis).
- Expanded definitions of bladder pain developed with the patient.
- Input, to include burning, pressure and discomfort.
- Validated patient-reported outcome instruments as recommended when the efficacy of drugs for treatment of patients with symptoms of BPS is assessed.
- Development of a simple, non-invasive diagnostic test for BPS.
- Development of a multi-disciplinary care model.

In addition, patient-relevant outcomes should be used in future trials for assessing interventions for BPS. Large, high-quality trials assessing specific interventions or comparisons of interventions with longer follow-up are needed. Current small trials testing numerous different interventions may be considered as research waste if they do not yield clinically useful knowledge. It is clear that researchers need to perform sample size calculations to ensure

that studies have appropriate statistical power to answer research questions.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahmadnia 2011

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 1

Ahmadnia 2011 *(Continued)*

Participants	**Number randomised:** 24 **Setting:** not reported **Country:** Iran **Sex:** female **Age, years:** not reported **Diagnosis:** PBS **Inclusion criteria:** patients (female) with painful bladder syndrome refractory to conventional oral therapies **Exclusion criteria:** not reported
Interventions	**Group A (n = 12):** 200 IU botulinum toxin A into trigone and lateral walls **Group B (n = 12):** NaCl **Treatment category in NMA:** neuromuscular blockade vs control
Outcomes	Outcome data in analysis (no usable data)
Funding	Not reported.
Notes	**Publication status:** abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly divided"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned. "Under short general anesthesia in the study group botulinum toxin A … was used, and in the control group, normal saline was injected through cystoscopic needle submucosally into trigone and lateral walls of the bladder"
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	Blinding not mentioned. "Under short general anesthesia in the study group botulinum toxin A … was used, and in the control group, normal saline was injected through cystoscopic needle submucosally into trigone and lateral walls of the bladder"
Selective reporting (reporting bias)	Unclear risk	Outcomes not specified in Methods (abstract only)
Other bias	Low risk	None detected

Bade 1997

Study characteristics

Methods	**Study design:** RCT

Bade 1997 *(Continued)*

	Study duration (months): 3
Participants	**Number randomised:** 20 **Setting:** 1 hospital **Country:** the Netherlands **Sex:** female **Age, years:** mean 52.8, range 24 to 79 **Diagnosis:** IC (NIDDK criteria) **Inclusion criteria:** patients with IC **Exclusion criteria:** not reported
Interventions	**Group A (n = 10):** pentosan polysulfate (PPS) **Group B (n = 10):** unspecified placebo Three months of twice-weekly instillations; each instillation for as long as tolerable **Treatment category in NMA:** PPS vs control
Outcomes	Outcome data in analysis Cure or improvement: improved subjective symptoms using visual analogue scale (1 point or greater reduction on the severity scale scoring 0 to 5 points): at 3 months Frequency: at 3 months Nocturia: at 3 months
Funding	Not reported
Notes	**Publication status:** full text [Notes from previous versions of the review] Attempted study author contact regarding SD for data, pain as outcome and who had UTI; received no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "assigned randomly using a code... After receiving treatment for 3 months, the code was broken..."
Allocation concealment (selection bias)	Unclear risk	Quote: "assigned randomly using a code... After receiving treatment for 3 months, the code was broken..." Comment: unclear if this refers to blinding or allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind, placebo-controlled study". Placebo not described
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	"double-blind, placebo-controlled study". Placebo not described

Bade 1997 *(Continued)*

Incomplete outcome data (attrition bias) Cure or improvement	Unclear risk	Number analysed not stated
Incomplete outcome data (attrition bias) Frequency	Low risk	9/10 (90%) included in intervention group (1 dropped out due to persisting symptoms); 10/10 included in control group
Incomplete outcome data (attrition bias) Nocturia	Low risk	9/10 (90%) included in intervention group (1 dropped out due to persisting symptoms); 10/10 included in control group
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Barbalias 2000

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 6
Participants	**Number randomised:** 36 **Setting:** not reported **Country:** Greece **Sex:** female **Age, years:** mean 45, range 26 to 69 **Diagnosis:** IC (NIDDK criteria) **Inclusion criteria:** women with diagnosis of IC **Exclusion criteria:** not reported
Interventions	**Group A (n = 24):** oxybutinin (10 mg tablets dissolved in 500 mL saline) **Group B (n = 12):** saline alone Filling to point of first desire to void. Catheter then clamped and released when at functional capacity. Further single days of treatment, weekly for 6 weeks, then monthly for 3 months. One week of inpatient treatment involving repeated cycles of bladder filling **Treatment category in NMA:** anticholinergics vs control
Outcomes	Outcome data in analysis Frequency: at 6 months
Funding	Not reported
Notes	**Publication status:** full text [Notes from previous versions of the review] Attempted study author contact re SD for data, pain as outcome, details of dropouts; received no response

Barbalias 2000 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "in a randomized fashion by computer assigned numbers"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned. "In the control group the bladder was filled only with normal saline and the same protocol guidelines were maintained as in the oxybutynin group". Intravesical instillation
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	Blinding not mentioned. "In the control group the bladder was filled only with normal saline and the same protocol guidelines were maintained as in the oxybutynin group". Intravesical instillation
Incomplete outcome data (attrition bias) Frequency	Unclear risk	Number analysed unclear. 1/24 dropped out from intervention group; 4/12 dropped out from control group; it is not clear how missing data were handled
Selective reporting (reporting bias)	Unclear risk	"Clinical amelioration" (cure) was defined but not fully reported in results
Other bias	Unclear risk	None detected

Bosch 2014

Study characteristics

Methods	**Study design:** RCT **Study duration (months):** 3
Participants	**Number randomised:** 43 **Setting:** single centre **Country:** USA **Sex:** 34 females and 9 males **Age, years:** mean 45.2 (SD 14.0) for Group A, mean 46.5 (SD 13.4) for Group B **Diagnosis:** IC/BPS, moderate to severe **Inclusion criteria:** men and women 18 to 65 years old, previously diagnosed with moderate or severe IC/BPS. Fulfilment of certain criteria including symptoms of urinary urgency, frequency or pain longer than 6 months, urinating at least 7 times a day, total score of 18 or greater on the OSPI and score of 15 or greater on the PUF **Exclusion criteria:** microbiologically proven urinary tract infection within 6 weeks at screening or randomisation; gross haematuria; intravesical therapy a month before or during the study; and/or history of malignancy, diabetes, central nervous system demyelinating disease, tuberculosis, hepatitis B, hepatitis C or human immunodeficiency disease. Female patients must not have been pregnant or lactating and must have used adequate birth control during the study. History and physical examination, comprehensive metabolic chemistry panel, complete blood count, urinalysis and culture, hepatitis B virus serology and a purified protein derivative skin test were also required

Bosch 2014 *(Continued)*

Interventions	**Group A (n = 21):** subcutaneous adalimumab. 80 mg loading dose, followed by 40 mg every 2 weeks **Group B (n = 22):** subcutaneous placebo Participants were allowed to continue on current medications except medications listed in the exclusion criteria **Treatment category in NMA:** immune modulators vs control
Outcomes	Outcome data in analysis Cure or improvement: 'moderately' or 'markedly' improved on GRA: at 12 weeks ICSI: at 12 weeks ICPI: at 12 weeks Adverse events: at 12 weeks (assumed from paper)
Funding	AbbVie (pharma business)
Notes	**Publication status:** full text The study was terminated early 'after half of the 43 patients demonstrated a dramatic and statistically significant clinical improvement'

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	Quote: "randomised in blinded fashion" Comment: unclear whether this refers to blinding or allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "'double blind"; "the study drug and placebo were provided in ready to use unit dose syringes that were identical"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	"double blind", using identical placebo
Incomplete outcome data (attrition bias) Cure or improvement	Unclear risk	Number analysed unclear. 2/21 dropped out from intervention group (due to "lack of efficacy"); 2/22 dropped out from placebo group (medical reasons unrelated to trial); it is not clear how missing data were handled
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Unclear risk	Number analysed not stated
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Unclear risk	Number analysed not stated

Bosch 2014 *(Continued)*

Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Number analysed not stated
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Carrico 2008

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 2
Participants	**Number randomised:** 30 **Setting:** single centre **Country:** USA **Sex:** female **Age, years:** average 44 **Diagnosis:** IC **Inclusion criteria:** women with IC **Exclusion criteria:** not reported
Interventions	**Group A (n = 15):** guided imagery. Listen to a 25-minute CD twice a day for 8 weeks **Group B (n = 15):** rest for 25 minutes twice daily for 8 weeks **Treatment category in NMA:** behavioural therapy vs control
Outcomes	Outcome data in analysis Cure or improvement: ‘moderately' or 'markedly’ improved on GRA: at 8 weeks Pain: VAS (assumed range 0 to 10): at 8 weeks ICSI: at 8 weeks ICPI: at 8 weeks
Funding	Ministrelli Program for Urology Research and Education (MPURE)
Notes	**Publication status:** full text

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomized … by drawing from a shuffled set of folders that included hidden notations of "Treatment group" or "Control group""

Carrico 2008 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "randomized by a blinded research staff member not involved in the study by drawing from a shuffled set of folders that included hidden notations of "Treatment group" or "Control group""
Blinding of participants and personnel (performance bias) All outcomes	High risk	Probably not done. 25-minute guided imagery compact disc vs sitting or lying down for 25 minutes
Blinding of outcome assessment (detection bias) Subjective outcome	High risk	Probably not done. 25-minute guided imagery compact disc vs sitting or lying down for 25 minutes
Incomplete outcome data (attrition bias) Cure or improvement	High risk	11/15 (73%) included in intervention group; 14/15 (93%) included in control group. 5 withdrew "for personal reasons (too busy, not able to follow protocol)"
Incomplete outcome data (attrition bias) Pain	High risk	11/15 (73%) included in intervention group; 14/15 (93%) included in control group. 5 withdrew "for personal reasons (too busy, not able to follow protocol)"
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	High risk	11/15 (73%) included in intervention group; 14/15 (93%) included in control group. 5 withdrew "for personal reasons (too busy, not able to follow protocol)"
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	High risk	11/15 (73%) included in intervention group; 14/15 (93%) included in control group. 5 withdrew "for personal reasons (too busy, not able to follow protocol)"
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Cartledge 2000

Study characteristics	
Methods	**Study design:** cross-over randomised trial **Study duration (months):** 1
Participants	**Number randomised:** 16 **Setting:** not reported **Country:** UK **Sex:** 12 females and 4 males **Age, years:** mean 51, range 26 to 76 **Diagnosis:** IC (NIDDK criteria) **Inclusion criteria:** male or female with IC by NIDDK criteria **Exclusion criteria:** history of diabetes or liver disease

Cartledge 2000 *(Continued)*

Interventions	**Group A:** L-arginine, given as capsules containing 400 mg of active compound, at a total dose of 2.4 grams/d **Group B:** an inert placebo, in identical capsules Number in each group not reported **Treatment category in NMA:** amino acid vs control
Outcomes	Outcome data in analysis (no usable data)
Funding	Not reported
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled crossover trial"; "an inert placebo, in identical capsules, was..."
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Carty 2017

Study characteristics

Methods	**Study design:** RCT **Study duration (months):** 1.5
Participants	**Number randomised:** 70 **Setting:** single centre **Country:** USA **Sex:** female **Age, years:** mean 46.03 (SD 15.10) for whole group, mean 44.89 (SD 15.34) for Group A, mean 47.72 (SD 14.88) for Group B **Diagnosis:** "chronic urogenital pain" **Inclusion criteria:** women with chronic urogenital pain conditions; 18 to 80 years old **Exclusion criteria:** patients who (a) had a current psychotic disorder; (b) were unable to communicate in English; (c) were unable to read; (d) were cognitively impaired or had dementia; or (e) were deemed too psychiatrically unstable by their clinician at the Women's Urology Center to meaningfully complete

Carty 2017 *(Continued)*

	this study. Participants were allowed to engage in the study regardless of current medication use and engagement in other treatment
Interventions	**Group A (n = 45):** 90-minute life stress interview (stress and emotion interview) **Group B (n = 20):** wait-list control (no interview) **Treatment category in NMA:** behavioural therapy vs control
Outcomes	Outcome data in analysis Pain: Brief Pain Inventory pain severity subscale; average of 4 items ranking pain on a scale ranging from 0 to 10: at 6 weeks
Funding	Not reported
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Probably not done. Interview vs wait-list Quote: "both the interviewer and participant were blinded to condition until baseline measures were completed"
Blinding of outcome assessment (detection bias) Subjective outcome	High risk	Probably not done. Interview vs wait-list Quote: "both the interviewer and participant were blinded to condition until baseline measures were completed"
Incomplete outcome data (attrition bias) Pain	High risk	37/45 (82%) included in intervention group (8 did not receive intervention) and 25/25 included in control group. 4/25 (16%) in control group did not "complete their follow-up evaluation", but it is unclear how missing data were handled
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Cervigni 2014

Study characteristics

Methods	**Study design:** RCT **Study duration (months):** 6
Participants	**Number randomised:** 110 **Setting:** 6 centres

Cervigni 2014 *(Continued)*

	Country: Italy **Sex:** female **Age, years:** mean 50.2, range 18 to 88 **Diagnosis:** BPS/IC. Diagnosis according to European Society for the Study of IC/PBS (ESSIC) criteria **Inclusion criteria:** patients aged 18 years or older with a diagnosis of BPS/IC, unresponsive to first-line non-invasive treatment (e.g. oral drugs considered to be a standard treatment for BPS/IC, such as antidepressants, antiepileptics, antihistaminics, cyclosporin A, pentosan polysulfate) or at first observation. Relevant inclusion criteria included the presence of pain (pelvic, pressure or discomfort) with at least 1 other urinary symptom such as urgency, increased urination frequency for at least 6 months, discomfort or pain during sexual intercourse **Exclusion criteria:** pregnant or breastfeeding women, presence of other confusable disease as the main cause of urinary symptoms, those who had undergone previous intravesical treatments. A minimum time of 3 months from last treatment to start of therapy was required for all patients
Interventions	**Group A (n = 74):** iAluRil® **Group B (n = 36):** DMSO (dimethyl sulfoxide) **Treatment category in NMA:** chondroitin sulfate + hyaluronic acid vs DMSO
Outcomes	Outcome data in analysis Cure or improvement: at least 50% VAS reduction in pain from baseline: at 6 months Pain: VAS (range 0 to 100): at 3 months Frequency: at 3 months ICSI: at 6 months ICPI: at 6 months Functional bladder capacity: at 3 months Adverse events: at 6 months
Funding	Sponsored by IBSA Farmaceutici Italia. This assistance was funded by IBSA Institut Biochimique SA
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a centralized randomization procedure was generated by the Moses-Oakland algorithm"
Allocation concealment (selection bias)	Low risk	Quote: "a centralized randomization procedure"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"An open-label design"; "due to the garlic-like taste of DMSO after intravesical administration, which would have been impossible to mask"
Blinding of outcome assessment (detection bias) Subjective outcome	High risk	"An open-label design"; "due to the garlic-like taste of DMSO after intravesical administration, which would have been impossible to mask"

Cervigni 2014 *(Continued)*

Blinding of outcome assessment (detection bias) Objective outcome	Low risk	Outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Cure or improvement	High risk	Review authors chose to use per-protocol analysis. 66/74 (89%) included in HA/CS (hyaluronic acid + chondroitin sulfate) group; 27/36 (75%) included in DMSO group
Incomplete outcome data (attrition bias) Pain	High risk	Review authors chose to use per-protocol analysis. 66/74 (89%) included in HA/CS group; 27/36 (75%) included in DMSO group
Incomplete outcome data (attrition bias) Frequency	Low risk	59/74 (80%) included in HA/CS group; 31/36 (86%) included in DMSO group
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Low risk	73/74 (99%) included in HA/CS group; 36/36 (100%) included in DMSO group
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Low risk	73/74 (99%) included in HA/CS group; 36/36 (100%) included in DMSO group
Incomplete outcome data (attrition bias) Functional bladder capacity	Low risk	44/74 (59%) included in HA/CS group; 25/36 (69%) included in DMSO group
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Chen 2005

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 3
Participants	**Number randomised:** 22 **Setting:** multi-centre **Country:** Canada **Sex:** 17 females and 5 males **Age, years:** mean 43.7 for Group A, mean 56.6 for Group B; range 18 to 85 for whole group **Diagnosis:** IC (NIDDK criteria)

Chen 2005 *(Continued)*

	Inclusion criteria: patients on medication to control irritative symptoms, provided dosage had not changed within the 30 days leading to the study. No dosage change was permitted during the protocol **Exclusion criteria:** pregnant or nursing, or other pathologies of the lower urinary tract (infection, detrusor overactivity and urologic manifestation of neurological disease), ulcerative IC, intravesical therapy or bladder hydrodistension 6 weeks before, current or previous malignancy, known chemical addiction, seizure or major psychiatric disorder, pertinent allergy, significant medical condition
Interventions	**Group A (n = 18):** 2 arms combined for this review. Arm 1: resiniferatoxin (RTX) 0.05 microMol/L solution in 10% ethanol in saline. Arm 2: RTX 0.1 microMol/L in 10% ethanol in saline **Group B (n = 4):** 10% ethanol in saline (placebo) All 3 trial arms had the option of 10 minute pre-treatment instillation of 2% lidocaine. Single-instillation treatment of 50 mL of solution retained for 30 minutes. Bladder then rinsed with saline **Treatment category in NMA:** calcium channel agonists vs control
Outcomes	Outcome data in analysis Pain: VAS (assumed range 0 to 10): at 12 weeks Frequency: at 12 weeks Nocturia: at 12 weeks ICSI: at 12 weeks ICPI: at 12 weeks Adverse events: at 12 weeks
Funding	Not reported
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized via a computer generated randomization schedule"
Allocation concealment (selection bias)	Low risk	Quote: "the size of the randomization block was not disclosed. Bliniding information was contained in sealed envelopes …. Breaking the blind was permitted only on a case-by-case basis and only in the event of an emergency"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind, placebo-controlled study". Solutions used for intervention and placebo groups "were identical in appearance"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	"double-blind, placebo-controlled study". Solutions used for intervention and placebo groups "were identical in appearance"
Incomplete outcome data (attrition bias) Pain	Low risk	All randomised participants were included in analysis

Chen 2005 *(Continued)*

Incomplete outcome data (attrition bias) Frequency	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Nocturia	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Chen 2014

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 6
Participants	**Number randomised:** 48 **Setting:** 3 departments of urology **Country:** China **Sex:** female **Age, years:** mean 38.3 (SD 5.4) for Group A, mean 37.8 (SD 4.4) for Group B, range 28 to 55 for whole group **Diagnosis:** IC/PBS (NIDDK criteria) **Inclusion criteria:** women with IC/PBS **Exclusion criteria:** patients with diabetes mellitus, mental disorder, hypertension, hypohepatia or renal insufficiency; receiving any treatment for IC/PBS within 3 months
Interventions	**Group A (n = 24):** sildenafil 25 mg (sildenafil is a phosphodiesterase type 5 (PDE5) inhibitor) **Group B (n = 24):** placebo regimen: daily low-dose sildenafil 25 mg or placebo for 12 weeks **Treatment category in NMA:** PDE5 inhibitor vs control
Outcomes	Outcome data in analysis

Chen 2014 *(Continued)*

	Cure or improvement: PORIS (Patient Overall Rating of Improvement in Symptoms) assessed and divided into worse, 0%, 25%, 50%, 75% and 100% improvement. The value of PORIS surpassing 50% was regarded as effective remedy: at 24 weeks Pain: VAS score (range 0 to 5): at 24 weeks Frequency per day: at 24 weeks Nocturia: at 24 weeks ICSI: at 24 weeks ICPI: at 24 weeks Adverse events: at 24 weeks
Funding	Zhejiang Provincial Top Key Discipline and Technology Foundation of Zhejiang Province
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a computer-generated block scheme for randomization"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double blind, placebo-controlled trial", using oral tablet. Placebo not described
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	"double blind, placebo-controlled trial", using oral tablet. Placebo not described
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Pain	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Frequency	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Nocturia	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Low risk	All randomised participants were included in analysis

Chen 2014 *(Continued)*

Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Chuang 2017

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 1
Participants	**Number randomised:** 90 **Setting:** 2 centres **Country:** Taiwan **Sex:** 80 females and 10 males **Age, years:** mean 53.9 (SD 12.9) for lipotoxin group (Group A), mean 47.8 (SD 9.9) for 'onabotulinumtoxinA in normal saline' group (Group A), mean 55.9 (SD 8.6) for Group B **Diagnosis:** IC/BPS (NIDDK criteria); Hunner's lesion not included **Inclusion criteria:** patients 20 years of age or older with IC/BPS in whom at least 6 months of conventional treatments had failed **Exclusion criteria:** not reported
Interventions	**Group A (n = 59):** 2 arms combined for this review. Arm 1: lipotoxin (a liposomal formulated botulinum toxin A), containing onabotulinumtoxinA 200 U with 80 mg sphingomyelin. Arm 2: 200 U g onabotulinumtoxinA in normal saline **Group B (n = 31):** normal saline **Treatment category in NMA:** neuromuscular blockade vs control
Outcomes	Outcome data in analysis Cure or improvement: ‘moderately' or 'markedly’ improved on GRA: at 4 weeks Pain: 10-point VAS: at 4 weeks Frequency: at 4 weeks Nocturia: at 4 weeks ICSI: at 4 weeks ICPI: at 4 weeks

Chuang 2017 *(Continued)*

	Functional bladder capacity: at 4 weeks Adverse events: at 4 weeks
Funding	Chang Gang Medical Foundation-Kaohsiung Branch (CMRPG8D004), Buddhist Tzu Chi General Hospital (TCRD-I-104-02) and Lipella Pharmaceuticals
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized by permutated block randomization" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind", "placebo-controlled" study. Study drugs and saline (placebo) for bladder instillation "were obtained in blinded fashion without recognizable labels from the hospital pharmacy"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	"double-blind", "placebo-controlled" study. Study drugs and saline (placebo) for bladder instillation "were obtained in blinded fashion without recognizable labels from the hospital pharmacy"
Blinding of outcome assessment (detection bias) Objective outcome	Low risk	Outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	59/61 (97%) included in intervention group (2 discontinued due to lack of efficacy); 31/31 included in control group
Incomplete outcome data (attrition bias) Pain	Low risk	59/61 (97%) included in intervention group (2 discontinued due to lack of efficacy); 31/31 included in control group
Incomplete outcome data (attrition bias) Frequency	Low risk	59/61 (97%) included in intervention group (2 discontinued due to lack of efficacy); 31/31 included in control group
Incomplete outcome data (attrition bias) Nocturia	Low risk	59/61 (97%) included in intervention group (2 discontinued due to lack of efficacy); 31/31 included in control group
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Low risk	59/61 (97%) included in intervention group (2 discontinued due to lack of efficacy); 31/31 included in control group
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Low risk	59/61 (97%) included in intervention group (2 discontinued due to lack of efficacy); 31/31 included in control group

Chuang 2017 *(Continued)*

Incomplete outcome data (attrition bias) Functional bladder capacity	Low risk	59/61 (97%) included in intervention group (2 discontinued due to lack of efficacy); 31/31 included in control group
Incomplete outcome data (attrition bias) Adverse events	Low risk	59/61 (97%) included in intervention group (2 discontinued due to lack of efficacy); 31/31 included in control group
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Davis 2008

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 4.5
Participants	**Number randomised:** 40 **Setting:** single centre **Country:** USA **Sex:** female **Age, years:** median 36.9 (IQR 31.9 to 45.1) for Group A, median 38.7 (IQR 26 to 42.7) for Group B **Diagnosis:** IC **Inclusion criteria:** females who were older than 18 years, diagnosed with IC within 1 year of the beginning of the study and previously untreated with either intravesical or oral PPS. To be included in the study, all subjects had to have the following examination requirements: cystoscopic examination under anaesthesia with hydrodistension and photo documentation showing petechial haemorrhage or ulcers; negative urine culture; score of at least 4 on a 9-point pain scale; 5 on the O'Leary-Sant IC Symptom Index; and 4 on IC Problem Index **Exclusion criteria:** bladder capacity greater than 350 mL on an awake cystometrogram; absence of intense urge with bladder filled to 150 mL water on cystometrogram; biphasic involuntary bladder contractions; absence of nocturia; voiding frequency less than 8 times per day (voiding diaries); remission of symptoms by antimicrobials, urinary antiseptics, anticholinergics or antispasmodics; bacterial cystitis within 3 months; recurrent bladder; genital herpes within 3 months; cervical, vaginal or urethral cancer; chemical, tubercular or radiation cystitis; benign or malignant bladder tumour; vaginitis; vesicle ureteral reflux or urethral diverticula; neurogenic bladder dysfunction; prior urinary diversion; receiving any intravesical treatment at time of enrolment; pregnant or lactating mother. A total of 33 subjects had a cystometrogram (median bladder capacity 131 mL). Subjects lacking this criterion (because it was painful) were entered into the study but must have met all other standard criteria for IC
Interventions	**Group A (n = 20):** intravesical 200 mg in 30 mL NaCl pentosan polysulfate sodium (PPS) + oral PPS **Group B (n = 20):** 30 mL of NaCl + oral PPS twice weekly for 6 weeks **Treatment category in NMA:** PPS vs control
Outcomes	Outcome data in analysis

Davis 2008 *(Continued)*

	Cure or improvement: moderately, greatly or completely improved, on patient global assessment questionnaire: at 18 weeks Adverse events: at 18 weeks
Funding	Ortho-McNeil Janssen Scientific Affairs, LLC, Raritan, New Jersey
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "restricted randomization with a size of 4 per block" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind", using intravesical saline solution as placebo. "The blinding process was monitored... by an independent pharmacist, who was responsible for preparing the trial intravesical treatment and placebo according to an FDA approved method"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	"double-blind", using intravesical saline solution as placebo. "The blinding process was monitored... by an independent pharmacist, who was responsible for preparing the trial intravesical treatment and placebo according to an FDA approved method"
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	21/21 included in intervention group; 20/21 included in control group
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

De Ridder 2013

Study characteristics

Methods	**Study design:** RCT **Study duration (months):** not reported
Participants	**Number randomised:** 36 **Setting:** 4 centres **Country:** Belgium **Sex:** 31 females and 5 males

De Ridder 2013 *(Continued)*

	Age, years: not reported **Diagnosis:** PBS/IC **Inclusion criteria:** men and women aged 18 to 75 years with history of symptoms of bladder pain/discomfort described as suprapubic pain related to bladder filling, accompanied by other symptoms such as daytime and/or nighttime frequency in the absence of infection or other pathology. All patients underwent urodynamic evaluation and cystoscopy with evidence of early bladder sensation and low maximum bladder capacity. We also considered in this study patients with negative macroscopic and bioptic findings of interstitial cystitis if significant symptoms were present. Patients should be willing and able to complete the necessary questionnaires **Exclusion criteria:** transitional cell carcinoma of the bladder or other significant malignancy; pregnant or lactating; suffering from significant bacteriuria; diagnosis of haematuria; neurogenic bladder; indwelling catheter; chronic bacterial prostatitis; currently receiving or having received investigational drugs ≤ 30 days before screening; currently receiving or having had prior therapy with intravesical treatment (e.g. Uracyst, Cystistat®, heparin, bacillus Calmette-Guérin (BCG)); receiving therapy for < 3 months with antidepressants, antihistaminics, hormonal agonists or antagonists; hence patient not stabilised on therapy (stable therapy defined as continuous treatment for ≥ 3 months); IC symptoms relieved by antimicrobials, anticholinergics or antispasmodics; functional bladder capacity > 400 mL; neurological disease affecting bladder function; any previous surgery or procedure having affected bladder function; current diagnosis of chemical, tuberculous or radiation cystitis; bladder or lower ureteral calculi; history of cancer within the last 5 years other than adequately treated non-melanoma skin cancer; active sexually transmitted disease; current vaginitis, endometriosis or any condition/disease that in the opinion of the investigator could interfere with patient compliance and/or interfere with interpretation of treatment results
Interventions	**Group A (n = 22):** 1 g/50 mL sodium chondroitin sulfate (2%) (Uracyst™) **Group B (n = 14):** DMSO (dimethyl sulfoxide, 5.4%) 27 g in 50 mL (RIMSO-50®) Weekly for 6 weeks Treatment category**in NMA:** chondroitin sulfate vs DMSO
Outcomes	Outcome data in analysis Cure or improvement: ‘moderately' or 'markedly’ improved on GRA: unclear time of measurement Pain: O'Leary-Sant Questionniare (Interstitial Cystitis Symptom and Problem Index) pain subscale (assumed 0 to 10 scale): unclear time of measurement ICSI: unclear time of measurement
Funding	EUROCEPT, The Netherlands
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias)	High risk	Stated as "patients were single-blind randomized", but methods of blinding were not described. Personnel probably not blinded. Intravesical instillation of chondroitin sulfate "in 20 ml vials" or DMSO "in 50 ml physiologic serum"

De Ridder 2013 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	Stated as "patients were single-blind randomized", but methods of blinding were not described. Intravesical instillation of chondroitin sulfate "in 20 ml vials" or DMSO "in 50 ml physiologic serum"
Incomplete outcome data (attrition bias) Cure or improvement	High risk	16/22 (73%) included in chondroitin sulfate group (withdrawal mainly due to lack of efficacy or side effects); 6/14 (43%) included in DMSO group (withdrawal mainly due to adverse effects)
Incomplete outcome data (attrition bias) Pain	Unclear risk	Number analysed unclear
Selective reporting (reporting bias)	High risk	Pain VAS (visual analogue scale), frequency and nocturia were specified in the methods section but were reported only as baseline characteristics in the results section. Functional bladder capacity was specified in the methods but was not reported in the results
Other bias	Low risk	None detected

Dimitrakov 2001

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 3
Participants	**Number randomised:** 30 **Setting:** not reported **Country:** not reported **Sex:** not reported **Age, years:** not reported **Diagnosis:** IC (NIDDK criteria) **Inclusion criteria:** patients with symptoms and signs of IC **Exclusion criteria:** not reported
Interventions	**Group A (n = not reported):** 1 of 2 doses (0.1 and 0.3 mg/kg of body weight) of recombinant human nerve growth factor **Group B (n = not reported):** placebo **Treatment category in NMA:** immune modulators vs control
Outcomes	Outcome data in analysis (no usable data)
Funding	Prostatitis Foundation of America and the Bulgarian Ministry of Health
Notes	**Publication status:** abstract
Risk of bias	

Dimitrakov 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"… patients … randomly received" either intervention or placebo
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided. Placebo not described
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	No information provided. Placebo not described
Selective reporting (reporting bias)	Unclear risk	Outcomes not specified in the methods section (abstract only)
Other bias	Low risk	None detected

El-Hefnawy 2015

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 1
Participants	**Number randomised:** 26 **Setting:** single centre (assumed from reports) **Country:** Egypt **Sex:** female **Age, years:** mean 32 (SD 6) for Group A, mean 33 (SD 7) for Group B **Diagnosis:** IC/BPS. Diagnosis according to IC Database Study criteria (Hanno 1999) **Inclusion criteria:** Patients with complaint suggestive of IC/BPS. Patients who were not improved on pain killers and analgesics after treatment for at least 3 months and were willing to participate in the study. At least 4 weeks elapsed before receiving either line of treatment **Exclusion criteria:** not reported
Interventions	**Group A (n = 14):** superior hypogastric plexus neurolysis **Group B (n = 12):** hydrodistension **Treatment category in NMA:** denervation vs hydrodistension
Outcomes	Outcome data in analysis Pain: VAS (assumed range 0 to 10): at 4 weeks Daytime frequency: at 4 weeks Nocturia: at 4 weeks

El-Hefnawy 2015 *(Continued)*

	ICSI: at 4 weeks ICPI: at 4 weeks Adverse events: at 4 weeks
Funding	Not reported
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated to receive either HD or SHN block according to results of closed envelope" Comment: unclear how envelopes were used to ensure random allocation
Allocation concealment (selection bias)	Unclear risk	Quote: "randomly allocated to receive either HD or SHN block according to results of closed envelope" Comment: unclear how envelopes were used to ensure random allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Superior hypogastric plexus neurolysis (SHN) vs hydrodistension (HD). SHN performed "In operating room, conscious sedation". Probably not done
Blinding of outcome assessment (detection bias) Subjective outcome	High risk	Superior hypogastric plexus neurolysis (SHN) vs hydrodistension (HD). SHN performed "In operating room, conscious sedation". Probably not done
Incomplete outcome data (attrition bias) Pain	High risk	12/14 (86%) included in SHN group (2 excluded due to failed initial test); 12/12 included in HD group
Incomplete outcome data (attrition bias) Frequency	High risk	12/14 (86%) included in SHN group (2 excluded due to failed initial test); 12/12 included in HD group
Incomplete outcome data (attrition bias) Nocturia	High risk	12/14 (86%) included in SHN group (2 excluded due to failed initial test); 12/12 included in HD group
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	High risk	12/14 (86%) included in SHN group (2 excluded due to failed initial test); 12/12 included in HD group
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	High risk	12/14 (86%) included in SHN group (2 excluded due to failed initial test); 12/12 included in HD group
Incomplete outcome data (attrition bias) Adverse events	High risk	12/14 (86%) included in SHN group (2 excluded due to failed initial test); 12/12 included in HD group

El-Hefnawy 2015 *(Continued)*

Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Evans 2011

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 4
Participants	**Number randomised:** 64 **Setting:** 23 centres **Country:** USA **Sex:** reported as 'mostly female (89%)'. Unclear denominator **Age, years:** range 21 to 85 **Diagnosis:** IC, moderate to severe **Inclusion criteria:** moderate to severe IC defined as scores of 13 or greater on the Pelvic Pain and Urgency/Frequency symptom questionnaire, and 7 or more on the O'Leary-Sant ICSI **Exclusion criteria:** IC symptoms for less than 6 months, PVR volume greater than 200 mL, history of allergic or anaphylactic reaction to mAbs or IgG fusion proteins
Interventions	**Group A (n = 34):** tanezumab (humanised anti-NGF (nerve growth factor) monoclonal antibody) intravenous dose of 200 g/kg **Group B (n = 30):** placebo Patients remained on existing non-prohibited oral medications as background therapy for interstitial cystitis **Treatment category in NMA:** immune modulators vs control
Outcomes	Outcome data in analysis Cure or improvement: 'moderately' or 'markedly improved on GRA: at 16 weeks Pain: numerical rating scale (range 0 to 10): at 16 weeks Frequency: at 6 weeks Adverse events: at 16 weeks
Funding	Pfizer
Notes	**Publication status:** full text

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomized using an automated tele-randomization system"

Evans 2011 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "randomized using an automated tele-randomization system"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind, placebo-controlled trial", using intravenous (IV) dose. Placebo not described
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	"double-blind, placebo-controlled trial", using intravenous (IV) dose. Placebo not described
Incomplete outcome data (attrition bias) Cure or improvement	High risk	19/34 (56%) included in intervention group; 13/30 (43%) included in control group
Incomplete outcome data (attrition bias) Pain	Low risk	27/34 (79%) included in intervention group; 22/30 (73%) included in control group
Incomplete outcome data (attrition bias) Frequency	Unclear risk	29/34 (85%) included in intervention group; 23/30 (77%) included in control group
Incomplete outcome data (attrition bias) Adverse events	Low risk	29/34 (85%) included in intervention group; 23/30 (77%) included in control group
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

FitzGerald 2009

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 3
Participants	**Number randomised:** 47 **Setting:** 6 clinical centres **Country:** USA **Sex:** 24 females and 23 males **Age, years:** mean 43, range 22 to 76 **Diagnosis:** IC/PBS or CP/CPPS. Clinical diagnosis **Inclusion criteria:** patients with symptoms for less than 3 years. Patients must have previously undergone at least 1 course of another form of therapy for their symptoms **Exclusion criteria:** patients who were intolerant to digital vaginal or rectal examination (i.e. unable to tolerate myofascial physical therapy treatments); participants who had previously undergone myofascial physical therapy for symptoms

FitzGerald 2009 *(Continued)*

Interventions	**Group A (n = 23):** myofascial physical therapy **Group B (n = 24):** global therapeutic massage **Treatment category in NMA:** physical therapy vs control
Outcomes	Outcome data in analysis Cure or improvement: 'moderately' or 'markedly' improved on GRA: at 12 weeks
Funding	The Urological Pelvic Pain Collaborative Research Network is a co-operative network of investigators from 20 clinical centres and a Data Co-ordinating Center funded by NIDDK, NIH
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned … via a prespecified sequence"
Allocation concealment (selection bias)	Unclear risk	Quote: "a prespecified sequence distributed in a series of sealed envelopes" Comment: unclear if envelopes were opaque and sequentially numbered
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "single-blind". Participants were not informed of treatment assignment but investigators stated that participants could not be blinded: "more than 90% were aware of their treatment group when queried at the end of the study". Study co-ordinator was blinded
Blinding of outcome assessment (detection bias) Subjective outcome	High risk	Quote: "single-blind". Participants were not informed of treatment assignment but investigators stated that participants could not be blinded: "more than 90% were aware of their treatment group when queried at the end of the study"
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	Data extracted from a subset of participants. All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

FitzGerald 2012

Study characteristics

Methods	**Study design:** RCT **Study duration (months):** 3
Participants	**Number randomised:** 81 **Setting:** 11 clinical centres **Country:** USA

FitzGerald 2012 *(Continued)*

	Sex: female **Age, years:** median 43, range 18 to 77 **Diagnosis:** IC/PBS **Inclusion criteria:** women with a clinical diagnosis of IC/PBS and recorded ratings for bladder pain, frequency and urgency, each at a usual level of at least 3 on a 0 to 10 scale, present for at least 3 months but not for longer than 3 years. An additional eligibility requirement was the finding of pelvic floor tenderness during vaginal examination by the study physician and confirmed by the study physical therapist **Exclusion criteria:** women were excluded from the study if they had not previously undergone at least 1 course of a standard therapy for IC/PBS, or if they had previously received treatment with pelvic floor myofascial physical therapy
Interventions	**Group A (n = 39):** pelvic floor myofascial physical therapy **Group B (n = 42):** global therapeutic massage **Treatment category in NMA:** physical therapy vs control
Outcomes	Outcome data in analysis Cure or improvement: 'moderately' or 'markedly' improved on GRA: at 12 weeks Pain: numerical Likert scale (range 0 to 10): at 12 weeks ICSI: at 12 weeks ICPI: at 12 weeks Adverse events: at 12 weeks
Funding	Not reported
Notes	**Publication status:** full text

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized" Comment: method of sequence generation judged to be unclear in FitzGerald 2009, which uses identical methods to this trial
Allocation concealment (selection bias)	Unclear risk	No information. Method of allocation concealment judged to be unclear in FitzGerald 2009, which uses identical methods to this trial
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "single-blind". Participants probably not blinded, as study authors state "the design and methods of this randomized trial are identical" to FitzGerald 2009, included in this review
Blinding of outcome assessment (detection bias) Subjective outcome	High risk	Quote: "single-blind". Participants probably not blinded. "Physician examiners and research nurses collecting outcome data were masked to treatment assignment"
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	All randomised participants were included in analysis

FitzGerald 2012 *(Continued)*

Incomplete outcome data (attrition bias) Pain	Low risk	38/39 (97%) included in intervention group; 40/42 (95%) included in control group. 3 withdrew from study, 1 due to dissatisfaction with treatment and 2 due to 'personal constraints'; group assignment unclear
Incomplete outcome data (attrition bias) Frequency	Low risk	
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Low risk	38/39 (97%) included in intervention group; 40/42 (95%) included in control group. 3 withdrew from study, 1 due to dissatisfaction with treatment and 2 due to 'personal constraints'; group assignment unclear
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Low risk	38/39 (97%) included in intervention group; 40/42 (95%) included in control group. 3 withdrew from study, 1 due to dissatisfaction with treatment and 2 due to 'personal constraints'; group assignment unclear
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Foster 2010

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 3
Participants	**Number randomised:** 271 **Setting:** multi-centre **Country:** USA **Sex:** 226 females and 45 males **Age, years:** mean 38.0 (SD 13.8) for Group A, mean 39.9 (SD 14.0) for Group B, median 38 for whole group **Diagnosis:** IC/PBS **Inclusion criteria:** men and women at least 18 years old who reported bladder pain/discomfort and urinary frequency of 3 or greater on separate 0 to 10 Likert scales during the previous 4 weeks at each of 2 baseline screening visits. Current symptoms had to have been present for a minimum of 6 weeks, and subjects were required to be treatment naïve, defined as having no prior significant treatment for IC/PBS **Exclusion criteria:** not reported
Interventions	**Group A (n = 135):** amitriptyline + educational and behavioural modification programme (EBMP) **Group B (n = 136):** placebo + EBMP

Foster 2010 *(Continued)*

	Dose regimen: dose of study drug was increased on a weekly basis from 10 to 25 mg, then to 50 mg after a call from the research co-ordinator confirming tolerability. At the end of 3 weeks, participants were evaluated and their dose increased to 75 mg daily **Treatment category in NMA:** antidepressants vs control
Outcomes	Outcome data in analysis Cure or improvement: 'moderately' or 'markedly' improved on GRA: at 12 weeks Pain: Likert pain scale (range 0 to 10): at 3 months Frequency: at 3 months Nocturia: at 3 months ICSI: at 3 months ICPI: at 3 months Adverse events: at 3 months
Funding	Not reported
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind", "placebo-controlled" trial, using oral tablet. Participants were randomised to study drug or "matching placebo". Probably done
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	"double-blind", using "matching" placebo. Probably done
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	Review authors chose to use number who completed the trial. 112/135 (83%) included in intervention group (7 missing due to AE); 119/136 (88%) included in control group (2 missing due to AE)
Incomplete outcome data (attrition bias) Pain	Unclear risk	Number analysed unclear. It is "not per intent to treat due to withdrawals and missing data"
Incomplete outcome data (attrition bias) Frequency	Low risk	92/135 (68%) included in intervention group; 95/136 (70%) included in control group
Incomplete outcome data (attrition bias) Nocturia	Low risk	92/135 (68%) included in intervention group; 95/136 (70%) included in control group

Foster 2010 *(Continued)*

Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Unclear risk	Number analysed unclear. It is "not per intent to treat due to withdrawals and missing data"
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Unclear risk	Number analysed unclear. It is "not per intent to treat due to withdrawals and missing data"
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Geirsson 1993

Study characteristics	
Methods	**Study design:** cross-over randomised trial **Study duration (months):** 1 (assumed from reports)
Participants	**Number randomised:** 12 **Setting:** not reported **Country:** Sweden **Sex:** female **Age, years:** median 41, range 22 to 80 **Diagnosis:** IC **Inclusion criteria:** female IC patients. No further details, but it is stated that "all patients had been treated with various conservative measures with lack of response or recurrence of symptoms" **Exclusion criteria:** not reported
Interventions	**Group A (n = not reported):** acupuncture 2 to 3 times a week for 4 to 5 weeks **Group B (n = not reported):** transcutaneous tibial nerve stimulation (TENS) by patients at home, 30 minutes per day for 4 weeks **Treatment category in NMA:** behavioural therapy vs physical therapy
Outcomes	Outcome data in analysis Adverse events: at 1 month (assumed from reports)
Funding	Supported by Swedish Medical Research Council and Gothenburg Medical Society
Notes	**Publication status:** full text
Risk of bias	

Geirsson 1993 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized … according to a cross-over design"; "allocation to initial treatment was done by the patient selecting an envelope containing a mark for either method"
Allocation concealment (selection bias)	Unclear risk	Quote: "allocation to initial treatment was done by the patient selecting an envelope containing a mark for either method" Comment: unclear if envelopes were sealed, opaque and sequentially numbered
Blinding of participants and personnel (performance bias) All outcomes	High risk	Probably not done. Accupuncture by a Chinese medical doctor vs TENS at home. TENS is defined as trancutaneous nerve stimulation of the tibial nerve
Blinding of outcome assessment (detection bias) Subjective outcome	High risk	Probably not done. Accupuncture by a Chinese medical doctor vs TENS at home. TENS is defined as trancutaneous nerve stimulation of the tibial nerve
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Number analysed unclear
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Gottsch 2011

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 3
Participants	**Number randomised:** 20 **Setting:** single centre **Country:** USA **Sex:** female **Age, years:** mean 43.9 (range 27 to 61) for Group A, mean 47.7 (range 22 to 61) for Group B **Diagnosis:** IC/PBS **Inclusion criteria:** adult women with IC/PBS were identified from the Female Urology Clinic at our hospital, which is a tertiary care referral centre. Women were eligible for enrolment if they had refractory pelvic pain in the bladder, urethra, vagina or perineum; pain with bladder filling or voiding; and urinary frequency greater than 12 voids per day **Exclusion criteria:** women with isolated overactive bladder symptoms, active urinary tract infection, pregnancy, genitourinary malignancy, suicidal or overtly psychotic behavior, postsurgical pain, pain from another source in the genitourinary tract (e.g. renal calculi), history of radiation therapy or history of genitourinary tuberculosis
Interventions	**Group A (n = 9):** periurethral injection of 50 U botulinum toxin A diluted in 2 cm^3 normal saline

Gottsch 2011 *(Continued)*

	Group B (n = 11): placebo injection of 2 cm^3 normal saline **Treatment category in NMA:** neuromuscular blockade vs control
Outcomes	Outcome data in analysis Pain: CPSI-F (a female modification of Chronic Prostitis Symptom Index) pain subscale (range 0 to 21): at 3 months Adverse events: at 3 months
Funding	Not reported
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind"; blinding methods not described. Periurethral injection botulinum toxin A vs saline (placebo). "The placebo injection … delivered in a similar fashion"
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	"double-blind"; blinding methods not described. Periurethral injection botulinum toxin A vs saline (placebo). "The placebo injection … delivered in a similar fashion"
Incomplete outcome data (attrition bias) Pain	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Gulpinar 2013

Study characteristics

Methods	**Study design:** RCT **Study duration (months):** 6
Participants	**Number randomised:** 53

Gulpinar 2013 *(Continued)*

	Setting: not reported **Country:** Turkey **Sex:** not reported **Age, years:** mean 48.47 **Diagnosis:** PBS/IC **Inclusion criteria:** patients with history of painful bladder syndrome/interstitial cystitis(PBS/IC) who had poor response or were refractory to previous treatment(s) **Exclusion criteria:** not reported
Interventions	**Group A (n = 30):** 800 mg/50 mL sodium hylauronic acid (1.6%) + 1 g/50 mL sodium chondroitin sulfate (2%) (iAluRil®) **Group B (n = 23):** 50 mL hyaluronic acid (Hyacyst®) Weekly in first month, once in 15 days in second month and monthly in third and fourth months, as total of 8 intravesical doses **Treatment category in NMA:** chondroitin sulfate vs control
Outcomes	Outcome data in analysis Pain: VAS (assumed 0 to 10): at 6 months Nocturia: at 6 months ICSI: at 6 months ICPI: at 6 months Adverse events: at 6 months
Funding	Not reported
Notes	**Publication status:** abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided. Intravesical therapy of 50 mL chondroitin sulfate or hyaluronic acid
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	No information provided
Incomplete outcome data (attrition bias) Pain	Unclear risk	Number analysed not stated

Gulpinar 2013 *(Continued)*

Incomplete outcome data (attrition bias) Nocturia	Unclear risk	Number analysed not stated
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Unclear risk	Number analysed not stated
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Unclear risk	Number analysed not stated
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Number analysed not stated
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Gulpinar 2015

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 6
Participants	**Number randomised:** 42 **Setting:** not reported **Country:** Turkey **Sex:** female **Age, years:** mean 47.10 (SD 10.70) for Group A, mean 48.90 (SD 17.18) for Group B **Diagnosis:** BPS/IC **Inclusion criteria:** female patients with BPS/IC were included in the study. Patients with complaints of chronic pelvic pain related to bladder filling accompanied by voiding frequency ≥ 8 times/24 h; nocturia ≥ 2 times per night or persistent urge for at least 24 weeks; an average pain score of ≥ 4 (VAS; 0 no pain, 10 unbearable pain); a negative pregnancy test; a sterile urine culture; and inadequate clinical response after 6 months of conservative and medical treatment were included in the study **Exclusion criteria:** patients with positive pregnancy test, current urinary infection or sexually transmitted disease; chemical cystitis; tuberculous or radiation cystitis; urolithiasis; urological malignancy; or endometriosis or urethral diverticulum; breastfeeding women were excluded from the study
Interventions	**Group A (n = 21):** 800 mg/40 mL sodium chondroitin sulfate (Gepan Instill®) **Group B (n = 21):** 50 mL/120 mg hyaluronic acid (Hyacyst®) Weekly in first month, once in 15 days in second month and monthly in third and fourth months, as total of 8 intravesical doses **Treatment category in NMA:** chondroitin sulfate vs hyaluronic acid

Gulpinar 2015 *(Continued)*

Outcomes	Outcome data in analysis Cure or improvement: treatment response according to VAS pain score changes ('strong benefit' defined as > 50% reduction in VAS score): at 6 months Adverse events: at 6 months
Funding	Not reported
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided. Intravesical therapy of 40 mL chondroitin sulfate vs 50 mL hyaluronic acid
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	No information provided
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Frequency	Low risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Ham 2012

Study characteristics

Methods	**Study design:** RCT **Study duration (months):** 3
Participants	**Number randomised:** 18

Ham 2012 *(Continued)*

	Setting: not reported **Country:** Korea **Sex:** female **Age, years:** mean 54.5 (SD 9.1) for Group A, mean 56.9 (SD 7.8) for Group B, median 55.8 for whole group **Diagnosis:** IC (NIDDK criteria) **Inclusion criteria:** women with IC refractory to classic medical treatment **Exclusion criteria:** not reported
Interventions	**Group A (n = 8):** 50 mL resiniferatoxin (RTX) in 10% ethanol + hydrodistension. (RTX = ultra potent analogue of chili pepper extract capsaicin) **Group B (n = 10):** hydrodistension **Treatment category in NMA:** calcium channel agonists vs control
Outcomes	Outcome data in analysis Pain: VAS (range 0 to 5): at 3 months Frequency (mean voids/d): at 3 months Nocturia: at 3 months Functional bladder capacity: at 3 months Adverse events: at 3 months
Funding	Not reported
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned. Hydrodistension vs hydrodistension + intravexial RTX "under general anesthesia"
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	Blinding not mentioned. Hydrodistension vs hydrodistension + intravexial RTX "under general anesthesia"
Blinding of outcome assessment (detection bias) Objective outcome	Low risk	Outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias)	Unclear risk	All randomised participants were included in analysis

Ham 2012 *(Continued)*

Pain		
Incomplete outcome data (attrition bias) Frequency	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Nocturia	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Functional bladder capacity	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Hanno 2015

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 1
Participants	**Number randomised:** 74 **Setting:** not reported **Country:** USA **Sex:** female **Age, years:** not reported **Diagnosis:** IC/PBS **Inclusion criteria:** women 18 to 80 years of age who had clinical evidence of IC/BPS for at least 6 months with moderate to severe pain and urinary frequency **Exclusion criteria:** not reported
Interventions	**Group A (n = 36):** AF-219 (P2X3 antagonist) **Group B (n = 38):** placebo **Treatment category in NMA:** P2X3 antagonist vs control
Outcomes	Outcome data in analysis Pain: numerical pain rating scale (assumed range 0 to 10): at 4 weeks Adverse events: at 4 weeks

Hanno 2015 *(Continued)*

Funding	Not reported
Notes	**Publication status:** abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "'randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants randomised to an oral drug or placebo. Placebo not described
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	Participants randomised to an oral drug or placebo. Placebo not described
Incomplete outcome data (attrition bias) Pain	Unclear risk	Number analysed unclear
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Number analysed unclear
Selective reporting (reporting bias)	Unclear risk	Outcomes not specified in methods (abstract only)
Other bias	Low risk	None detected

Herati 2011

Study characteristics

Methods	**Study design:** RCT **Study duration (months):** 0.06 (48 hours)
Participants	**Number randomised:** 30 **Setting:** not reported **Country:** USA **Sex:** not reported **Age, years:** not reported **Diagnosis:** IC/PBS **Inclusion criteria:** consecutive IC/PBS patients **Exclusion criteria:** not reported

Herati 2011 *(Continued)*

	Number randomised: 30
Interventions	**Group A (n = 14):** caffeine 100 mg **Group B (n = 16):** placebo **Treatment category in NMA:** caffeine vs control
Outcomes	Outcome data in analysis - no usable data
Funding	The Fishbein Family IC Research Foundation Grant
Notes	**Publication status:** abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized … using a four block randomization scheme" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"placebo-controlled, double-blind study", using a pill or placebo. Placebo not described
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	"double-blind", using a pill or placebo. Placebo not described
Selective reporting (reporting bias)	High risk	ICPI listed in methods but not reported in results
Other bias	Low risk	None detected

Hsieh 2012

Study characteristics

Methods	**Study design:** RCT **Study duration (months):** 6
Participants	**Number randomised:** 70 **Setting:** not reported **Country:** Taiwan **Sex:** not reported **Age, years:** mean 45.9 (SD 7.8) for Group A, mean 46.1 (SD 7.6) for Group B **Diagnosis:** IC (NIDDK criteria) **Inclusion criteria:** patients with IC

Hsieh 2012 *(Continued)*

	Exclusion criteria: not reported
Interventions	**Group A (n = 35):** hydrodistension plus bladder training (talk with physician, attempt to increase inter-void interval) **Group B (n = 35):** hydrodistension (bladder filled with normal saline to maximal capacity at pressure of 80 cmh^2) **Treatment category in NMA:** behavioural therapy vs control
Outcomes	Outcome data in analysis Frequency: at 24 weeks Nocturia: at 24 weeks
Funding	Not reported
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Hydrodistension (HD) + bladder training (BT) vs HD. Probably not done
Blinding of outcome assessment (detection bias) Subjective outcome	High risk	Hydrodistension (HD) + bladder training (BT) vs HD. Probably not done
Incomplete outcome data (attrition bias) Frequency	High risk	28/35 (80%) included in HD + BT group; 23/35 (66%) included in HD group. Missing data due to participants unable to return to follow-up or provide urinary diaries
Incomplete outcome data (attrition bias) Nocturia	High risk	28/35 (80%) included in HD + BT group; 23/35 (66%) included in HD group. Missing data due to participants unable to return to follow-up or provide urinary diaries
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Irani 2004

Study characteristics

Methods	**Study design:** RCT

Irani 2004 *(Continued)*

	Study duration (months): 24
Participants	**Number randomised:** 30 **Setting:** multi-centre (assumed from reports) **Country:** Iran **Sex:** female **Age, years:** mean 40.8 (SD 13.96) for Group A, mean 36 (SD 12.84) for Group B **Diagnosis:** IC (NIDDK criteria) **Inclusion criteria:** met NIDDK diagnostic criteria, selected from among women with irritative symptoms and bladder pain, post cystoscopy under anaesthesia, bladder hydrodistension, other preliminary evaluations **Exclusion criteria:** immunocompromising conditions; steroid, warfarin or immunosuppressant administration; pregnancy; vesicoureteral reflux; history of intravesical instillation in the last 3 months; positive HIV serology; positive cutaneous PPD; males (due to risk of catheterisation)
Interventions	**Group A (n = 15):** 120 mg bacillus Calmette-Guérin (BCG) **Group B (n = 15):** 50 cc NaCl **Treatment category in NMA:** immune modulators vs control
Outcomes	Outcome data in analysis Cure or improvement: 'responded to treatment' defined as over 40% improvement in valid scores of Wisconsin University for interstitial cystitis at 24 months Pain: pelvic pain VAS (10 cm rulers) at 24 months Frequency: at 24 months Functional bladder capacity: at 24 months Adverse effects: at 24 months
Funding	Not reported
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Low risk	Quote: "... nominating the drugs and listing the patients were done by a third person not enrolled in the study"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind", "placebo-controlled" study, using "vials of placebo with similar appearance", "vials nominated blindly as drugs A and B"; "the staff who were involved with the therapy were blind to the drug type"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	"double-blind", "placebo-controlled" study, using "vials of placebo with similar appearance", "vials nominated blindly as drugs A and B"; "the staff who were involved with the therapy were blind to the drug type"

Irani 2004 *(Continued)*

Blinding of outcome assessment (detection bias) Objective outcome	Low risk	Outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Pain	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Frequency	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Functional bladder capacity	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Ismail 2016

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 2
Participants	**Number randomised:** 30 **Setting:** not reported **Country:** not reported **Sex:** 26 females and 4 males **Age, years:** range 17 to 45 **Diagnosis:** IC/BPS **Inclusion criteria:** patients diagnosed to have IC/BPS **Exclusion criteria:** not reported
Interventions	**Group A (n = 15):** intravesical 100 U botulinum toxin A injected into trigone under general anaesthesia **Group B (n = 15):** equivalent amount of normal saline **Treatment category in NMA:** neuromuscular blockade vs control
Outcomes	Outcome data in analysis

Ismail 2016 *(Continued)*

	Adverse events: at 0.5 months
Funding	Not reported
Notes	**Publication status:** abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "single-blinded". Unclear who is blinded and how. Intravesical instillation of BoNT-A or "the equivalent amount of normal saline" under general anaesthesia
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	Quote: "single-blinded". Unclear who is blinded and how. Intravesical instillation of BoNT-A or "the equivalent amount of normal saline" under general anaesthesia
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Number analysed not stated
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Kanter 2016

Study characteristics

Methods	**Study design:** RCT **Study duration (months):** 2
Participants	**Number randomised:** 20 **Setting:** not reported **Country:** USA **Sex:** female **Age, years:** mean 46.3 (SD 15.2) for Group A, mean 44.4 (SD 13.9) for Group B **Diagnosis:** IC/BPS (American Urological Association criteria) **Inclusion criteria:** patients with IC/BPS. Negative urinalysis or urine culture within 2 months of enrolment and ability to speak and understand English. We recruited only patients who were currently undergoing first- or second-line treatments, as defined by the AUA (American Urological Association), and who had not made changes in their IC/BPS treatment regimen within 4 weeks of beginning their assigned intervention. First-line treatments include relaxation/stress management, pain management

Kanter 2016 *(Continued)*

	and self-care/behavioural modification. Second-line therapy involves physical therapy, in addition to oral or intravesical medications **Exclusion criteria:** patients who were treatment-naïve or undergoing third-line or higher treatments at the time of enrolment; patients with unevaluated haematuria, urinary retention, history of cystectomy, augmentation cystoplasty or urinary diversion; history of radiation- or chemotherapy-induced cystitis or pregnant or lactating
Interventions	**Group A (n = 9):** 8-week group mindfulness-based stress reduction meditation programme (seven 2 hour courses, every week, with all-day retreat in 5th week) plus current care regimen. Also given 4-CD guide and a book **Group B (n = 11):** usual care **Treatment category in NMA:** behavioural therapy vs control
Outcomes	Outcome data in analysis Cure or improvement: Global Response Assessment as 'being improved'. Not clear whether this is defined as 'moderate' and 'marked' improvement or 'moderate', 'marked' and 'slight' improvement: at 8 weeks Pain: VAS (assumed range 0 to 10): at 8 weeks ICSI: at 8 weeks ICPI: at 8 weeks
Funding	National Center for Research Resources and National Center for Advancing Translational Sciences of the NIH (grant # ULI TR001449)
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized … by a computer-generated sequence"
Allocation concealment (selection bias)	Low risk	Quote: "allocation was concealed in serially numbered, opaque, sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Probably not done. Stress reduction class + usual care vs usual care
Blinding of outcome assessment (detection bias) Subjective outcome	High risk	Probably not done. Stress reduction class + usual care vs usual care
Incomplete outcome data (attrition bias) Cure or improvement	High risk	8/9 (89%) included in intervention group (1 lost to follow-up before intervention); 11/11 in control group
Incomplete outcome data (attrition bias) Pain	High risk	8/9 (89%) included in intervention group (1 lost to follow-up before intervention); 11/11 in control group

Kanter 2016 *(Continued)*

Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	High risk	8/9 (89%) included in intervention group (1 lost to follow-up before intervention); 11/11 in control group
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	High risk	8/9 (89%) included in intervention group (1 lost to follow-up before intervention); 11/11 in control group
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Kasyan 2012

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 3
Participants	**Number randomised:** 32 **Setting:** not reported **Country:** Russia **Sex:** female **Age, years:** not reported **Diagnosis:** BPS/IC **Inclusion criteria:** female patients with BPS/IC **Exclusion criteria:** not reported
Interventions	**Group A (n = 15):** 100 IU of botulinum toxin A in 10 mL of NaCl into the trigone **Group B (n = 17):** hydrodistension **Treatment category in NMA:** neuromuscular blockade vs hydrodistension
Outcomes	Outcome data in analysis Pain: 10-point VAS (unclear minimum/maximum score): at 3 months ICSI: at 3 months ICPI: at 3 months Adverse events: at 3 months
Funding	None
Notes	**Publication status:** abstract
Risk of bias	

Kasyan 2012 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned. Hydrodistension vs injection (under spinal anaesthesia through a cystoscope using a flexible needle in the trigone of the bladder)
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	Blinding not mentioned. Hydrodistension vs injection (under spinal anaesthesia through a cystoscope using a flexible needle in the trigone of the bladder)
Incomplete outcome data (attrition bias) Pain	Unclear risk	Number analysed not stated
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Unclear risk	Number analysed not stated
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Unclear risk	Number analysed not stated
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Number analysed not stated
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Kim 2012

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 3
Participants	**Number randomised:** 18 **Setting:** not reported **Country:** Korea **Sex:** not reported **Age, years:** median 55.8 ± 6.9 (unknown whether IQR) **Diagnosis:** PBS/IC

Kim 2012 *(Continued)*

	Inclusion criteria: consecutive patients with proven PBS/IC refractory to traditional medical treatment **Exclusion criteria:** not reported
Interventions	**Group A (n = not reported):** resiniferatoxin (RTX) + hydrodistension (RTX = ultra potent analogue of chili pepper extract capsaicin) **Group B (n = not reported):** hydrodistension **Treatment category in NMA:** calcium channel agonists vs control
Outcomes	Outcome data in analysis - no usable data
Funding	Industrial Source Technology Development Programme of the Ministry of Knowledge Economy (MKE) of Korea and the National Research Foundation of Korea (NRF) grant funded by the Korean government
Notes	**Publication status:** abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned. Hydrodistension + intravesical RTX vs hydrodistension
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	Blinding not mentioned. Hydrodistension + intravesical RTX vs hydrodistension
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Kim 2015

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 1
Participants	**Number randomised:** 38 **Setting:** multi-centre **Country:** Korea **Sex:** not reported **Age, years:** mean 63.76 (SD 7.70) for Group A, mean 63.62 (SD 9.34) for Group B **Diagnosis:** IC/PBS

Kim 2015 *(Continued)*

	Inclusion criteria: patients who have had symptoms of IC/BPS for at least 6 months and had Hunner's lesion **Exclusion criteria:** not reported
Interventions	**Group A (n = 21):** transurethral fulguration **Group B (n = 17):** hydrodistension **Treatment category in NMA:** fulguration vs hydrodistension
Outcomes	Outcome data in analysis Pain: VAS (assumed range 0 to 10): at 1 month
Funding	Not reported
Notes	**Publication status:** abstract Trial stopped early: "… the authors felt a clear superiority of one procedure over the other and enrollment after the 38th patient was stopped for ethical reasons"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly divided".
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Probably not done. Fulguration vs hydrodistension (HD)
Blinding of outcome assessment (detection bias) Subjective outcome	High risk	Probably not done. Fulguration vs hydrodistension (HD)
Incomplete outcome data (attrition bias) Pain	Unclear risk	Number analysed not stated. 7/21 (33%) dropped out from fulguration group; 11/17 (64%) dropped out from HD group. Unclear how missing data were handled
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Korting 1999

Study characteristics

Methods	**Study design:** RCT **Study duration (months):** 3
Participants	**Number randomised:** 53

Korting 1999 *(Continued)*

	Setting: not reported **Country:** USA **Sex:** not reported **Age, years:** mean 46.6 (SD 14.3) for Group A (n = 21), mean 52.7 (SD 13.6) for Group B (n = 26), mean 56.3 (SD 10.2) for Group A withdrawals (n = 6) **Diagnosis:** IC (NIH criteria) **Inclusion criteria:** female patients with IC **Exclusion criteria:** male sex, pregnancy or unreliable plans for avoiding pregnancy, unstable medical condition, prior use of L-arginine
Interventions	**Group A (n = 27):** L-arginine 500 mg TDS for 3 months **Group B (n = 26):** placebo **Treatment category in NMA:** amino acid vs control
Outcomes	Outcome data in analysis Cure or improvement: change for the better in overall symptoms on 2 questionnaires: at 3 months Frequency per day: at 3 months Nocturia: at 3 months Adverse events: at 3 months
Funding	Not reported
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "'simple block randomization … using a random numbers table"
Allocation concealment (selection bias)	Low risk	Randomisation "was performed by the Investigational Drug Service of the Yale New Haven Hospital Pharmacy"; "the researchers and patients were blinded to patient assignment until after completion of the trial and all followup interviews". Probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind"; participants received study drug or "identical appearing placebo … capsules"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	"double-blind"; participants received study drug or "identical appearing placebo … capsules"
Incomplete outcome data (attrition bias) Cure or improvement	High risk	Reviewers extracted per-protocol analysis data. 21/27 (78%) included in intervention group; 26/26 included in control group
Incomplete outcome data (attrition bias)	Low risk	Number analysed not stated, but "an intention to treat analysis … was performed … using the methods suggested by Lewis and Machin"

Korting 1999 *(Continued)*

Frequency		
Incomplete outcome data (attrition bias) Nocturia	Low risk	Number analysed not stated, but "an intention to treat analysis … was performed … using the methods suggested by Lewis and Machin"
Incomplete outcome data (attrition bias) Adverse events	High risk	21/27 (78%) included in intervention group (6 withdrew); 25/26 included in control group (1 withdrew)
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Kuo 2009

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 24
Participants	**Number randomised:** 70 **Setting:** not reported **Country:** Taiwan **Sex:** 56 females and 11 males **Age, years:** not reported **Diagnosis:** IC/PBS **Inclusion criteria:** patients with IC/PBS who had failed conventional treatments **Exclusion criteria:** not reported
Interventions	**Group A (n = 46):** botulinum toxin A (100 or 200 units) + hydrodistension 2 weeks later. In Group A, 15 patients: 200 IU botox, 29 patients: 100 IU botox **Group B (n = 24):** hydrodistension All patients continued with oral pentosan polysulfate during the trial **Treatment category in NMA:** neuromuscular blockade vs control
Outcomes	Outcome data in analysis Cure or improvement: 'moderately' or 'markedly' improved on GRA: at 12 months Pain: 10-point VAS (unclear minimum/maximum score): at 3 months Daytime frequency: at 3 months Nocturia: at 3 months ICSI: at 3 months ICPI: at 3 months Functional bladder capacity: at 3 months

Kuo 2009 *(Continued)*

	Adverse events: at > 6 months
Funding	Not reported. One of the study authors is a consultant and investigator for Allergan
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Sub-urothelial injection of BoNT-A followed by cystoscopic hydrodistension (HD) 2 weeks later vs cystoscopic HD using "similar methods as in BoNT-A groups" Unclear if HD was repeated 2 weeks later in HD group. Blinding probably not done
Blinding of outcome assessment (detection bias) Subjective outcome	High risk	Sub-urothelial injection of BoNT-A followed by cystoscopic hydrodistension (HD) 2 weeks later vs cystoscopic HD using "similar methods as in BoNT-A groups" Unclear if HD was repeated 2 weeks later in HD group. Blinding probably not done
Blinding of outcome assessment (detection bias) Objective outcome	Low risk	Outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	44/46 (96%) included in intervention group (2 refused treatment on the day it was scheduled); 23/24 (96%) included in control group (1 refused treatment on the day it was scheduled)
Incomplete outcome data (attrition bias) Pain	Low risk	44/46 (96%) included in intervention group (2 refused treatment on the day it was scheduled); 23/24 (96%) included in control group (1 refused treatment on the day it was scheduled)
Incomplete outcome data (attrition bias) Frequency	Low risk	44/46 (96%) included in intervention group (2 refused treatment on the day it was scheduled); 23/24 (96%) included in control group (1 refused treatment on the day it was scheduled)
Incomplete outcome data (attrition bias) Nocturia	Low risk	44/46 (96%) included in intervention group (2 refused treatment on the day it was scheduled); 23/24 (96%) included in control group (1 refused treatment on the day it was scheduled)
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Low risk	44/46 (96%) included in intervention group (2 refused treatment on the day it was scheduled); 23/24 (96%) included in control group (1 refused treatment on the day it was scheduled)
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Low risk	44/46 (96%) included in intervention group (2 refused treatment on the day it was scheduled); 23/24 (96%) included in control group (1 refused treatment on the day it was scheduled)

Kuo 2009 *(Continued)*

Incomplete outcome data (attrition bias) Functional bladder capacity	Low risk	44/46 (96%) included in intervention group (2 refused treatment on the day it was scheduled); 23/24 (96%) included in control group (1 refused treatment on the day it was scheduled)
Incomplete outcome data (attrition bias) Adverse events	Low risk	44/46 (96%) included in intervention group (2 refused treatment on the day it was scheduled); 23/24 (96%) included in control group (1 refused treatment on the day it was scheduled)
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Kuo 2016

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 2
Participants	**Number randomised:** 60 **Setting:** 2 teaching hospitals **Country:** Taiwan **Sex:** 52 females and 8 males **Age, years:** mean 52.9 (SD 14.3, range 20 to 82) for Group A, mean 50.2 (SD 13.2, range 22 to 71) for Group B **Diagnosis** IC/BPS (NIDDK criteria); Hunner's lesion not included **Inclusion criteria:** IC/BPS patients who had failed at least 6 months of conventional treatments. Patients who had been treated with at least 2 types of treatment modalities including non-steroid anti-inflammatory drugs, oral pentosan polysulfate sodium, intravesical instillation of heparin, hyaluronic acid or tricyclic antidepressant for at least 6 months but symptoms remained unchanged or relapsed **Exclusion criteria:** (1) exclusion criteria by NIDDK; (2) use of anticholinergic drugs for treatment of lower urinary tract symptoms that have an effect; (3) severe cardiopulmonary disease such as congestive heart failure, arrhythmia, poorly controlled hypertension; not able to receive regular follow-up; (4) bladder outlet obstruction on enrolment; (5) urinary retention, PVR (postvoid residual) 150 mL; (6) uncontrolled, confirmed diagnosis of acute urinary tract infection; (7) laboratory abnormalities at screening including alanine aminotransferase (ALT) > 3 times upper limit of the normal range, aspartate aminotransferase (AST) > 3 times upper limit of the normal range, abnormal serum creatinine level > 2 times upper limit of the normal range; (8) use of transurethral catheter; (9) pregnant and lactating woman or woman who intends to become pregnant during the study or who has myasthenia gravis or Eaton-Lambert syndrome; (10) any other serious disease or condition considered by the investigator not suitable for entry into the trial; (11) participation in an investigational drug trial within 1 month before entering this study; (12) unable or unwilling to provide written informed consent for the study; (13) incomplete 3-day micturition diary, according to the study protocol; (14) intestinal bladder augmentation with angioplasty for treatment of overactive bladder
Interventions	**Group A (n = 40):** botulinum toxin A (100 units) + hydrodistension **Group B (n = 20):** NaCl injection + hydrodistension **Treatment category in NMA:** neuromuscular blockade vs control

Kuo 2016 *(Continued)*

Outcomes	Outcome data in analysis Cure or improvement: patients considered 'successful' when they reported improvement on GRA of 1 or more points): at 3 months Pain: 10-point VAS (unclear minimum/maximum score): at 8 weeks Frequency (voids/day): at 8 weeks Nocturia: at 8 weeks ICSI: at 8 weeks ICPI: at 8 weeks Functional bladder capacity: at 8 weeks Adverse events: at 2 months.
Funding	Buddhist Tzu Chi General Hospital
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "'permuted block randomization code in a 2:1 ratio, which was centrally controlled by the clinical pharmacists" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "'permuted block randomization code in a 2:1 ratio, which was centrally controlled by the clinical pharmacists"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind, placebo-controlled trial". Sub-urothelial injection of either BoNT-A or "the equivalent amount of normal saline"; doctors, patients and nurses "did not know which solution was injected into their bladders"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	"double-blind, placebo-controlled trial". Sub-urothelial injection of either BoNT-A or "the equivalent amount of normal saline"; doctors, patients and nurses "did not know which solution was injected into their bladders"
Blinding of outcome assessment (detection bias) Objective outcome	Low risk	Outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Pain	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Frequency	Low risk	All randomised participants were included in analysis

Kuo 2016 *(Continued)*

Incomplete outcome data (attrition bias) Nocturia	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Functional bladder capacity	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Lazzeri 1996

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 6
Participants	**Number randomised:** 36 **Setting:** not reported **Country:** Italy **Sex:** 23 females and 13 males **Age, years:** mean 50.9 (SD 13.1) for Group A, mean 53.2 (SD 11.4) for Group B **Diagnosis:** "severe bladder pain" **Inclusion criteria:** women and men with severe bladder pain. Pelvic pain for at least 6 months and no urinary tract infection (tuberculosis included) within the last 3 months, functional disorders of the lower urinary tract such as detrusor instability, calculi or proliferative vesical pathology **Exclusion criteria:** patients with urethral syndrome were excluded based on abnormalities noted during urodynamic evaluation (dysfunctional external urethral sphincter); patients with Hunner's ulcer at cystoscopy were also excluded, but those with moderate pathological abnormality of the bladder mucosa (edema, rare mast cells and plasma cellular inflammation) were included in the study. Before the study was begun, all patients were assessed for current or previous psychiatric illness, and those with significant psychiatric disease were excluded. However, psychological or related symptoms were noted
Interventions	**Group A (n = 18):** 10 µm capsaicin 30 cc NaCl

Lazzeri 1996 *(Continued)*

	Group B (n = 18): NaCl at 42°C Twice weekly for 1 month **Treatment category in NMA:** calcium channel agonists vs control
Outcomes	Outcome data in analysis Cure or improvement: improvement in pain and symptoms (e.g. frequency), to the point that no medication was required: at 6 months Pain: numerical rating scale (range 0 to 9) on pain frequency and intensity: at 6 months Adverse events: at 6 months
Funding	Not reported
Notes	**Publication status:** full text Notes from previous versions of the review: previous review authors excluded this trial from the original review because patients with Hunner's lesions were excluded. We have included this trial as inclusion criteria meet the diagnosis of bladder pain syndrome

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding not mentioned, but in the control group, "the same procedure [as intravesical capsaicin intervention] was used but with saline 42°C, which mimics the burning or warm sensation of capsaicin as described previously [ref provided]"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	Blinding not mentioned, but in the control group, "the same procedure [as intravesical capsaicin intervention] was used but with saline 42°C, which mimics the burning or warm sensation of capsaicin as described previously [ref provided]"
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	17/18 included in intervention group (1 refused treatment at 4 weeks and withdrew); 18/18 included in control group
Incomplete outcome data (attrition bias) Pain	Low risk	17/18 included in intervention group (1 refused treatment at 4 weeks and withdrew); 18/18 included in control group
Incomplete outcome data (attrition bias) Adverse events	Low risk	17/18 included in intervention group (1 refused treatment at 4 weeks and withdrew); 18/18 included in control group
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Lazzeri 2000

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 3
Participants	**Number randomised:** 18 **Setting:** not reported **Country:** Italy **Sex:** 15 females and 3 males **Age, years:** mean 43.4 **Diagnosis:** "hypertensive disorder and severe pain" **Inclusion criteria:** men and women with hypersensitive disorder and severe bladder pain. Frequency greater than 8 voids, nocturia greater than 2 voids, daily urgency and bladder pain for at least 6 months. Furthermore, we considered absent urinary tract infection, including tuberculosis, within the last 3 months; absent functional disorders of the lower urinary tract as detrusor overactivity; and no calculi or proliferative vesical pathology **Exclusion criteria:** patients diagnosed with urethral syndrome were excluded from the study based on abnormalities identified at urodynamic evaluation such as dysfunctional behaviour of the external urethral sphincter. Those for whom cystoscopy revealed Hunner's ulcer were also excluded, but we included in our analysis patients with moderate pathological abnormalities such as edema, rare mast cells and plasmacellular inflammation. Before study initiation, all patients were assessed for current or previous psychiatric illness; those with significant psychiatric disease were also excluded from analysis. However, psychological or associated symptoms were recorded
Interventions	**Group A (n = 9):** resiniferatoxin (RTX) 10 µm in 0.1% ethanol (RTX = ultra potent analogue of chili pepper extract capsaicin) **Group B (n = 9):** NaCl **Treatment category in NMA:** calcium channel agonists vs control
Outcomes	Outcome data in analysis Pain: numerical rating scale (range 0 to 9) on pain frequency and intensity: at 3 months Frequency: at 3 months Nocturia: at 3 months Adverse events: at 3 months
Funding	Not reported
Notes	**Publication status:** full text

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided.

Lazzeri 2000 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	"The same procedure" used to instill resiniferatoxin or saline (placebo). During infusion 4 in intervention group "noticed a light warm or burning sensation at the suprapubic and/or urethral level but those who received placebo noticed no sensation".
Blinding of outcome assessment (detection bias) Subjective outcome	High risk	"The same procedure" used to instill resiniferatoxin or saline (placebo). During infusion 4 in intervention group "noticed a light warm or burning sensation at the suprapubic and/or urethral level but those who received placebo noticed no sensation".
Incomplete outcome data (attrition bias) Pain	Unclear risk	Number analysed not stated.
Incomplete outcome data (attrition bias) Frequency	Unclear risk	Number analysed not stated.
Incomplete outcome data (attrition bias) Nocturia	Unclear risk	Number analysed not stated.
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Number analysed not stated.
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section.
Other bias	Low risk	Not detected.

Leadership 201 Trial 2016

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 1.5
Participants	**Number randomised:** 69 **Setting:** 31 sites (19 in Canada and 12 in USA) **Country:** Canada, USA **Sex:** female **Age, years:** mean 52.1 (SD 14.9) for Group A, mean 53.1 (SD 12.9) for Group B **Diagnosis:** IC/BPS **Inclusion criteria:** women 18 to 75 years old with a diagnosis of IC/BPS for greater than 6 months but 15 years or less, and bladder pain for 12 months or longer, were eligible for enrolment in a screening period of 9 to 21 days if they met inclusion criteria including baseline mean pain 5 or greater on an 11-point scale, BPIC-SS score 19 or greater, 20 baseline combined O'Leary-Sant ICSI/PI21 score 8 or greater, at least 8 urinary voids per 24 hours and history of cystoscopy within 36 months, revealing signs consistent with IC/BPS diagnosis including but not restricted to Hunner's lesion

Leadership 201 Trial 2016 *(Continued)*

	Exclusion criteria: women were excluded from analysis if they had pelvic floor pain greater than 5 of 10 as assessed by the investigator, BMI less than 18 or greater than 39 kg/m^2, recent cystoscopy with therapeutic hydrodistension within 3 months or bladder surgery within 3 years
Interventions	**Group A (n = 37):** daily 200 mg AQX-1125 capsule (oral) **Group B (n = 32):** placebo Participants in this trial were allowed to remain on stable doses of most IC/BPS medications. The 2 most common medications were pentosan polysulfate sodium and amitriptyline **Treatment category in NMA:** AQX-1125 vs control
Outcomes	Outcome data in analysis Pain: numerical rating scale (range 0 to 10): at 4 weeks ICSI: at 4 weeks ICPI: at 4 weeks
Funding	Aquinox Pharmaceuticals
Notes	**Publication status:** full text

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "centrally ramdomized"
Allocation concealment (selection bias)	Low risk	Quote: "centrally ramdomized"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind, placebo controlled" study, using a single daily capsule of study drug or "matched placebo"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	"double-blind, placebo controlled" study, using a single daily capsule of study drug or "matched placebo"
Incomplete outcome data (attrition bias) Pain	Low risk	All randomised participants were included in analysis ("missing data imputed using the last observation carried forward approach")
Incomplete outcome data (attrition bias) Frequency	Low risk	
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Low risk	All randomised participants were included in analysis ("missing data imputed using the last observation carried forward approach")
Incomplete outcome data (attrition bias)	Low risk	All randomised participants were included in analysis ("missing data imputed using the last observation carried forward approach")

Leadership 201 Trial 2016 *(Continued)*

Interstitial Cystitis Problem Index		
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Lee 2014

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 2
Participants	**Number randomised:** 80 **Setting:** not reported **Country:** Taiwan **Sex:** not reported **Age, years:** mean 46.5 (SD 10.2) for Group A, mean 49.5 (SD 11.8) for Group B **Diagnosis:** IC/BPS **Inclusion criteria:** BPS/IC patients **Exclusion criteria:** not reported
Interventions	**Group A (n = 40):** e-health system (Internet intervention to change habitual behaviour; no treatment, with questionnaires, SMS question/answer service for symptom relief) **Group B (n = 40):** control (unclear what this entails - includes treatment) **Treatment category in NMA:** behavioural therapy vs control
Outcomes	Outcome data in analysis Pain: VAS (assumed range 0 to 10): at 8 weeks ICSI: at 8 weeks ICPI: at 8 weeks
Funding	Supported in part by Taichung Hospital and National Science Council of Taiwan
Notes	**Publication status:** full text

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned"

Lee 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Probably not done. E-health system vs control treatment Quote: "treatment was only given to the patients in the control group"
Blinding of outcome assessment (detection bias) Subjective outcome	High risk	Probably not done. E-health system vs control treatment Quote: "treatment was only given to the patients in the control group"
Incomplete outcome data (attrition bias) Pain	Low risk	33/40 (83%) included in intervention group; 32/40 (80%) included in control group. 7 and 8 from each group excluded for not filling out the questionnaire before or after testing
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Low risk	33/40 (83%) included in intervention group; 32/40 (80%) included in control group. 7 and 8 from each group excluded for not filling out the questionnaire before or after testing
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Low risk	33/40 (83%) included in intervention group; 32/40 (80%) included in control group. 7 and 8 from each group excluded for not filling out the questionnaire before or after testing
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Lee 2016

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 2
Participants	**Number randomised:** 56 **Setting:** not reported **Country:** Taiwan **Sex:** not reported **Age, years:** not reported **Diagnosis:** IC/BPS **Inclusion criteria:** IC/BPS patients **Exclusion criteria:** not reported
Interventions	**Group A (n = 29):** self-management telecare system (patient video education, mobile phone app, lifestyles) **Group B (n = 27):** control (no detail)

Lee 2016 *(Continued)*

	Treatment category in NMA: behavioural therapy vs control
Outcomes	Outcome data in analysis Pain: VAS (assumed 0 to 10): at 8 weeks ICSI: at 8 weeks ICPI: at 8 weeks
Funding	None
Notes	**Publication status:** abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned. Video education system vs control
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	Blinding not mentioned. Video education system vs control
Incomplete outcome data (attrition bias) Pain	Unclear risk	Number analysed not stated
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Unclear risk	Number analysed not stated
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Unclear risk	Number analysed not stated
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Lu 2015

Study characteristics

Methods	**Study design:** RCT

Lu 2015 *(Continued)*

	Study duration (months): 12
Participants	**Number randomised:** 24 **Setting:** single centre **Country:** China **Sex:** not reported **Age, years:** mean 44.1 (SD 6.7, range 34 to 54) for Group A, mean 45.0 (SD 8.8, range 30 to 60) for Group B **Diagnosis:** IC **Inclusion criteria:** patients with IC **Exclusion criteria:** not reported
Interventions	**Group A (n = 11):** heparin-lidocaine instillation **Group B (n = 13):** intravesical hyaluronic acid instillation **Treatment category in NMA:** anticoagulants + local anaesthetics vs hyaluronic acid
Outcomes	Outcome data in analysis Cure: complete remission: at 12 months Pain: VAS (range 0 to 6): at 12 months Frequency, daily: at 12 months Adverse events: at 12 months (assumed from reports)
Funding	Not reported
Notes	**Publication status:** full text Publication in Chinese language with English abstract. Information was extracted mainly from the abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly divided" Comment: no further information available (paper in Chinese)
Allocation concealment (selection bias)	Unclear risk	No information available (paper in Chinese)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information available (paper in Chinese). Intravesical instillation of heparin-lidocaine vs hyaluronic acid
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	No information available (paper in Chinese). Intravesical instillation of heparin-lidocaine vs hyaluronic acid
Incomplete outcome data (attrition bias)	Low risk	All randomised participants were included in analysis

Lu 2015 *(Continued)*

Cure or improvement		
Incomplete outcome data (attrition bias) Pain	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Frequency	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Unclear risk	No information available (paper in Chinese)
Other bias	Low risk	None detected

Manning 2014

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 3
Participants	**Number randomised:** 53 **Setting:** 3 centres **Country:** Australia **Sex:** female **Age, years:** mean 54 for Group A, mean 53 for Group B **Diagnosis:** IC/PBS (NIDDK criteria) **Inclusion criteria:** female patients with long-standing refractory IC/PBS. Being refractory was defined as having failed 2 or more recognised treatments **Exclusion criteria:** known history of recurrent urinary tract infection (UTI), current pregnancy, bladder malignancy, steroid use, voiding difficulty
Interventions	**Group A (n = 26):** botox + hydrodistension. Trigone avoided **Group B (n = 27):** saline + hydrodistension **Treatment category in NMA:** neuromuscular blockade vs control
Outcomes	Outcome data in analysis Cure or improvement: clinically significant improvement defined as reduction in baseline score ≥ 50% in O'Leary-Sant symptom scores: at 3 months Frequency: at 3 months Nocturia: at 3 months ICSI: at 3 months ICPI: at 3 months

Manning 2014 *(Continued)*

	Functional bladder capacity: at 3 months Adverse events: at 3 months
Funding	Not reported. One of the study authors is on Advisory Board for Allergan
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a series of three separate computer-generated randomisation numbers for each centre"
Allocation concealment (selection bias)	Low risk	Randomisation numbers were "provided by the mathematics department and were held confidentially by pharmacy. De-identified syringes were delivered to theatre"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind". Sub-urothelial injection of saline or AboBTXA in de-identified syringe with hydrodistension under general anaesthesia. "Patients and treating doctors were blinded to initial treatment allocation"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	"double-blind". Sub-urothelial injection of saline or AboBTXA in de-identified syringe with hydrodistension under general anaesthesia. "Patients and treating doctors were blinded to initial treatment allocation"
Blinding of outcome assessment (detection bias) Objective outcome	Low risk	Outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Frequency	Low risk	25/26 included in intervention group; 26/27 included in control group. 1 in each group missing due to incomplete bladder diary
Incomplete outcome data (attrition bias) Nocturia	Low risk	25/26 included in intervention group; 26/27 included in control group. 1 in each group missing due to incomplete bladder diary
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Functional bladder capacity	Low risk	25/26 included in intervention group; 26/27 included in control group. 1 in each group missing due to incomplete bladder diary

Manning 2014 *(Continued)*

Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Matsumoto 2013

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 2
Participants	**Number randomised:** 30 **Setting:** not reported **Country:** Japan **Sex**: 27 females and 1 male (participants in analysis only) **Age, years:** mean 65.2 (SD 7.9) for Group A, mean 64.5 (SD 4.5) for Group B (participants in analysis only) **Diagnosis:** IC/PBS (clinical diagnosis) **Inclusion criteria:** patients aged > 50 years with IC/PBS, who fulfilled the diagnostic criteria for IC proposed by the clinical guideline for IC. Stable history of IC/PBS symptoms ≥ 12 weeks after bladder hydrodistension, total ICSI score ≥ 7 and bladder pain (question 4 on ICSI) ≥ 4 **Exclusion criteria** > 200 mL of average voided volume; urinary tract infection and vaginitis; urolithiasis; significant hepatic, renal, cardiac or cerebrospinal disease; neurological bladder (e.g. spinal cord injury, Parkinson's disease); surgery and/or radiotherapy to the pelvis; use of any dietary and/or antioxidant supplement; initiation of bladder training in the 12 weeks before the start of the study; initiation or discontinuation or change of the dose of the following drugs within 4 weeks after registration: antidepressant, anticholinergic drug, antihistaminergic drug, any drugs for lower urinary tract symptoms and steroids
Interventions	**Group A (n = not reported):** hydrogen-rich water 3 packs/d (1 pack, 200 mL) **Group B (n = not reported):** placebo water 3 packs/d (1 pack, 200 mL) Regimen: 8 weeks 18 analysed in Group A, 10 analysed in Group B **Treatment category in NMA:** hydrogen-rich water vs control
Outcomes	Outcome data in analysis Pain: VAS (range 0 to 10): at 8 weeks ICSI: at 8 weeks ICPI: at 8 weeks Adverse events: at 8 weeks

Matsumoto 2013 *(Continued)*

Funding	Public Health Research Foundation Comprehensive Support Project for Clinical Research Office on lifestyle-related disease
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the randomization was performed by an independent statistician and was stratified by the Public Health Research Centre" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "the randomization was performed by an independent statistician and was stratified by the Public Health Research Centre" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind, placebo-controlled" trial, using hydrogen-rich water and "placebo water". Placebo not described
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	"double-blind, placebo-controlled" trial. Placebo not described
Incomplete outcome data (attrition bias) Pain	Unclear risk	Number randomised per group not stated. 30 randomised; 28 analysed (18 in intervention group, 10 in placebo group)
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Unclear risk	Number randomised per group not stated. 30 randomised; 28 analysed (18 in intervention group, 10 in placebo group)
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Unclear risk	Number randomised per group not stated. 30 randomised; 28 analysed (18 in intervention group, 10 in placebo group)
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Number analysed or number randomised per group not stated
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Mayer 2005

Study characteristics

Methods	**Study design:** RCT

Mayer 2005 *(Continued)*

	Study duration (months): 17 (for the purpose of this review, data at 8.5 months' follow-up were used in analysis)
Participants	**Number randomised:** 265 **Setting:** multi-centre **Country:** USA **Sex:** 217 females and 48 males **Age, years:** mean 46.1 for 217 women **Diagnosis:** IC (NIDDK criteria) **Inclusion criteria:** eligible participants were at least 18 years old and received a diagnosis of IC, confirmed by cystoscopy and hydrodistension, according to National Institutes of Health-NIDDK criteria. All patients were required to have urinary frequency (self-reported 11 or more daily) and pain/discomfort (4 or more on a 0 to 9 Likert scale) for at least 24 weeks before study entry. Minimum of 12 weeks of treatment with any standard form of therapy or combination of therapies for IC must have failed; patients could not have been previously treated with BCG **Exclusion criteria 1 (medical history, comorbid conditions and tests):** any history of bladder calculus, tuberculous cystitis; neurological disease affecting bladder function; bladder cancer, urethral cancer, prostate cancer (men only); other neoplasms requiring systemic therapy. Prior 12 weeks: genital herpes. Prior 6 weeks: positive urine culture (100,000 colony count). Concurrent: active tuberculosis requiring ongoing therapy; immunocompromised or known positive for HIV; vesicoureteral reflux; unable to void spontaneously; active urethral calculus, ureteral calculus, urethral diverticulum; documented chronic bacterial prostatitis (men only); active vaginitis, pregnancy, breastfeeding (women only); severe debilitating medical conditions; at least 1 voided volume 75 cc in a 24-hour period; residual urine volume 150 cc by ultrasound or catheter (men only) **Exclusion criteria 2 (prior and concurrent treatment):** any history of: intravesical BCG, known allergy to or intolerance of BCG; cyclophosphamide; pelvic radiation; augmentation cystoplasty, cystectomy or cystolysis; neurectomy, implanted peripheral nerve stimulator. Prior 24 weeks: botulinum toxin injections for voiding dysfunction; urinary incontinence surgery; other bladder or urethral surgery that could interfere with bladder function; TURP, TUIP, TUIBN, TUMT, TUNA, balloon dilation of the prostate, open prostatectomy or any other prostate treatment such as cryotherapy or thermal therapy (men only); transvaginal surgery, hysterectomy, prolapse surgery, vaginal delivery or C-section (women only). Prior 12 weeks: hydrodistension, any intravesical treatment. Prior 6 weeks: urethral dilation, urodynamics, cystoscopy, bladder biopsy. Prior 4 weeks: initiation of any new medications for IC; any use of pentosan polysulfate; participation in another intervention study. Concurrent: isoniazid, rifampin, other antituberculosis therapies; anticoagulant therapy with the exception of low-dose aspirin
Interventions	**Group A (n = 131):** 1 mL of live TICE bacillus Calmette-Guérin (BCG) dissolved in 49 mL of normal saline **Group B (n = 134)**: 50 mL of normal saline Up to six 50 mL instillations, each lasting up to 2 hours. Interval of 6 days to 3 weeks between instillations, and all completed within 10 weeks **Treatment category in NMA:** immune modulators vs control
Outcomes	Outcome data in analysis Cure or improvement: response to instillation at week 34 (from start of treatment). This is defined as report of moderate or marked improvement on GRA, as well as recording no new IC treatments, no additional narcotic analgesia and no increase in IC medication dosage during weeks 31 to 34 Pain: VAS (range 0 to 9): at 34 weeks ICSI: at 34 weeks ICPI: at 34 weeks

Mayer 2005 *(Continued)*

	Functional bladder capacity: at 34 weeks Adverse events: at 34 weeks
Funding	Co-operative agreements from NIDDK, University of Maryland General Clinical Research Centre Grant, General Clinical Research Centres Program, National Centre for Research Resources, NIH (National Institutes of Health)
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind, placebo-controlled". Placebo not described. Intravesical BCG vs intravesical placebo
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	"double-blind, placebo-controlled". Placebo not described. For improvement outcome, "a blinded, centralised review of the GRA [global response assessment) and medication diaries was performed". Unclear for other outcomes
Blinding of outcome assessment (detection bias) Objective outcome	Low risk	Outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Pain	Low risk	120/131 (92%) included in intervention group; 126/134 (94%) included in placebo group
Incomplete outcome data (attrition bias) Frequency	Low risk	
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Low risk	120/131 (92%) included in intervention group; 126/134 (94%) included in placebo group
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Low risk	120/131 (92%) included in intervention group; 126/134 (94%) included in placebo group
Incomplete outcome data (attrition bias)	Low risk	109/131 (83%) included in intervention group; 113/134 (84%) included in placebo group

Mayer 2005 *(Continued)*

Functional bladder capacity		
Incomplete outcome data (attrition bias) Adverse events	Low risk	129/131 (98%) included in intervention group; 132/134 (99%) included in placebo group
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Mirkin 2012

Study characteristics	
Methods	**Study design:** RCT**Study duration (month):** 0.2
Participants	**Number randomised:** 23 **Setting:** not reported **Country:** Russia **Sex:** female **Age, years:** mean 38, SD 11 **Diagnosis:** PBS **Inclusion criteria:** women with PBS **Exclusion criteria:** not reported
Interventions	**Group A (n = 15):** incobotulinumtoxin A 200IU with 20 ml distilled water with 200 mcl 0.1 N HCl and 2 ml DMSO (dimethyl sulfoxide) **Group B (n = 8):** NaCl 25 ml **Treatment category in NMA:** neuromuscular blockade + DMSO versus control
Outcomes	Outcome data in analysis Pain: VAS (assumed range 0 to 10) at 5 days Frequency: at 5 days Adverse events: at 5 days
Funding	NMTC International
Notes	**Publication status:** abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"

Mirkin 2012 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned. Intravesical electromotive incobotulinumtoxinA and DMSO (20 ml) versus saline (25 ml).
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	Blinding not mentioned. Intravesical electromotive incobotulinumtoxinA and DMSO (20 ml) vs. Saline (25 ml).
Incomplete outcome data (attrition bias) Pain	Unclear risk	Number analysed not stated.
Incomplete outcome data (attrition bias) Frequency	Unclear risk	Number analysed not stated.
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Number analysed not stated.
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section.
Other bias	Low risk	Not detected.

Mirkin 2015

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 1
Participants	**Number randomised:** 68 **Setting:** not reported **Country:** Russia **Sex:** female **Age, years:** not reported **Diagnosis:** BPS **Inclusion criteria:** women with BPS **Exclusion criteria:** not reported
Interventions	**Group A (n = 38):** hyaluronic acid (HA) 40 mg/50 mL plus 15 mg of tacrolimus (anticytokine substance). Tacrolimus was preliminarily dissolved in dimethyl sulfoxide (DMSO) 15 mg/5 mL and was mixed with HA before instillation **Group B (n = 30):** HA 40 mg/50 mL (BioCyst) twice a week for 3 months **Treatment category in NMA:** anticytokines vs control

Mirkin 2015 *(Continued)*

Outcomes	Outcome data in analysis Pain: VAS (assumed range 0 to 10): at 1 month Frequency: at 1 month
Funding	Not reported
Notes	**Publication status:** abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned. Intravesical instillation of hyaluronic acid (HA) vs HA + anticytokine substances (tacrolimus)
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	Blinding not mentioned. Intravesical instillation of hyaluronic acid (HA) vs HA + anticytokine substances (tacrolimus)
Incomplete outcome data (attrition bias) Pain	Unclear risk	Number analysed not stated. 2/19 (11%) dropped out from HA group; 3/19 (16%) dropped out from HA + tacrolimus group, all due to pain after instillation. Unclear how missing data were handled
Incomplete outcome data (attrition bias) Frequency	Unclear risk	Number analysed not stated. 2/19 (11%) dropped out from HA group; 3/19 (16%) dropped out from HA + tacrolimus group, all due to pain after instillation. Unclear how missing data were handled
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Moldwin 2015

Study characteristics

Methods	**Study design:** RCT **Study duration (months):** 1
Participants	**Number randomised:** 74 **Setting:** not reported **Country:** USA **Sex:** female **Age, years:** not reported

Moldwin 2015 *(Continued)*

	Diagnosis: IC/BPS with moderate to severe pain **Inclusion criteria:** women with IC/BPS with moderate to severe pain **Exclusion criteria:** not reported
Interventions	**Group A (n = 36):** AF-219 **Group B (n = 38):** placebo **Regimen:** AF-219 was started at 50 mg BID and was titrated up by 50 mg BID every day until 300 mg or until the highest tolerable dose **Treatment category in NMA:** P2X3 antagonist vs control
Outcomes	Outcome data in analysis Adverse events: at 1 month
Funding	Afferent Pharmaceuticals, Inc
Notes	**Publication status:** abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind, placebo controlled study". Placebo not described
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	"double-blind, placebo controlled study". Placebo not described
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Number analysed not reported
Selective reporting (reporting bias)	Unclear risk	Outcomes not specified in methods (abstract only)
Other bias	Low risk	None detected

Mulholland 1990

Study characteristics

Methods	**Study design:** RCT**Study duration (months):** 3
Participants	**Number randomised:** 110

Mulholland 1990 *(Continued)*

	Setting: 5 centres **Country:** USA **Sex:** 98 females and 12 males **Age, years:** mean 43.3 for Group A, mean 45.3 for Group B **Diagnosis:** IC **Inclusion criteria:** patients with the following examination requirement and symptom complex: urgency expressed as moderate on a 5-point analog scale; frequency of at least 10 voids per day; nocturia of at least 2 voids per night; pain as recorded on a 5-point analog scale; continuous duration of symptom for at least 1 year; failed previous conventional therapy such as Clorpactin, hydrodilation or DMSO; average voided volume of 200 mL measured over 3-day period; negative urine culture and cytology; cystoscopic examination under anaesthesia showing petechial haemorrhages or ulcers with gross blood in the fluid return and bladder capacity of 800 mL or less **Exclusion criteria:** patients with any of the following conditions: younger than 18 years; pregnancy; premenopausal and not practicing effective means of birth control; evidence of active bleeding peptic ulcer disease; bleeding diathesis; anticoagulant therapy; long-term use of narcotics; known allergy to pentosan polysulfate sodium; lack of availability for the duration of the study or inability to follow instructions; use of artificial sweeteners; lactating mothers; signs of recurrent bacteriuria; obvious neurological impairment; previous treatment with known bladder irritants; bladder carcinoma; urinary tuberculosis; schistosomiasis; treatment with Elmiron within 6 weeks of study
Interventions	**Group A (n = 54):** pentosan polysulfate (PPS, oral) **Group B (n = 56):** placebo **Treatment category in NMA:** PPS vs control
Outcomes	Outcome data in analysis Cure or improvement: patient self-evaluation: overall improved: at 3 months Pain: VAS (range 0 to 5): at 12 weeks Adverse events: at 12 weeks
Funding	PPS and placebo supplied by Medical Market Specialities, Inc., Boonton, New Jersey, USA
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned … with a computer-generated random code"
Allocation concealment (selection bias)	Low risk	Quote: "all investigators were blinded during the study with the code established and maintained by a separate centre"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind"; "identically-appearing placebo capsules were given in the same manner" as study drug
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	"double blind"; "identically-appearing placebo capsules were given in the same manner" as study drug

Mulholland 1990 *(Continued)*

Incomplete outcome data (attrition bias) Cure or improvement	Low risk	51/54 (94%) included in intervention group; 47/56 (84%) included in control group. "It is likely that lack of efficacy was responsible for patients dropping out"; "only 1 PPS and 2 placebo patients discontinued treatment due to adverse reactions"
Incomplete outcome data (attrition bias) Pain	Unclear risk	Number analysed not reported
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Number analysed not reported
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Nguan 2005

Study characteristics	
Methods	**Study design:** cross-over randomised trial **Study duration (months):** 5
Participants	**Number randomised:** 26 **Setting:** multi-centre **Country:** Canada **Sex:** female **Age, years:** not reported **Diagnosis:** IC (NIDDK criteria) **Inclusion criteria:** patients with IC **Exclusion criteria:** not reported
Interventions	**Group A (n = 13):** acidic-buffered solution with pH of 5.0 **Group B (n = 13):** neutral buffered solution (H2PO4) with pH of 7.5 Single instillation via catheter of 100 mL solution, lasting for 30 minutes. Bladder then drained and washed twice with sterile de-ionised water; a second 100 mL solution then instilled **Treatment category in NMA:** buffer solutions vs control
Outcomes	Outcome data in analysis Pain: 10-point numerical rating scale (assumed range 0 to 9): at 5 minutes after instillation
Funding	Interstitial Association, USA
Notes	**Publication status:** full text Cross-over trial. Data for the first phase only were sought for this review

Nguan 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned"; "in blocks of four"; "generated using appropriate software" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned. Bladder instillation with acidic vs neutral buffered solution
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	Blinding not mentioned. Bladder instillation with acidic vs neutral buffered solution
Incomplete outcome data (attrition bias) Pain	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Nickel 2009

Study characteristics

Methods	**Study design:** RCT**Study duration (months):** 0.5
Participants	**Number randomised:** 102 **Setting:** 19 centres **Country:** USA and Canada **Sex:** 99 female and 3 male **Age, years:** median 42.5 (range 20 to 70) for Group A, median 49.0 (range 21 to 74) for Group B **Diagnosis:** IC/PBS (clinical diagnosis) **Inclusion criteria:** men and women aged 18 to 75 years with a history of symptoms of bladder pain/discomfort ≥ 4 on a 10-point Likert scale, described as suprapubic pain related to bladder filling, accompanied by other symptoms including increased daytime and nighttime frequency (≥ 8 and ≥ 2, respectively) in the absence of infection or other pathology, with or without the typical cystoscopic appearance of IC. Symptoms of abnormal urinary frequency and bladder pain/discomfort must have been present for ≥ 3 months before study entry, as well as anterior vaginal wall/bladder wall pain on bimanual examination **Exclusion criteria:** patients were excluded from the study if any of the following criteria were present: (1) currently receiving local anaesthetic analogue therapy or had received treatment for IC/PBS within 4 weeks before baseline visit; (2) unable to void spontaneously; (3) history of cardiac arrhythmias, other cardiac conduction disturbances and/or significant cardiovascular disease; (4) liver disease; (5) pelvic

Nickel 2009 *(Continued)*

	radiotherapy; (6) tuberculous cystitis; (7) neurological disease affecting bladder function; (8) bladder cancer, or carcinoma in situ, or urethral cancer; (9) bladder, urethral or ureteric calculi or clinical evidence of urethritis; (10) severely debilitating or urgent concurrent medical condition; (11) men with history of prostate cancer or an unevaluated suspicious prostate examination, or who were receiving treatment for chronic bacterial prostatitis, as documented by a positive urine culture; or previous history of recurrent bacterial UTI; (12) women who were pregnant or breastfeeding or had symptoms of bladder pain/discomfort and urinary frequency present only during menstruation; (13) women of child-bearing potential, or men with partners of child-bearing potential, who were not prepared to commit to use of a reliable form of contraception during the course of the study
Interventions	**Group A (n = 50):** PSD597 (200 mg lidocaine + 8.4% sodium bicarbonate solution to a final volume of 10 mL) (PSD597 = intravesical alkalinised lidocaine) **Group B (n = 52):** saline **Treatment category in NMA:** local anaesthetics vs control
Outcomes	Outcome data in analysis Cure or improvement: 'moderately' or 'markedly' improved on GRA: at 15 days Pain: 10-point Likert scale (assumed range 0 to 9 as reported in Nickel 2010 but could be 1 to 10): at 15 days ICSI: at 15 days ICPI: at 15 days Adverse events: at 15 days
Funding	Plethora Solutions Plc
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind, placebo-controlled" trial. Blinding methods not described. Bladder instillation of 10 mL of local anaesthestic or 10 mL of saline (placebo)
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	"double-blind, placebo-controlled" trial. Blinding methods not described. Bladder instillation of 10 mL of local anaesthestic or 10 mL of saline (placebo)
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	45/50 (90%) included in intervention group; 50/52 (96%) included in control group
Incomplete outcome data (attrition bias) Pain	Low risk	45/50 (90%) included in intervention group; 50/52 (96%) included in control group

Nickel 2009 *(Continued)*

Incomplete outcome data (attrition bias) Frequency	Low risk	
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Low risk	45/50 (90%) included in intervention group; 48/52 (92%) included in control group
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Low risk	45/50 (90%) included in intervention group; 48/52 (92%) included in control group
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Nickel 2010

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 3
Participants	**Number randomised:** 65 **Setting:** multi-centre **Country:** Canada, USA **Sex:** 64 females and 1 male **Age, years:** mean 45.5 (SD 16.07) for Group A, mean 44.4 (SD 14.87) for Group B **Diagnosis:** IC/PBS. Clinical diagnosis consistent with the IC Database Study (Hanno 1999), and definition of IC/PBS described at the NIH Urologic Chronic Pelvic Pain Consensus Symposium (Baltimore, December 2007) **Inclusion criteria:** females and males at least 18 years of age with clinical diagnosis of IC/PBS and no medical condition or therapy that would exclude safe concomitant use of chondroitin sulfate were evaluated in this clinical trial. Patients met all of the following inclusion criteria for this study: female or male patient 18 years or older; negative bacterial urine culture from urine collected aseptically during the screening period; patient-reported average urinary frequency at least 11 times per 24-hour period during the screening period, as captured by a 2-day diary; average pain/discomfort score of at least 4 on a 0 to 9 Likert pain scale during the screening period. In addition, all female patients of child-bearing age had a negative urine pregnancy test at baseline, or assurance of previous surgery, condition or state rendering conception impossible **Exclusion criteria:** patients who met any of the following criteria: lactating females; currently receiving or having previously received investigational drugs within 30 days of screening; received any intravesical therapy for IC/PBS within 4 months of first study instillation; received any oral therapy for IC/PBS within 2 months of first study instillation (an exception is permitted for oral tricyclic antidepressants). Patients were excluded if they were prescribed antihistamines, hormonal agonists or antagonist therapies within the last 2 months (they could be included if doses of these therapies had been stable during

Nickel 2010 *(Continued)*

	the last 2 months and did not change during the duration of the study); had neurological disease that is known to or may affect bladder function; had previous surgeries or procedures that affected bladder function; had a current diagnosis of chemical tuberculosis or radiation cystitis; had a history of bladder or lower ureteral calculi; had a history of cancer within the last 5 years other than adequately treated non-melanoma skin cancer; were known to have an active sexually transmitted disease; were known to have current vaginitis; or had current endometriosis confirmed by laparoscopy or biopsy. Patients receiving allowable pre-study therapies for IC/PBS were asked not to change these regimens throughout the course of treatment and follow-up periods. Instead, to manage any episodes of increased pain associated with IC/PBS, the following analgesic therapies were allowed: narcotic analgesics, urinary analgesics, non-steroidal anti-inflammatory drugs, salicylate and other non-narcotic analgesics
Interventions	**Group A (n = 33):** 20 mL of 2% sodium chondroitin sulfate **Group B (n = 32):** 20 mL NaCl **Treatment category in NMA:** chondroitin sulfate vs control
Outcomes	Outcome data in analysis Cure or improvement: 'moderately' or 'markedly' improved on GRA: at 12 weeks Pain: 10-point Likert scale (range 0 to 9): at 7 weeks Frequency: at 7 weeks ICSI: at 12 weeks ICPI: at 12 weeks Adverse events: at 12 weeks
Funding	Watson Pharmaceuticals, Inc.
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized … after a predetermined randomization schedule"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind". Intravesical instillation of study drug or vehicle control. "Blinding … was maintained throughout the study by use of identical patient kits containing identically appearing active or vehicle control vials and packaging"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	Quote: "double-blind". Intravesical instillation of study drug or vehicle control. "Blinding … was maintained throughout the study by use of identical patient kits containing identically appearing active or vehicle control vials and packaging"
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	29/33 (88%) included in intervention group (2 discontinued due to consent withdrawal, 1 due to lack of efficacy, 1 lost to follow-up); 29/33 (88%) included in control group (1 discontinued due to adverse event, 1 due to consent withdrawal); LOCF also used

Nickel 2010 *(Continued)*

Incomplete outcome data (attrition bias) Pain	Low risk	29/33 (88%) included in intervention group (2 discontinued due to consent withdrawal, 1 due to lack of efficacy, 1 lost to follow-up); 29/33 (88%) included in control group (1 discontinued due to adverse event, 1 due to consent withdrawal); LOCF also used
Incomplete outcome data (attrition bias) Frequency	Low risk	29/33 (88%) included in intervention group (2 discontinued due to consent withdrawal, 1 due to lack of efficacy, 1 lost to follow-up); 29/33 (88%) included in control group (1 discontinued due to adverse event, 1 due to consent withdrawal); LOCF also used
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Low risk	29/33 (88%) included in intervention group (2 discontinued due to consent withdrawal, 1 due to lack of efficacy, 1 lost to follow-up); 29/33 (88%) included in control group (1 discontinued due to adverse event, 1 due to consent withdrawal); LOCF also used
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Low risk	29/33 (88%) included in intervention group (2 discontinued due to consent withdrawal, 1 due to lack of efficacy, 1 lost to follow-up); 29/33 (88%) included in control group (1 discontinued due to adverse event, 1 due to consent withdrawal); LOCF also used
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Nickel 2012a

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 2.8
Participants	**Number randomised:** 98 **Setting:** multi-centre **Country:** USA **Sex:** female **Age, years:** mean 44.4 (SD 14.59) for Group A, mean 46.8 (SD 14.06) for Group B. 8 women (8.2%) were aged 65 and above **Diagnosis:** IC/BPS **Inclusion criteria:** women were considered for inclusion in the present study if they had been diagnosed or re-diagnosed with IC/BPS within the previous 2 years; had a subject-reported average urinary frequency of 8 times/24 hours during the screening period, as captured by a 3-day diary; had a pain/pressure/discomfort score of 40 to 80 mm on a pain visual analog scale (VAS) during the screening period; and had an inadequate clinical response after 6 months of conservative treatment. Conservative treatment could have included ≥ 1 of the following: patient education, timed voiding and behavioural modification therapy, dietary restrictions, stress reduction and/or oral therapy with tricyclic antidepressants, antihistamines, antimuscaranic (anticholinergic) agents, α-adrenergic blockers or analgesics. Subjects were also required to have had a negative urine pregnancy test at screening and had to

Nickel 2012a *(Continued)*

	agree to use an acceptable form of birth control, as agreed to by the investigator, during the study period, if of child-bearing potential **Exclusion criteria:** subjects were excluded from participation if they were lactating; had previously received investigational products or devices within 30 days of screening; had previously received Uracyst; had had symptoms of IC/BPS for > 8 years; or had received any intravesical therapy (including hydrodistension), oral pentosan polysulfate or oral chondroitin within 12 weeks of screening. They were also excluded if they had received any of the following medications within 4 weeks of screening, unless such medications had been administered at a stable dose during that month and no changes had been made to these medications during the study: tricyclic antidepressants, antihistamines (use of antihistamines as needed for allergies were allowed), anticonvulsants, adrenergic blockers, hormonal agonists or antagonists or anticholinergic agents. Also, women were excluded if they had used ≥ 70 mg of morphine equivalents of opioids weekly within 4 weeks of screening; were currently receiving therapy with invasive neuromodulation; had any current condition that could be confused with IC/BPS or could confuse the presentation of IC/BPS; had a screening period postvoid residual urine volume > 100 mL; or had a history of bladder or lower ureteral calculi or previous surgery or procedures that could have affected bladder function or any cancer within 5 years before screening, other than adequately treated non-melanoma skin cancer
Interventions	**Group A (n = 49):** 20 mL of 2% sodium chondroitin sulfate **Group B (n = 49):** 20 mL of NaCl Weekly for 8 weeks **Treatment category in NMA:** chondroitin sulfate vs control
Outcomes	Outcome data in analysis Cure or improvement: 'moderately' or 'markedly' improved at 15 days: at 11 weeks Pain: VAS (assumed range 0 to 100): at 11 weeks Frequency: at 11 weeks ICSI: at 11 weeks ICPI: at 11 weeks Adverse events: at 11 weeks
Funding	Watson Pharmaceuticals, Inc.
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the treatment assignment was made according to a randomization schedule generated using a permuted block by a randomisation statistician (independent from the project statistician)" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "the treatment assignment was made according to a randomization schedule generated using a permuted block by a randomisation statistician (independent from the project statistician)" Comment: probably done

Nickel 2012a *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind". Bladder instillation of study drug or inactive control ("the identical phosphate-buffered saline vehicle used")
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	Quote: "double-blind". Bladder instillation of study drug or inactive control ("the identical phosphate-buffered saline vehicle used")
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	41/49 included in intervention group (discontinued due to 1 adverse event, 1 consent withdrawal, 5 lack of efficacy, 1 lost to follow-up); 40/49 included in control group (discontinued due to 1 consent withdrawal, 5 lack of efficacy, 2 lost to FU, 1 other); LOCF
Incomplete outcome data (attrition bias) Pain	Low risk	All randomised participants were included in analysis (assumption made - inconsistent reporting of denominators)
Incomplete outcome data (attrition bias) Frequency	Low risk	All randomised participants were included in analysis (assumption made - inconsistent reporting of denominators)
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Low risk	All randomised participants were included in analysis (assumption made - inconsistent reporting of denominators)
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Low risk	All randomised participants were included in analysis (assumption made - inconsistent reporting of denominators)
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis (assumption made - inconsistent reporting of denominators)
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Nickel 2012b

Study characteristics	
Methods	**Study design:** RCT**Study duration (months):** 3
Participants	**Number randomised:** 161 **Setting:** 35 centres **Country:** USA, Canada, Denmark, Finland, France, Germany **Sex:** 147 females and 14 males **Age, years:** mean 49.9 (SD 13.6, range 19 to 76) for Group A (30 mg/d, n = 54), mean 49.6 (SD 14.6, range 21 to 80) for Group A (60 mg/d, n = 55), mean 52.1 (SD 14.0, range 22 to 79) for Group B (n = 52) **Diagnosis:** IC, moderate to severe

Nickel 2012b *(Continued)*

	Inclusion criteria: participants had moderate to severe IC based on scores of 13 or more on the Pelvic Pain and Urgency/Frequency Questionnaire and 7 or greater on the O'Leary-Sant ICSI. Study inclusion also required evidence of cystoscopy within 2 years of screening to confirm the absence of other significant lower urinary tract pathology and the presence or absence of cystoscopic features of IC. Study continuation required completion of 4 or more daily worst pain severity scores during the 7 days before randomisation, with a mean daily worst pain severity score of 4 or more on an 11-point numerical rating scale (range 0 (no IC pain) to 10 (IC pain as bad as you can imagine)). Mean severity score was the average of 24-hour worst pain severity scores recorded for the 7 days before randomisation. Mean micturition frequency per 24 hours of 8 or more (derived from the symptom diary before randomisation) was also required **Exclusion criteria:** IC symptoms less than 6 months; PVR urine volume greater than 200 mL at screening; history, diagnosis, signs or symptoms of any clinically significant psychiatric disorder; MVV less than 50 mL or greater than 350 mL during 3 consecutive days; total volume voided greater than 3000 mL on average per 24 hours; greater than 1 haematuria on dipstick test at screening, unless fully investigated to rule out significant urological disease; and/or microbiologically proven urinary tract infection at screening or randomisation
Interventions	**Group A (n = 109):** PD-0299685 (Ca2 Channel 2 Ligand) **Group B (n = 52):** placebo **Regimen:** after the run-in, patients received placebo, 30 mg PD-0299685 daily (administered as 15 mg BID) or 60 mg PD-0299685 daily (administered as 30 mg BID) for 12 weeks **Treatment category in NMA:** calcium channel agonists vs control
Outcomes	Outcome data in analysis Cure or improvement: based on GRA (assumed from reports): at 12 weeks Pain: 11-point numerical rating scale (range 0 to 10): at 12 weeks Frequency per 24 hours: at 12 weeks ICSI: at 12 weeks Adverse events: at 12 weeks
Funding	Pfizer
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the randomization list was created with computer-generated pseudo-random code using the method of random permuted blocks"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind, placebo-controlled" trial. Placebo not described
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	"double-blind, placebo-controlled" trial. Placebo not described

Nickel 2012b *(Continued)*

Incomplete outcome data (attrition bias) Cure or improvement	High risk	71/109 (65%) included in intervention group; 40/52 (76%) included in control group
Incomplete outcome data (attrition bias) Pain	High risk	64/109 (59%) included in intervention group; 37/52 (71%) included in control group
Incomplete outcome data (attrition bias) Frequency	High risk	76/109 (70%) included in intervention group; 43/52 (83%) included in control group
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	High risk	70/109 (64%) included in intervention group; 40/52 (77%) included in control group
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Nickel 2015

Study characteristics	
Methods	**Study design** RCT**Study duration (months):** 6
Participants	**Number randomised:** 369 **Setting:** 67 sites **Country:** USA and Canada **Sex:** 332 females and 36 males **Age, years:** median 44.0 (range 18 to 87) for Group A (100 mg QD, n = 128), median 42.0 (range 19 to 85) for Group A (100 mg TID, n = 122), median 44.0 (range 18 to 78) for Group B (n = 118) **Diagnosis:** IC/PBS (NIDDK criteria) **Inclusion criteria:** study participants were men and women 18 years of age or older with IC/BPS based on a total score of 8 or greater on ICSI and a score of greater than 0 on each component item (bladder pain, urinary urgency, frequency and nocturia) that was unrelated to urinary tract infection for at least 6 months before screening: eligible patients experienced an average of at least 10 voids per day (i.e. 30 or more voids during 3 consecutive days), of which 1 or more occurred during the night (i.e. score of 1 or greater on ICSI item 3) **Exclusion criteria:** key eligibility criteria also required that patients had not received intravesical therapy (e.g. bladder distension, dimethyl sulfoxide) or undergone cystoscopy during the 4 weeks before screening. They had no evidence of microscopic haematuria or evaluation positive for significant urological disease within the prior year. In addition, they had not received drugs known to affect IC/BPS symptoms (i.e. antidepressants, antihistamines, antispasmodics or anticholinergics) within the 4 weeks before screening
Interventions	**Group A (n = 251):** pentosan polysulfate (PPS, oral)

Nickel 2015 *(Continued)*

	Group B (n = 118): placebo
	Regimen: PPS 100 mg QD (i.e. once a day) or PPS 100 mg TID (i.e. 3 times a day) for 24 weeks
	Treatment category in NMA: PPS vs control
Outcomes	Outcome data in analysis
	Cure or improvement: 'moderately' or 'markedly' improved on GRA: at 24 weeks
	Pain: 11-point numerical rating scale (range 0 to 10): at 24 weeks
	Frequency: at 24 weeks
	Adverse events: at 24 weeks
Funding	Janssen Research & Development
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized … based on a computer generated randomization schedule"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind, placebo-controlled" trial, using "matching placebo"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	"double-blind, placebo-controlled" trial, using "matching placebo"
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	For missing data, "the last observed data were carried forward to the end point for analysis" (despite large number discontinuing trial: 106/251 from intervention group and 55/118 from control group discontinued)
Incomplete outcome data (attrition bias) Pain	Low risk	232/251 (92%) included in intervention group; 111/118 (94%) included in control group
Incomplete outcome data (attrition bias) Frequency	Low risk	232/251 (92%) included in intervention group; 111/118 (94%) included in control group
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Nickel 2016

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 2
Participants	**Number randomised:** 82 **Setting:** not reported **Country:** not reported **Sex:** 70 females and 12 males **Age, years:** mean 45.3 (range 22 to 74) for Group A, mean 51.4 (range 24 to 77) for Group B **Diagnosis:** IC/BPS **Inclusion criteria:** male and female patients aged ≥ 18 years. Female patients had to meet 1 of the following criteria: non-child-bearing potential: postmenopausal, defined as women who aged ≥ 45 years with amenorrhoea for 24 consecutive months; child-bearing potential: were not pregnant or lactating and abstinent, or using adequate contraception. Inclusion criteria also required evidence of cystoscopy within 2 years of screening confirming the absence of significant lower urinary tract pathology and the presence or absence of cystoscopic features of interstitial cystitis/bladder pain syndrome (IC/BPS). Patients were randomised if at visit 2 (randomisation), they met the continuation criteria of completed 4 or more average bladder pain scores within any of the 7 days before randomisation with a mean average bladder pain intensity score of 4 or greater (on an 11-point NRS) and a mean micturition frequency of 8 or greater per 24 hours during any 3 consecutive days in the previous 7 days **Exclusion criteria** key exclusion criteria were patients with body mass index > 39 kg/m^2; pregnant women, lactating women, women suspected of being pregnant and women wishing to become pregnant during the course of the study; patients with symptoms of IC/BPS for < 6 months before screening; patients with postvoid residual volume > 200 mL at screening; patients with mean voided volume < 40 and > 400 mL per micturition as measured over 1 day of the 7-day e-diary period completed before randomisation (visit 2); patients with total daily volume voided > 3500 mL, as confirmed by the e-diary completed before randomisation
Interventions	**Group A (n = 40):** 20 mg subcutaneous tanezumab **Group B (n = 42):** placebo **Treatment category in NMA:** immune modulators vs control
Outcomes	Outcome data in analysis Pain: 11-point numerical rating scale (range 0 to 10): at 8 weeks Adverse events: at 8 weeks
Funding	Pfizer
Notes	**Publication status:** full text This paper reports multiple trials. Data for this review were extracted only from "Study A4091035"

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"

Nickel 2016 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind, placebo-controlled" trial using subcutaneous dosing. Placebo not described
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	"double-blind, placebo-controlled" trial using subcutaneous dosing. Placebo not described
Incomplete outcome data (attrition bias) Pain	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Nomiya 2017

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 1
Participants	**Number randomised:** 20 **Setting:** not reported **Country:** Japan **Sex:** 19 females and 1 male **Age, years:** mean 66.9 (SD 17.0) for Group A, mean 72.5 (SD 8.8) for Group B **Diagnosis:** IC **Inclusion criteria:** patients with refractory IC, defined as persisting symptom of O'Leary and Sant Interstitial Cystitis Symptom Index/Problem Index (OSSI/OSPI) score greater than 6 points, respectively, and numerical rating scale for pain (NRS) more than 3 out of 10 points, despite multiple conventional therapies such as lifestyle modification, hydrodistension and oral medication **Exclusion criteria:** not reported
Interventions	**Group A (n = 10):** 6-week weekly 20,000 U heparin and 5 mL 4% lidocaine in phosphate-buffered saline at pH 7.5 (intravesical instillation) **Group B (n = 10):** 6-week weekly 20,000 U heparin in 30 mL physiological saline **Treatment category in NMA:** local anaesthetics vs control
Outcomes	Outcome data in analysis

Nomiya 2017 *(Continued)*

	Cure or improvement: 'markedly or moderately improved' on GRA: at 4 weeks Pain: 10-point numerical rating scale (unclear minimum/maximum score): at 4 weeks Frequency: at 4 weeks Nocturia: at 4 weeks ICSI: at 4 weeks ICPI: at 4 weeks Adverse events: at 4 weeks
Funding	Iida Grant of Mitsui Memorial Hospital
Notes	**Publication status:** abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: blinding methods not described. Intravesical instillation of heparin + lidocaine vs heparin
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	Quote: "double-blind" Comment: blinding methods not described. Intravesical instillation of heparin + lidocaine vs heparin
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Pain	High risk	7/10 included in intervention group (3 withdrew because of symptom worsening); 10/10 included in control group
Incomplete outcome data (attrition bias) Frequency	High risk	7/10 included in intervention group (3 withdrew because of symptom worsening); 10/10 included in control group
Incomplete outcome data (attrition bias) Nocturia	High risk	7/10 included in intervention group (3 withdrew because of symptom worsening); 10/10 included in control group
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	High risk	7/10 included in intervention group (3 withdrew because of symptom worsening); 10/10 included in control group

Nomiya 2017 *(Continued)*

Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	High risk	7/10 included in intervention group (3 withdrew because of symptom worsening); 10/10 included in control group
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

O'Reilly 2004

Study characteristics	
Methods	**Study design** RCT **Study duration (months):** 2.8
Participants	**Number randomised:** 56 **Setting:** not reported **Country:** Australia **Sex:** not reported **Age, years:** not reported **Diagnosis:** IC (NIDDK criteria) **Inclusion criteria:** patients with interstitial cystitis who fulfilled the National Institutes of Health National Institute for Diabetes and Digestive and Kidney Diseases criteria were prospectively recruited from our urogynaecology clinics. They were well-motivated patients in whom interstitial cystitis had failed to respond to various oral and intravesical therapies. Inclusion criteria consisted of ability to give informed consent, ability to perform treatment during 84 days and attend for follow-up, pain on bladder filling relieved by emptying; suprapubic, urethral, vaginal or perineal pain; glomerulations at cystoscopy and decreased bladder capacity or compliance at urodynamics **Exclusion criteria:** younger than 18 years of age, duration of symptoms less than 12 months, daytime frequency less than 7 times in 12 hours and nocturia less than 2 times, detrusor overactivity on urodynamics, bladder tumour or calculus, urinary tract infection, radiation-induced cystitis and any cause of peripheral neuropathy or degenerative conditions of the spinal cord
Interventions	**Group A (n = 29):** transdermal posterior tibial nerve stimulation using active device (laser on for 30 seconds over SP6/Sanyinjiao acupuncture point, once daily for 12 weeks): at home **Group B (n = 27):** placebo device **Treatment category in NMA:** behavioural therapy vs control
Outcomes	Outcome data in analysis Pain: SF-36 bodily pain score (range 100 to 0, with higher scores indicating less pain): at 12 weeks ICSI: at 12 weeks

O'Reilly 2004 *(Continued)*

	ICPI: at 12 weeks
Funding	Not reported
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trandermal laser therapy using an active or placebo device "The sham devices were identical but inactivated so that neither patient nor recruiter were aware of device type"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	Trandermal laser therapy using an active or placebo device "The sham devices were identical but inactivated so that neither patient nor recruiter were aware of device type"
Incomplete outcome data (attrition bias) Pain	Low risk	29/29 included in intervention group; 27/27 included in control group. "Intermittent missing data" imputed with "horizontal mean imputation"
Incomplete outcome data (attrition bias) Frequency	Low risk	
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Low risk	27/29 included in intervention group; 26/27 included in control group. "Intermittent missing data" were imputed with "horizontal mean imputation"
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Low risk	27/29 included in intervention group; 26/27 included in control group. "Intermittent missing data" were imputed with "horizontal mean imputation"
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Oliver 2013

Study characteristics

Methods	**Study design:** RCT **Study duration (months):** 3

Oliver 2013 *(Continued)*

Participants	**Number randomised:** 10 **Setting:** not reported **Country:** USA **Sex:** 8 females and 2 males **Age, years:** average 68 **Diagnosis:** IC (Hunner's ulcer-type) **Inclusion criteria:** patients presenting with Hunner's ulcer-type IC were recruited for the study beginning in January 2012. The study included patients with urgency, frequency and chronic pelvic pain consistent with IC as well as cystoscopy and biopsy confirming the presence of Hunner's ulcers **Exclusion criteria:** patients were excluded if they had an active urinary tract infection, history of bladder malignancy, recent bladder surgery, allergy to triamcinolone or were pregnant or unable to undergo anaesthesia
Interventions	**Group A (n = 5):** triamcinolone injection (10 mL of triamcinolone acetonide, 40 mg/mL) of Hunner's ulcers **Group B (n = 5):** fulguration (using Bugbee electrocautery) Once-only treatment **Treatment category in NMA:** immune modulator vs fulguration
Outcomes	Outcome data in analysis - no usable data
Funding	None
Notes	**Publication status:** abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	Concealment methods not described. Stated only as "Patients were blinded to the type of procedure they received. The surgeon was blinded … until just prior to the start of surgery in the operating room"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Probably not done (fulguration vs triamcinolone injection). Surgeons could not be blinded
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	Stated as "patients were blinded to the type of procedure they received", even though how this was achieved was not explicit, given the different modes of treatment
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Parsons 2012

Study characteristics	
Methods	**Study design:** cross-over randomised trial **Study duration (months):** 0.001 (1 hour)
Participants	**Number randomised:** 28 **Setting:** 4 sites **Country:** USA **Sex:** not reported **Age, years:** not reported **Diagnosis:** IC (NIDDK criteria) **Inclusion criteria:** IC patients meeting all of the clinical criteria of the NIDDK, with the exception that cystoscopy under anaesthesia was not required. In addition, they had to have a score of at least 15 on the Pelvic Pain and Urgency/Frequency Patient Symptom Scale **Exclusion criteria:** patients taking tricyclic antidepressants, neurontin or narcotics were excluded. Patients taking any other medications had to have been on them for a minimum of 3 months
Interventions	**Group A (n = not reported):** 50,000 units heparin + 200 mg lidocaine HCL (hydrochloride) + 420 mg sodium bicarbonate in 15 mL water **Group B (n = not reported):** 420 mg sodium bicarbonate in 15 mL water **Treatment category in NMA:** anticoagulants + local anaesthetics vs control
Outcomes	Outcome data in analysis - no usable data
Funding	Urigen Pharmaceuticals
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized". "All subjects received both drug and control... in a blinded and random order"
Allocation concealment (selection bias)	Low risk	Quote: "The blind was provided by the statistician for all treatments such that no site knew what treatment was given"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled, crossover trial ... control was an excipient, sodium bicarbonate"; "the blinded kits containing the medications or control were supplied to each site's pharmacy"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	Quote: "double-blind, placebo-controlled, crossover trial ... control was an excipient, sodium bicarbonate"; "the blinded kits containing the medications or control were supplied to each site's pharmacy"
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section

Parsons 2012 *(Continued)*

Other bias	Low risk	None detected

Payne 2005

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 3
Participants	**Number randomised:** 163 **Setting:** 30 centres **Country:** USA **Sex:** 140 females and 23 males **Age, years:** mean 47, range 20 to 77 **Diagnosis:** IC (diagnosis made on clinical and cystoscopic grounds) **Inclusion criteria:** patients at least 18 years of age with a diagnosis of IC confirmed by visualisation of glomerulations at cystoscopy/hydrodistension, symptoms of bladder pain and urinary urgency for at least 6 months; urinary frequency while awake at least 8 times a day; nocturia at least twice a night; a pain score of at least 4 (on a 0 to 9 Likert scale) on average over the 30 days before study drug treatment; and at least 1 voided volume of 75 cc or greater in 24 hours during the screening period **Exclusion criteria:** patients with Hunner's ulcers. Other exclusion criteria were as follows: (1) currently pregnant or breastfeeding; (2) presence of ulcers on pre-treatment cystoscopy; (3) intravesical therapy or bladder hydrodistension within the previous 60 days; (4) initiation of pentosan polysulfate sodium (Elmiron) within previous 16 weeks; (5) use of fentanyl patches, morphine sulfate, methadone or B&O Supprettes within the previous 30 days; (6) prior augmentation cystoplasty, cystectomy or cystolysis, neurectomy (i.e. hypogastric nerve plexus ablation) or implanted peripheral nerve stimulator that has affected bladder function; (7) history of ureteral reflux; patients with a history of childhood urinary tract infections, recurrent urinary tract infections as an adult (defined as more than 3 culture-documented episodes within the previous 12 months) or pyelonephritis at any time must have a cystourethogram to rule out ureteral reflux; (8) evidence of renal impairment, hepatic impairment or clinically significant cardiovascular, respiratory or psychiatric disease; (9) urinary tract infection or prostatic infection within 3 months before study entry; (10) active genital herpes or vaginitis; (11) urethral diverticulum; (12) uterine, cervical, vaginal or urethral cancer within 5 years before study entry (13) history of cyclophosphamide or chemical cystitis, urinary tuberculosis or radiation cystitis; (14) history of bladder tumours (benign or malignant)
Interventions	**Group A (n = 119):** 3 arms combined for this review: A: resiniferatoxin (RTX) 0.01 microMol/L solution in 10% ethanol in saline. Arm B: RTX 0.05 microMol/L solution in 10% ethanol in saline. Arm C: RTX 0.10 microMol/L solution in 10% ethanol in saline **Group B (n = 44):** 10% ethanol in saline (placebo) **Group A & B:** bladder then drained and rinsed with normal saline. Pre-treatment instillation with lidocaine solution (initially 50 mL of 2% lidocaine for 10 minutes, increased later in study to 100 mL of 4% lidocaine for 30 minutes). Single instillation treatment of 50 mL of RTX solution or placebo retained for 30 minutes **Treatment category in NMA:** calcium channel agonists (3 arms) vs control
Outcomes	Outcome data in analysis Cure or improvement: ‘moderately' or 'markedly’ improved on GRA: at 4 weeks

Payne 2005 *(Continued)*

	Pain: numerical rating scale (pain score from diary) (range 0 to 9): at 12 weeks Adverse events: at 4 weeks
Funding	ICOS Corporation (American biotechnology company)
Notes	**Publication status:** full text Notes from previous versions of the review: attempted study author contact regarding data for pain, void volume and frequency. No response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was centrally performed and stratified by center in blocks according to a computer-generated random number table"
Allocation concealment (selection bias)	Low risk	Quote: "randomization was centrally performed and stratified by center in blocks according to a computer-generated random number table"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "'double-blind, placebo-controlled" trial. "All patients and site personnel were blinded to treatment assignment except for study pharmacists responsible for preparing study drug"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	Quote: "'double-blind, placebo-controlled" trial. "All patients and site personnel were blinded to treatment assignment except for study pharmacists responsible for preparing study drug"
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	Review authors chose to use available case analysis. 116/119 (97%) included in intervention group; 43/44 (98%) included in control group
Incomplete outcome data (attrition bias) Pain	Low risk	119/119 included in intervention group; 43/44 included in control group (1 missing post-baseline efficacy assessment). "Missing data were imputed with last-observation-carried forward"
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Payne 2014

Study characteristics

Methods	**Study design:** RCT **Study duration (months):** 6
Participants	**Number randomised:** 16

Payne 2014 *(Continued)*

	Setting: single institution **Country:** USA **Sex:** 14 females and 2 males **Age, years:** mean 53.7, range 24 to 88 **Diagnosis:** IC (NIDDK criteria) **Inclusion criteria:** adults diagnosed by investigators with IC/BPS as the primary cause of their lower urinary tract symptoms. Symptoms were present for > 6 months and were refractory to standard therapies; current pain and urgency scores were ≥ 4/10 on a visual analogue scale. Cystoscopy with bladder distension under anaesthesia was required at some point in the diagnostic evaluation **Exclusion criteria:** NIDDK exclusion criteria were employed and residual urine > 100 cc was exclusionary. Prior botox injection and neurostimulators were not allowed
Interventions	**Group A (n = 14):** varying dose of botox injection into trigone and detrusor **Group B (n = 2):** saline injection Once-only treatment **Treatment category in NMA:** neuromuscular blockade vs control
Outcomes	Outcome data in analysis Cure or improvement: 'moderately' or 'markedly' improved on GRA: at 6 months (assumed from reports) Adverse events: at 6 months (assumed from reports)
Funding	Investigator-initiated grant from Allergan
Notes	**Publication status:** abstract "… the study was stopped due to futility without reaching the target recruitment goal after eight months with no enrollment"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized … by drawing presealed envelopes"
Allocation concealment (selection bias)	Unclear risk	Quote: "randomized … by drawing presealed envelopes" Comment: unclear if envelopes were opaque and sequentially numbered
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind" trial. Injections in the trigone (sub-epithelial level) of botulinum toxin or "placebo" (not described). Participants "were pretreated with … lidocaine in the bladder … prior to injection along with an oral narcotic and anxiolytic"
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	"double-blind" trial. Injections in the trigone (sub-epithelial level) of botulinum toxin or "placebo" (not described). Participants "were pretreated with … lidocaine in the bladder … prior to injection along with an oral narcotic and anxiolytic"
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	All randomised participants were included in analysis ("only two subjects were randomized to placebo")

Payne 2014 *(Continued)*

Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis ("only two subjects were randomized to placebo")
Selective reporting (reporting bias)	High risk	Pain, ICSI, ICPI and "24 hour bladder dairy variables" were mentioned in the methods but were not reported in the results
Other bias	Low risk	None detected

Peeker 2000

Study characteristics	
Methods	**Study design:** cross-over randomised trial **Study duration (months):** 3
Participants	**Number randomised:** 21 **Setting:** not reported **Country:** USA **Sex:** 20 females and 1 male **Age, years:** mean 59 (range 36 to 79) for 11 women with ulcerative (classic) disease; mean 43 (range 24 to 61) for 9 women and 1 man with non-ulcerative disease **Diagnosis:** IC (NIDDK criteria) **Inclusion criteria:** patients with IC who had non-ulcer disease **Exclusion criteria:** not reported
Interventions	**Group A (n = not reported):** 6 × weekly instillations via catheter with bacillus Calmette-Guérin (BCG). Dose of 5 × 108 colony-forming units, reconstituted with 1 mL of saline and diluted with 50 mL of saline. Each instillation for duration of up to 2 hours **Group B (n = not reported):** 6 × weekly instillations of dimethyl sulfoxide (DMSO). 50 mL of solution at concentration of 500 mg/mL **Treatment category in NMA:** immune modulators vs DMSO
Outcomes	Outcome data in analysis - no usable data
Funding	BCG ampules were provided by OncoTICE, Organon Teknika, Askim, Sweden
Notes	**Publication status:** full text Notes from previous versions of the review: very poor data available. Numbers in each treatment group are missing. Study author contacted, no response

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "the randomizaton procedure was performed"

Peeker 2000 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "the randomizaton procedure was performed by 1 of us … who subsequently did not participate in the care or final evaluation of patients"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Stated as "double-blind", cross-over study; "evaluation was performed blindly"; "data concerning given substance were concealed until evaluation". However, "the given substance could not be blinded due to the distinctive breath odor of dimethyl sufoxide"
Blinding of outcome assessment (detection bias) Subjective outcome	High risk	Stated as "double-blind", cross-over study; "evaluation was performed blindly"; "data concerning given substance were concealed until evaluation". However, "the given substance could not be blinded due to the distinctive breath odor of dimethyl sufoxide"
Selective reporting (reporting bias)	High risk	Outcomes reported in the results were not specified in the methods, except the primary outcome ("subjective improvement")
Other bias	High risk	Some patients may have received both treatments. "Patients randomly underwent [treatment] and, if not improved, were treated with the other substance after a washout period, the end of which constituted the point of final analysis"

Perez-Marrero 1988

Study characteristics	
Methods	**Study design:** cross-over randomised trial **Study duration (months):** 1.5
Participants	**Number randomised:** 33 **Setting:** single centre **Country:** Canada **Sex:** 30 females and 3 males **Age, years:** mean 48 **Diagnosis:** IC (diagnosis made clinically and with cystoscopy/biopsy) **Inclusion criteria:** patients with IC **Exclusion criteria:** not reported
Interventions	**Group A (n = 15):** 50 mL of 50% dimethyl sulfoxide (DMSO) **Group B (n = 18):** 50 mL of normal saline Four treatments, each 2 weeks apart, involving outpatient bladder instillations given via catheter and lasting at least 15 minutes. After a 4-week 'rest' period, the 2 groups crossed over, to complete instillations with the 'other' treatment (i.e. placebo for Group A and DMSO for Group B). Timing of assessment is unclear, but it looks to have occurred soon after each phase of treatment was given **Treatment category in NMA:** DMSO vs control
Outcomes	Outcome data in analysis Cure or improvement: response to treatment rated as moderate or marked improvement: at 6 weeks (assumed from reports) (at end of first period, which was "4 treatments … at 2-week intervals")

Perez-Marrero 1988 *(Continued)*

Funding	Not reported
Notes	**Publication status:** full text Cross-over trial. Data for the first phase only were sought for this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	"an evaluator blinded, complete crossover study". Review authors assumed that patients and carers were not blinded, given breath odor caused by DMSO bladder instillation mentioned in another trial (Peeker 2000), along with NICE guidance. "All instillations were performed by a nurse … who had no other involvement"
Blinding of outcome assessment (detection bias) Subjective outcome	High risk	"an evaluator blinded, complete crossover study". Review authors assumed that patients were not blinded
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	15/15 included in intervention group; 17/18 (94%) included in control group (1 excluded as she was "found to be pregnant after the first instillation")
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Peters 1997

Study characteristics

Methods	**Study design:** RCT **Study duration (months):** 27 (for the purpose of this review, data for 8 months were used in the analysis)
Participants	**Number randomised:** 33 **Setting:** single centre **Country:** USA **Sex:** female **Age, years:** median 44 (range 30 to 71) for Group A, median 40 (range 23 to 56) for Group B **Diagnosis:** IC (NIDDK criteria) **Inclusion criteria:** women with IC **Exclusion criteria:** immunocompromised patients, concomitant steroid medications, chemotherapy for other carcinomas, warfarin sodium anticoagulation therapy, pregnancy or unwillingness to practice

Peters 1997 *(Continued)*

	protected intercourse, intravesical therapy for IC within 3 months before the study, grade III or greater vesicoureteral reflux
Interventions	**Group A (n = not reported):** 50 mg Tice strain bacillus Calmette-Guérin (BCG) **Group B (n = not reported):** 50 mL of sterile saline Weekly instillations × 6, each comprising 50 mL volume instilled via Foley catheter. Fluid retained for 2 hours, although temporary drainage and re-instillation permitted if discomfort during 2 hours **Numbers analysed:** Group A: 17; Group B: 15 **Treatment category in NMA:** immune modulators vs control
Outcomes	Outcome data in analysis Cure or improvement: 'responders' to treatment, defined as moderate improvement, greatly improved or cured in subjective rating of overall symptoms at 6 months Pain: RAND-36 question pain score (assumed range 100 to 0, with higher scores indicating less pain) at 6 months Adverse events: at 6 months
Funding	Supported in part by grant from the William Beaumont Hospital Research Institute [author affiliated] and by PerImmune, Inc., Rockville, Maryland
Notes	**Publication status:** full text Notes from previous versions of the review: attempted to contact study author regarding outcome data in terms of treatment group, rather than just responder/non-responder. Replied 11/06 "looking for data"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	Quote: "randomized in a double-blind fashion" Comment: unclear whether this refers to blinding or allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind, placebo controlled". Intravesical treatments of study drug or "placebo (sterile saline)". "The subjects and investigators remained blinded to experimental group assignments until all subjects had completed at least 6 months of followup"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	"double-blind, placebo controlled". Intravesical treatments of study drug or "placebo (sterile saline)". "The subjects and investigators remained blinded to experimental group assignments until all subjects had completed at least 6 months of followup"
Incomplete outcome data (attrition bias) Cure or improvement	Unclear risk	33 randomised, 15 included in intervention group; 15 included in control group. Group assignment of "the 3 unevaluable subjects" unclear
Incomplete outcome data (attrition bias)	Unclear risk	33 randomised, 15 included in intervention group; 15 included in control group. Group assignment of "the 3 unevaluable subjects" unclear

Peters 1997 *(Continued)*
Pain

Incomplete outcome data (attrition bias) Adverse events	Unclear risk	33 randomised, 17 included in intervention group; 15 included in control group. Group assignment of 1 missing subject unclear
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Pinto 2016

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 3
Participants	**Number randomised:** 19 **Setting:** not reported **Country:** Portugal **Sex:** female **Age, years:** mean 47 (SD 8, range 35 to 60 for Group A; mean 49 (SD 10, range 31 to 61) for Group B **Diagnosis:** BPS/IC **Inclusion criteria:** women with refractory BPS/IC and a minimum pain score of 4 on a 0 to 10 visual analogue scale (VAS) **Exclusion criteria:** not reported
Interventions	**Group A (n = 10):** 100 U of OnaBotA in 10 mL saline (intratrigonal injection) **Group B (n = 9):** 10 mL saline **Treatment category in NMA:** neuromuscular blockade vs control
Outcomes	Outcome data in analysis Pain: VAS (assumed range 0 to 10): at 3 months Frequency: at 3 months Adverse events: at 3 months
Funding	Allergan
Notes	**Publication status:** abstract

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"

Pinto 2016 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind, placebo-controlled trial" Comment: intratrigonal injection of OnaBotA or saline. Placebo not described
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	Quote: "double-blind, placebo-controlled trial" Comment: intratrigonal injection of OnaBotA or saline. Placebo not described
Incomplete outcome data (attrition bias) Pain	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Frequency	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Sairanen 2005

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 6
Participants	**Number randomised:** 64 **Setting:** 7 urological units **Country:** Finland **Sex:** 53 females and 11 males **Age, years:** mean 56.2 (SD 14.7) for Group A, mean 59.7 (SD 13.0) for Group B **Diagnosis:** IC (NIDDK criteria) **Inclusion criteria:** patients meeting NIDDK criteria for IC. Serum transaminase, bilirubin and serum cholesterol had to be within normal range **Exclusion criteria:** history of cancer in the last 10 years; untreated hypertension or renal insufficiency
Interventions	**Group A (n = 32):** cyclosporin A (CyA) **Group B (n = 32):** pentosan polysulfate (PPS) **Regimen:** 1.5 mg/kg CyA twice daily or 100 mg PPS 3 times daily for a period of 6 months

Sairanen 2005 *(Continued)*

	Treatment category in NMA: immune modulators vs PPS
Outcomes	Outcome data in analysis Cure or improvement: based on GRA (assumed from reports): at 6 months Pain: VAS (0 to 10 centimetres): at 6 months Frequency: at 6 months Nocturia: at 6 months ICSI: at 6 months ICPI: at 6 months Adverse events: at 6 months
Funding	Finnish Urological Association
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Low risk	Quote: "randomization was centralized. Closed envelopes were divided into 2 identical blocks, and a nurse not otherwise involved in the study opened the envelopes containing the name of the drug"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label" Comment: probably not done
Blinding of outcome assessment (detection bias) Subjective outcome	High risk	Quote: "open-label" Comment: probably not done
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	Review authors chose to use number who completed trial: 29/32 included in PPS group (1 missing due to gross haematuria, 2 discontinued as not benefiting from treatment); 29/32 (3 discontinued including 1 due to AE) included in cyclosporin A group
Incomplete outcome data (attrition bias) Pain	Low risk	Review authors chose to use number who completed trial: 29/32 included in PPS group (1 missing due to gross haematuria, 2 discontinued as not benefiting from treatment); 29/32 (3 discontinued including 1 due to AE) included in cyclosporin A group
Incomplete outcome data (attrition bias) Frequency	Low risk	Review authors chose to use number who completed trial: 29/32 included in PPS group (1 missing due to gross haematuria, 2 discontinued as not benefiting from treatment); 29/32 (3 discontinued including 1 due to AE) included in cyclosporin A group
Incomplete outcome data (attrition bias) Nocturia	Low risk	Review authors chose to use number who completed trial: 29/32 included in PPS group (1 missing due to gross haematuria, 2 discontinued as not benefit-

Sairanen 2005 *(Continued)*

		ing from treatment); 29/32 (3 discontinued including 1 due to AE) included in cyclosporin A group
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Low risk	Review authors chose to use number who completed trial: 29/32 included in PPS group (1 missing due to gross haematuria, 2 discontinued as not benefiting from treatment); 29/32 (3 discontinued including 1 due to AE) included in cyclosporin A group
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Low risk	Review authors chose to use number who completed trial: 29/32 included in PPS group (1 missing due to gross haematuria, 2 discontinued as not benefiting from treatment); 29/32 (3 discontinued including 1 due to AE) included in cyclosporin A group
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Sairanen 2009

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 3
Participants	**Number randomised:** 75 **Setting:** not reported **Country:** not reported **Sex:** 71 females and 4 males **Age, years:** mean 57.9 (SD 14.7) for Group A, mean 61.4 (SD 11.3) for Group B **Diagnosis:** PBS/IC **Inclusion criteria:** patients with PBS/IC **Exclusion criteria:** not specified
Interventions	**Group A (n = 38):** 50 mL Tice strain BCG (bacillus Calmette-Guérin) **Group B (n = 37):** 50 mL 50% dimethyl sulfoxide (DMSO) **Treatment category in NMA:** immune modulator vs DMSO
Outcomes	Outcome data in analysis Cure or improvement: GRA (global assessment to treatment response), much better or completely cured
Funding	Not reported
Notes	**Publication status:** full text

Sairanen 2009 *(Continued)*

This paper reports multiple trials. Data for this review were extracted from only 1 study comparing DMSO and BCG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	No information provided
Incomplete outcome data (attrition bias) Cure or improvement	Unclear risk	31/37 (84%) included in DMSO group; 31/38 (84%) included in BCG group
Selective reporting (reporting bias)	Unclear risk	Insufficient information (RCT is part of a paper reporting multiple trials)
Other bias	Low risk	None detected

Sant 2003

Study characteristics

Methods	**Study design:** RCT **Study duration (months):** 6
Participants	**Number randomised:** 121 **Setting:** 7 institutions **Country:** USA **Sex:** 108 females and 13 males **Age, years:** mean 47.8 (SD 13.9) for Group A, mean 48.7 (SD 15.1) for Group B, mean 43.7 (SD 15.1) for Group C, mean 41.0 (SD 15.5) for Group D **Diagnosis:** IC (NIDDK criteria) **Inclusion criteria:** eligible participants had to be at least 18 years old, receive a diagnosis of IC confirmed by cystoscopy and hydrodistension, according to NIH NIDDK criteria. Moderate symptoms of urinary frequency (at least 11 times daily) and pain/discomfort (at least 4 on a 0 to 9 Likert scale) for at least 24 weeks before study entry **Exclusion criteria:** not reported
Interventions	**Group A (n = 31):** hydroxyzine alone

Sant 2003 *(Continued)*

	Group B (n = 29): pentosan polysulfate (PPS) alone **Group C (n = 30):** hydroxyzine and PPS combination therapy **Group D (n = 31):** placebo **Regimen:** the dose of PPS was one 100 mg capsule 3 times daily. The target dose of hydroxyzine was 50 mg daily taken at bedtime titrated from 10 to 25 to 50 mg daily during 3 weeks **Treatment category in NMA:** antihistamines vs PPS vs PPS + antihistamines vs control
Outcomes	Outcome data in analysis Cure or improvement: 'moderately' or 'markedly' improved on GRA: at 24 weeks Pain: pain score (score range 0 to 9): at 24 weeks ICSI: at 24 weeks ICPI: at 24 weeks Adverse events: at 24 weeks
Funding	NIDDK, NIH (individual study authors have relationships with pharmaceutical companies)
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized … using a randomized block design stratified by clinical site" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double masked". Placebo not described
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	"double masked". Placebo not described
Incomplete outcome data (attrition bias) Cure or improvement	High risk	Review authors chose to use number who completed trial: 24/31 (63%) in hydroxyzine group; 26/29 (90%) in PPS group; 23/30 (77%) in PPS + hydroxyzine group; 23/31 (74%) in placebo group
Incomplete outcome data (attrition bias) Pain	Unclear risk	Number analysed not stated
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Unclear risk	Number analysed not stated

Sant 2003 *(Continued)*

Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Unclear risk	Number analysed not stated
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Shirvan 2015

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 1
Participants	**Number randomised:** 40 **Setting:** not reported **Country:** Iran **Sex:** female **Age, years:** not reported **Diagnosis:** PBS **Inclusion criteria:** known female patients with PBS, who were treated according to therapeutic recommendations by American Urological Association Guideline with no success **Exclusion criteria:** not reported
Interventions	**Group A (n = 20):** hydrodistension with 400 mg SinaCurcumin in 500 cc normal saline **Group B (n = 20):** hydrodistension with 500 cc normal saline only **Treatment category in NMA:** immune modulators vs control
Outcomes	Outcome data in analysis; no usable data
Funding	Not reported
Notes	**Publication status:** abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"

Shirvan 2015 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned. Hydrodistension (HD) with 500 cc saline vs HD with curcumin in 500 cc saline
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	Blinding not mentioned. Hydrodistention (HD) with 500 cc saline vs HD with curcumin in 500 cc saline
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Singh 2003

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 6
Participants	**Number randomised:** 30 **Setting:** not reported **Country:** UK **Sex:** not reported **Age, years:** not reported **Diagnosis:** IC (NIH criteria) **Inclusion criteria:** patients who met NIH modified diagnostic and exclusion criteria for IC. All patients also had to undergo cystoscopy to confirm the presence of Hunner's ulcers or glomerulations **Exclusion criteria:** not reported
Interventions	**Group A (n = 15):** 40 mg/50 mL sodium hyaluronate (Cystostat) **Group B (n = 15):** DMSO (dimethyl sulfoxide, 5.4%) 27 g in 50 mL (RIMSO-50) **Regimen:** Group A: weekly for 4 weeks, then monthly for 2 months; Group B: 2 weekly for 3 months **Treatment category in NMA:** hyaluronic acid vs DMSO
Outcomes	Outcome data in analysis; no usable data
Funding	Not reported
Notes	**Publication status:** abstract Notes from previous versions of the review: previously excluded from the last review as no reported data
Risk of bias	

Singh 2003 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Selective reporting (reporting bias)	Unclear risk	This abstract presented no outcome data. "We present the rest of the data when all patients should have had a six months' follow-up"
Other bias	Low risk	None detected

Souza 2012

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 0.7
Participants	**Number randomised:** 22 **Setting:** single centre **Country:** Brazil **Sex:** 18 females and 4 males **Age, years:** mean 54.9 (SD 5.1) for Group A, mean 55.3 (SD 5.8) for Group B **Diagnosis:** IC/PBS (diagnostic criteria according to the 'IC Data Base Study'; referenced as Hanno 1999) **Inclusion criteria:** females and males with clinical diagnosis of IC/PBS and no medical condition or therapy that would exclude safe concomitant use of Cystex; negative bacterial urine culture; patient-reported average urinary frequency of at least 11 times per 24 hour period during the screening period **Exclusion criteria:** to be included, urine must have been sterile at time of diagnosis and assessment and urinary cytology negative; all other diseases that could cause pelvic symptoms were excluded
Interventions	**Group A (n = 11):** Cystex for 3 weeks with a self-titration protocol. Cystex defined as "acriflavin hydrochloride 15.00 mg; methenamine 250.00 mg; methylene blue 20.00 mg; beladona extract 15.00 mg" **Group B (n = 11):** placebo for 3 weeks **Treatment category in NMA:** parasympathomimetic (+ urinary antiseptics) vs control
Outcomes	Outcome data in analysis Pain: VAS (assumed 0 to 100): at 21 days Functional bladder capacity: at 21 days Adverse events: at 21 days

Souza 2012 *(Continued)*

Funding	Not reported
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "'Randomization is being performed by computer-generated random allocation sequence"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"placebo-controlled and double blind design". Study drug "capsule" vs "placebo capsules, identical in form, colour and taste to the ones of the active formulation"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	"placebo-controlled and double blind design". Study drug "capsule" vs "placebo capsules, identical in form, colour and taste to the ones of the active formulation"
Blinding of outcome assessment (detection bias) Objective outcome	Low risk	Outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Pain	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Frequency	Low risk	
Incomplete outcome data (attrition bias) Functional bladder capacity	Low risk	All randomised participants were included in analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Taha 2007

Study characteristics

Methods	**Study design:** RCT

Taha 2007 *(Continued)*

	Study duration (months): 24
Participants	**Number randomised:** 36 **Setting:** not reported **Country:** Egypt **Sex:** not reported **Age, years:** not reported **Diagnosis:** IC (NIDDK criteria) **Inclusion criteria:** patients who met NIH NIDDK criteria for IC and reported at least moderate pain and frequency for a minimum of 6 months **Exclusion criteria:** not reported
Interventions	**Group A (n = 36):** bacillus Calmette-Guerin (BCG) instillation **Group B (n = 36):** 300 IU botulinum toxin A injection **Regimen:** Group A: once-only treatment; Group B: 6 weekly instillations **Treatment category in NMA:** immune modulators vs neuromuscular blockade
Outcomes	Outcome data in analysis Cure or improvement: positive clinical response with no additional treatment for intractable interstitial cystitis (no further definition provided)
Funding	Faculty of Medicine, Tanta University
Notes	**Publication status:** abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "'randomly divided into two groups (cases 1, 3, 5 & 2, 4, 6)" Comment: this is likely to be alternate allocation
Allocation concealment (selection bias)	High risk	Quote: "'randomly divided into two groups (cases 1, 3, 5 & 2, 4, 6)" Comment: this is likely to be alternate allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Probably not done. Intravesical instillation of BCG vs intravesical injection of botulinum toxin A (BTX-A)
Blinding of outcome assessment (detection bias) Subjective outcome	High risk	Probably not done. Intravesical instillation of BCG vs intravesical injection of botulinum toxin A (BTX-A)
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	16/18 (89%) included in BCG group; 16/18 (89%) included in BTX-A group
Selective reporting (reporting bias)	Unclear risk	Outcomes not specified in methods (abstract only)

Taha 2007 *(Continued)*

Other bias	Low risk	None detected

Thilagarajah 2001

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 3
Participants	**Number randomised:** 36 **Setting:** not reported **Country:** UK **Sex:** 33 females and 1 male (participants who completed study) **Age, years:** median 42, range 23 to 73 **Diagnosis:** PBD (painful bladder disease) **Inclusion criteria:** patients with a diagnosis of PBD, based on the following criteria: (1) clinical history of suprapubic pain, frequency and occasionally urgency, nocturia and dysuria, lasting for < 3 months despite repeatedly negative urine culture; (2) petechial haemorrhages apparent on cystoscopy after distension; (3) histological examination of bladder biopsies taken from patients, which showed a chronic inflammatory infiltrate with submucosal angiogenesis and increased collagen deposition in the muscle. The basement membrane also appeared discontinuous; (4) urodynamic studies were deemed unnecessary for a diagnosis of PBD as, in keeping with previous studies, results obtained in this group of patients are too variable to be valid **Exclusion criteria:** patients were excluded from the study if they had taken antibiotics or NSAIDs or had undergone intravesical therapy in the preceding month; in women, if there was any possibility of pregnancy, as there is a theoretical risk of teratogenic effects in the fetus under H2-antagonist treatment; if there was a history of renal/hepatic impairment or blood dyscrasias, as these may worsen or become apparent during treatment with cimetidine; if there was concomitant treatment with drugs metabolised within the liver using the P450 cytochrome family of enzymes (warfarin, phenytoin, quinidine, theophylline and tricyclic antidepressants), as cimetidine can inhibit these enzymes
Interventions	**Group A (n = 18):** cimetidine **Group B (n = 18):** placebo **Regimen:** oral cimetidine 400 mg or placebo (both twice daily) **Treatment category in NMA:** antihistamines vs control
Outcomes	Outcome data in analysis; no usable data
Funding	Not reported
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"

Thilagarajah 2001 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "blindly allocated" Comment: unclear whether this refers to blinding or allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind"; "at the end of the study, the allocation of groups was revealed"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	"double blind"; "at the end of the study, the allocation of groups was revealed"
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

van Ophoven 2004

Study characteristics	
Methods	**Study design:** RCT **Setting:** single centre **Study duration (months):** 4
Participants	**Number randomised:** 50 **Setting:** single centre **Country:** Germany **Sex:** 44 females and 6 males **Age, years:** mean 50.5 (SD 14.4) for Group A, mean 60.2 (SD 17.5) for Group B **Diagnosis:** IC (NIDDK criteria) **Inclusion criteria:** women and men who met symptom criteria of the NIDDK for IC. All patients had received previous conservative medical treatment, including hydrostatic distension, intravesical instillations (e.g. dimethyl sulfoxide, hyaluronic acid) or oral medication (e.g. antiallergics, sodium pentosan polysulfate), which at best achieved short symptomatic relief **Exclusion criteria:** previous or current intake of amitriptyline
Interventions	**Group A (n = 25):** amitriptyline **Group B (n = 25):** placebo **Regimen:** 4 months with a self-titration protocol that allowed them to escalate drug dosage in 25 mg increments at 1 week intervals (maximum dosage 100 mg) **Treatment category in NMA:** antidepressants vs control
Outcomes	Outcome data in analysis Cure or improvement: subjective cure at 4 months Pain: VAS (0 to 100 mm) on pain intensity: at 4 months

van Ophoven 2004 *(Continued)*

	Functional bladder capacity: at 4 months Adverse events: at 4 months
Funding	Study drug supplied by Bayer Pharmaceutical, Germany
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation "using a block randomization design". Probably done
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind"; "placebo-controlled". The drug was supplied by manufacturer; placebo was supplied by the university hospital pharmacy, "which packed and blinded placebo and drug tablets"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	"double blind"; "placebo-controlled". The drug was supplied by manufacturer; placebo was supplied by the university hospital pharmacy, "which packed and blinded placebo and drug tablets"
Blinding of outcome assessment (detection bias) Objective outcome	Low risk	Outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	24/25 (1 dropped out due to AE) included in intervention group; 24/25 (1 dropped out due to AE) included in control group
Incomplete outcome data (attrition bias) Pain	Low risk	24/25 (1 dropped out due to AE) included in intervention group; 24/25 (1 dropped out due to AE) included in control group
Incomplete outcome data (attrition bias) Frequency	Low risk	
Incomplete outcome data (attrition bias) Functional bladder capacity	Low risk	24/25 (1 dropped out due to AE) included in intervention group; 24/25 (1 dropped out due to AE) included in control group
Incomplete outcome data (attrition bias) Adverse events	Low risk	24/25 (1 dropped out due to AE) included in intervention group; 24/25 (1 dropped out due to AE) included in control group
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

van Ophoven 2006

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 3
Participants	**Number randomised:** 21 **Setting:** not reported **Country:** Germany **Sex:** female **Age, years:** mean 65.5, SD 8.8, range 42.2 to 78.0 **Diagnosis:** IC (NIDDK criteria) **Inclusion criteria:** patients 18 years of age or older who met diagnostic criteria of the NIDDK for IC **Exclusion criteria:** not stated
Interventions	**Group A (n = 14):** hyperbaric oxygen (HBO) **Group B (n = 7):** placebo **Regimen:** 90 minutes treatment in a hyperbaric chamber pressurised with 100% O2 to 2.4 atmosphere absolute for 30 treatment sessions or 1.3 atmosphere absolute, breathing normal air in the control group. Treatment was given in daily sessions, 6 times a week during treatment **Treatment category in NMA:** hyperbaric oxygen vs control
Outcomes	Outcome data in analysis Cure or improvement: 'moderately' or 'markedly' improved on GRA: at 3 months Pain: pain VAS (mm): at 3 months Functional bladder capacity: at 3 months Adverse events: at 3 months
Funding	Fishbein Family Foundation
Notes	**Publication status:** full text

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomly assigned" using "code"; "the code was broken after evaluation at 3 months"
Allocation concealment (selection bias)	Unclear risk	"randomly assigned" using "code"; "the code was broken after evaluation at 3 months". Unclear whether this refers to blinding or allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind", "sham-controlled". Treatment given via facial mask at chamber pressure of 2.4 ata. Sham treatment "was conducted identically" except for a facial mask used at a faintly increased pressure of 1.3 to 1.4 ata

van Ophoven 2006 *(Continued)*

Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	"double-blind", "sham-controlled". Treatment given via facial mask at chamber pressure of 2.4 ata. Sham treatment "was conducted identically" except for a facial mask used at a faintly increased pressure of 1.3 to 1.4 ata
Blinding of outcome assessment (detection bias) Objective outcome	Low risk	Outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Cure or improvement	High risk	12/14 (85%; 1 dropped out due to a mild oxygen intoxication, 1 due to poor adherence to protocol) included in treatment group; 7/7 included in control group
Incomplete outcome data (attrition bias) Pain	Low risk	Quote: "For the 2 dropouts, the latest evaluable post-baseline observation was analyzed"
Incomplete outcome data (attrition bias) Frequency	Low risk	
Incomplete outcome data (attrition bias) Functional bladder capacity	Low risk	Quote: "for the 2 dropouts, the latest evaluable post-baseline observation was analyzed"
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Number analysed not reported
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Wang 2017a

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 6.5
Participants	**Number randomised:** 31 **Setting:** 12 sites **Country:** USA and Canada **Sex:** 26 females and 5 males **Age, years:** mean 50.6 (SD 10.68, range 38 to 78) for Group A, mean 46.2 (SD 13.56, range 25 to 69) for Group B **Diagnosis:** IC/PBS **Inclusion criteria:** adult (≥ 18 to 80 years, inclusive) men and women with IC/BPS based on a total score ≥ 8 on the validated O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) and chronic bladder pain for at least 6 months before screening, accompanied by urinary urgency, urinary frequency (≥ 8 voids daily) and/ or nocturia. On the basis of patient self-assessment of pain using a 11-point numeri-

Wang 2017a *(Continued)*

	cal rating scale (NRS) (0 = "no pain", 10 = "worst pain imaginable"), the mean of average pain intensity scores for the last 7 days of screening had to be ≥ 5 based on at least 6 of 7 days. Other key eligibility criteria required that patients had no evidence of a urinary tract infection or significant urological disease, including neurogenic bladder and diabetic cystopathy, and had not received intravesical therapy or undergone cystoscopy during the 6 weeks before screening **Exclusion criteria:** patients were excluded if they had received opioid analgesic at a dosage of oral morphine equivalent ≥ 40 mg/d or had changed drugs known to affect IC/BPS-associated pain (i.e. antidepressants, antihistamines, antispasmodics, anticholinergics, anticonvulsants) within the 4 weeks before screening
Interventions	**Group A (n = 14):** subcutaneous fulranumab 9 mg every 4 weeks **Group B (n = 17):** matching placebo **Treatment category in NMA:** immune modulators vs control
Outcomes	Outcome data in analysis Cure or improvement: ≥ 50% improvement in average pain intensity score. Time of measurement unclear Pain: numerical rating scale (range 0 to 10) at 12 weeks Frequency: at 12 weeks Nocturia: at 12 weeks ICSI: at 12 weeks Adverse events: at 26 weeks
Funding	Janssen Research & Development
Notes	**Publication status:** full text Study was terminated prematurely. The FDA placed ongoing studies on study drug 'on clinical hold' because of safety concern. "As a result, the sponsor discontinued this study prematurely, after having enrolled only 31 of the targeted 70 patients"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized … based on a computer-generated randomization schedule"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind, placebo-controlled" study using subcutaneous injection of study drug or "matching placebo"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	"double-blind, placebo-controlled" study using subcutaneous injection of study drug or "matching placebo"
Incomplete outcome data (attrition bias)	Low risk	All randomised participants were included in analysis (4/14 and 3/17 withdrew from study; "the last observed data were carried forward")

Wang 2017a *(Continued)*

Cure or improvement		
Incomplete outcome data (attrition bias) Pain	Low risk	All randomised participants were included in analysis (4/14 and 3/17 withdrew from study; "the last observed data were carried forward")
Incomplete outcome data (attrition bias) Frequency	Low risk	All randomised participants were included in analysis (4/14 and 3/17 withdrew from study; "the last observed data were carried forward")
Incomplete outcome data (attrition bias) Nocturia	Low risk	All randomised participants were included in analysis (4/14 and 3/17 withdrew from study; "the last observed data were carried forward")
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Low risk	All randomised participants were included in analysis (4/14 and 3/17 withdrew from study; "the last observed data were carried forward")
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis (4/14 and 3/17 withdrew from study; "the last observed data were carried forward")
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Warren 2000

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 4.5
Participants	**Number randomised:** 50 **Setting:** 6 centres **Country:** USA **Sex:** 45 females and 5 males **Age, years:** mean 49.7 (SD 16.0) for Group A, mean 54.8 (SD 8.9) for Group B **Diagnosis:** IC (NIDDK criteria) **Inclusion criteria:** those who met published NIDDK criteria. When cystoscopy was performed by others, we obtained reports of past procedures and confirmed Hunner's ulcers or glomerulations. Semi-quantitative assessment of bladder pain on a scale of mild, discomforting, distressing, horrible and excruciating, and urgency on a scale of never, rarely, sometimes, frequently and always was obtained from each patient. For study inclusion, at least 2 of 3 criteria were required, including interstitial cystitis pain that was distressing or worse, urinary urgency sometimes or more often and/or urinary frequency for 8 or more waking hours. Patients on pentosan polysulfate were required to withdraw from the medication during the study because of anecdotal reports of improvement months after initiation. Other interstitial cystitis therapy was continued if it had been administered for 2 months or longer **Exclusion criteria:** patients were excluded from the study when they were pregnant or breastfeeding, could not swallow or absorb oral medications, could not follow instructions or participate for 18 weeks

Warren 2000 *(Continued)*

	or had known renal or liver disease. Those with a clean midstream voided urine sample that yielded 1 3 105/mL or greater bacteria of any species were also excluded from the study. In addition, patients with allergy or intolerance to a study antibiotic participated but did not receive that antibiotic, and those who could not receive 2 or more study antibiotics were excluded from the study
Interventions	**Group A (n = 25):** antibiotic regimen **Group B (n = 25):** placebo **Regimen:** 18 weeks of placebo or antibiotics, including rifampin 300 mg OD plus a sequence of doxycycline 100 mg BD, erythromycin 250 mg QDS, metronidazole 500 mg QDS, clindamycin 300 mg QDS, amoxicillin 500 mg TDS and ciprofloxacin 250 mg BD for 3 weeks each **Treatment category in NMA:** antibiotics vs control
Outcomes	Outcome data in analysis Cure or improvement: subjective cure: at 18 weeks (assumed from reports) Adverse events: at 18 weeks.
Funding	Interstititial Association; Bayer, Hoechst Marion Roussel, Pharmacia and Upjohn and Roerig Pfizer
Notes	**Publication status:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind, placebo controlled". Placebo not described
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	Quote: "double-blind, placebo controlled". Placebo not described
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	18/25 (72%; 7 withdrew due to perceived AE or unrelieved IC symptom or both) included in intervention group; 19/25 (2 withdrew before treatment, 4 withdrew due to diarrhoea, unrelieved symptoms, stress or constitutional symptoms) included in control group
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Yang 2011

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 4
Participants	**Number randomised:** 58 **Setting:** 11 clinics **Country:** USA and Canada **Sex:** 48 females and 10 males **Age, years:** mean 51.3 (SD 10.3) for Group A, mean 51.8 (SD 11.6) for Group B **Diagnosis:** IC/PBS (clinical criteria) **Inclusion criteria:** men and women older than 18 years. Eligibility required fulfilment of all of certain criteria, including (1) persistent symptoms of urinary frequency and pain rated at least 4 on a scale of 0 to 10, (2) failure of at least 24 weeks of active treatment with a minimum of 3 standard forms of therapy or combination of therapies for IC/PBS, (3) cystoscopic diagnosis of IC/PBS in the past with findings of glomerulations and/or ulcerations and (4) screening cystoscopy within the 24 weeks before study entry to evaluate for an unevaluated pathological condition **Exclusion criteria:** "there were additional exclusion criteria" [exclusion criteria not reported]. Except for medications listed in the exclusion criteria, subjects were allowed to continue on the current medication regimen
Interventions	**Group A (n = 39):** an immunosuppressant 1 gram daily, mycophenolate mofetil (MMF) for 14 days, then 1 gram BID for 10 weeks **Group B (n = 19):** placebo **Treatment category in NMA:** immune modulators vs control
Outcomes	Outcome data in analysis Cure or improvement: ‘moderately' or 'markedly’ improved on GRA: at 16 weeks Pain: defined as ratings on a '10-point scale' with score range 0 to 10 (but 0 to 10 is actually an 11-point scale) at 16 weeks ICSI: at 16 weeks ICPI: at 16 weeks Adverse events: at 16 weeks
Funding	NIDDK Cooperative Agreements
Notes	**Publication status** full text The trial was "prematurely halted". "A black box warning for MMF [mycophenolate mofetil] was issued" by manufacturer. Early termination recommended by monitoring committee due to lack of efficacy, increased safety concerns and slow recruitment. 19/39 in intervention group were not receiving study drug at the primary end point (14 due to study suspension and 5 due to drug tolerability)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Yang 2011 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "randomized … in a 2:1 ratio"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Placebo-controlled" trial, using "matching placebo"
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	"Placebo-controlled" trial, using "matching placebo"
Incomplete outcome data (attrition bias) Cure or improvement	Low risk	39/39 included in intervention group; 18/19 included in control group
Incomplete outcome data (attrition bias) Pain	Low risk	39/39 included in intervention group; 18/19 included in control group
Incomplete outcome data (attrition bias) Interstitial Cystitis Symptom Index	Low risk	39/39 included in intervention group; 18/19 included in control group
Incomplete outcome data (attrition bias) Interstitial Cystitis Problem Index	Low risk	39/39 included in intervention group; 18/19 included in control group
Incomplete outcome data (attrition bias) Adverse events	Low risk	All randomised participants were included in analysis
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Yassin 2011

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 6
Participants	**Number randomised:** 28 **Setting:** not reported **Country:** Egypt **Sex:** 23 females and 5 males **Age, years:** not reported

Yassin 2011 *(Continued)*

	Diagnosis: PBS/IC **Inclusion criteria:** patients with PBS/IC who did not respond to any of the conventional treatment modalities **Exclusion criteria:** not reported
Interventions	**Group A (n = 18):** 200 IU of botulinum toxin A into 20 mL of normal saline + hydrodistension **Group B (n = 10):** NaCl + hydrodistension **Treatment category in NMA:** neuromuscular blockade vs control
Outcomes	Outcome data in analysis Cure or improvement: subjective Improvement (no definition) at 6 months (assumed from reports) Adverse events: at 6 months
Funding	None
Notes	**Publication status:** abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly divided"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned. Submucosal injection of botuinum toxin A or normal saline "under general anaesthetics … with video recording of the injection sites in a similar mapping in both groups"
Blinding of outcome assessment (detection bias) Subjective outcome	Unclear risk	Blinding not mentioned. Submucosal injection of botuinum toxin A or normal saline "under general anaesthetics … with video recording of the injection sites in a similar mapping in both groups"
Incomplete outcome data (attrition bias) Cure or improvement	Unclear risk	Appeared that all randomised participants were included in analysis, but no description of missing data was provided
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Appeared that all randomised participants were included in analysis, but no description of missing data was provided
Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

Zakaria 2016

Study characteristics	
Methods	**Study design:** RCT **Study duration (months):** 4
Participants	**Number randomised:** 30 **Setting:** not reported **Country:** Egypt **Sex:** male **Age, years:** range 30 to 50 **Diagnosis:** IC/PBS **Inclusion criteria:** male patients who had interstitial cystitis/painful bladder syndrome **Exclusion criteria:** not reported
Interventions	**Group A (n = 15):** transcutaneous electrical nerve stimulation (TENS) for 15 minutes, once daily, 3×/week for 4 months. 2 suprapubic electrodes and 2 under the lower back (T10-L1). Square wave form, 80 to 100 Hz frequency, 10 to 30 mA amplitude, pulse width 50 to 60 us. Traditional physical therapy (PFMT) and medical care (clomipramine, a tricyclic antidepressant) also received **Group B (n = 15):** sham TENS, traditional physical therapy (PFMT) and medical care (clomipramine, a tricyclic antidepressant) **Treatment category in NMA:** physical therapy vs control
Outcomes	Outcome data in analysis Pain: VAS (range 0 to 10) at 4 months
Funding	Not reported
Notes	**Publication status:** full text

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly divided"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	TENS vs sham TENS (with physical therapy)
Blinding of outcome assessment (detection bias) Subjective outcome	Low risk	TENS vs sham TENS (with physical therapy)
Incomplete outcome data (attrition bias) Pain	Low risk	All randomised participants were included in analysis

Zakaria 2016 *(Continued)*

Selective reporting (reporting bias)	Low risk	Results included all outcomes specified in the methods section
Other bias	Low risk	None detected

AE: adverse event.
ALT: alanine aminotransferase.
AST: aspartate aminotransferase.
BCG: bacille Camille-Guerin.
BMI: body mass index.
BoNT-A: botulinum toxin type A.
BPS: bladder pain syndrome.
BT: bladder training.
CP: chronic prostatitis.
CPPS: chronic pelvic pain syndrome.
CPSI-F: female modification of Chronic Prostitis Symptom Index.
CS: chondroitin sulfate.
DMSO: dimethyl sulfoxide.
EBMP: educational and behavioural modification programme.
GRA: Global Response Assessment.
HA: hyaluronic acid.
HD: hydrodistension.
IC: interstitial cystitis.
ICPI: Interstitial Cystitis Problem Index.
ICSI: Interstitial Cystitis Symptom Index.
IgG: immunoglobulin G.
IQR: interquartile ratio.
LOCF: last observation carried forward.
mAbs: monoclonal antibodies.
NGF: nerve growth factor.
NIDDK: National Institute of Diabetes and Digestive and Kidney Disease.
NIH: National Institutes of Health.
NMA: network meta-analysis.
NSAID: non-steroidal anti-inflammatory drug.
OSPI: O'Leary and Sant Interstitial Cystitis Problem Index.
OSSI: O'Leary and Sant Interstitial Cystitis Symptom Index.
PBD: painful bladder disease.
PBS: painful bladder syndrome.
PDE5: phosphodiesterase-5 inhibitor.
PORIS: Patient Overall Rating of Improvement in Symptoms.
PPS: pentosan polysulfate.
PUF: Pelvic Pain and Urgency/Frequency Questionnaire.
PVR: postvoid residual.
RCT: randomised controlled trial.
RTX: resiniferatoxin.
SD: standard deviation.
SHN: superior hypogastric plexus neurolysis.
TENS: transcutaneous electrical nerve stimulation.
TUIBN: transurethral incision of the bladder neck.
TUIP: transurethral incision of the prostate.
TUMT: transurethral microwave therapy.
TUNA: transurethral needle ablation.
TURP: transurethral resection of the prostate.
UTI: urinary tract infection.
VAS: visual analogue scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Akiyama 2014	Not a relevant study design. Treatments are not the same for all participants
Baert 1975	Not a relevant population (includes mixed diagnoses, e.g. cystitis, prostatitis, urethritis, as well as "spasm following diagnostic or therapeutic procedures of the genitourinary tract (cystoscopies, urethral dilatation, pyelography, catheterisation)")
Choa 1983	Not a relevant population. Includes "urethral syndrome", which is an old term for symptoms similar to BPS, but it is not BPS in its current definition
Costantini 2003	Not a relevant population. Includes "urethral syndrome", which is an old term for symptoms similar to BPS, but it is not BPS in its current definition
Gallego-Vilar 2013	Not a relevant population. A very particular group of participants (DMSO (dimethyl sulfoxide) responders) that are not consistent with other participants in the network meta-analysis
Keay 2007	Not a relevant intervention. RCT of biomarker
Ko 2016	Not a relevant study design. High suspicion that randomisation was not done by participants. Reports data by number of procedure rather than by number of participants. Data are reported by number of procedures, not by number of participants. Compares transurethral resection (TUR) vs transurethral coagulation (TUC). Possibly linked to the Lee 2015 study. Available as meeting abstract only with no contact details for study authors
Lai 2013	Not a relevant comparison. Compares different regimens of interstitial hyaluronic acid instillation
Lee 2015	Not a relevant study design. High suspicion that randomisation was not done by participant, as participants received more than 1 procedure. Reports data by number of procedures, not by number of participants. Compares transurethral resection (TUR) vs transurethral coagulation (TUC). Possibly linked to the Ko 2016 study. Available as meeting abstract only with no contact details for study authors
Li 2016	Not a relevant population. Includes cystitis induced by ketamine misuse
Lubeck 2001	Not a relevant comparison. Compares 3 doses of pentosan polysulfate (PPS) and no other intervention
Netto 1980	Not a relevant population. Active infection among participants is mentioned
Nickel 2005	Not a relevant comparison. Compares 3 doses of pentosan polysulfate (PPS) and no other intervention
Peters 2007	Not a relevant comparison. Compares 2 types of neuromodulation (sacral nerve stimulation vs pudendal nerve stimulation)

BPS: bladder pain syndrome.
DMSO: dimethyl sulfoxide.
PPS: pentosan polysulfate.
RCT: randomised controlled trial.
TUC: transurethral coagulation.
TUR: transurethral resection.

Characteristics of studies awaiting classification *[ordered by study ID]*

Aboyan 2018

Methods	**Study design:** RCT

Aboyan 2018 *(Continued)*

Participants	**Sex:** not specified **Age (mean):** Group A: 57.1 years; Group B: 58.63 years **Condition:** BPS/IC **Target sample size:** 37 reported, original target not stated
Interventions	**Group A (n = 19):** intravesical hyaluronic acid alone **Group B (n = 18):** intravesical hyaluronic acid in combination with oral chondroitin
Outcomes	Time point/follow-up unclear: "visual analogue pain scale (VAS), interstitial cystitis symptom index (ICSI), interstitial cystitis problem index (ICPI), voiding diary for frequency/nocturia"
Notes	**Funding:** not stated **Trial registration number:** none reported **Publication type:** conference abstract **Status in relation to this review:** new study

Asumpinwong 2018

Methods	**Study design:** RCT
Participants	**Sex:** female **Age:** 18 years or over **Condition:** BPS (VAS score of 4) **Target sample size:** 62
Interventions	**Group A:** intravesical heparin instillation with conservative treatment **Group B:** conservative treatment alone (no description of 'conservative treatment')
Outcomes	Follow-up: 12 weeks after treatment, when these outcomes will be measured: pain (VAS); daytime frequency; QoL; adverse effects
Notes	**Funding:** not reported **Trial registration number:** TCTR20180912004 **Publication type:** trial registration **Status in relation to this review:** new ongoing study **Recruitment started:** 1 October 2018 (anticipated) **Recruitment due to end:** 29 January 2021

Bosch 2018

Methods	**Study design:** RCT

Bosch 2018 *(Continued)*

Participants	**Sex:** female **Age:** 18 to 65 years **Condition:** IC/BPS - participants with "moderate to severe IC/BPS as defined with scores of 7 on the O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI)" **Target sample size:** 42
Interventions	**Group A (n = 28):** subcutaneous certolizumab pegol 400 mg **Group B (n = 14):** placebo (sterile saline) Certolizumab pegol is an anti-tumour necrosis factor-alpha agent (i.e. an anti-TNF-alpha agent)
Outcomes	Follow-up: 18 weeks: GRA; ICSI; ICPI; pain (pain intensity numerical rating scale (MCID used as 30% reduction from baseline))
Notes	**Funding:** UCB (Union Chimique Belge), Brussels, Belgium (biopharmaceutical company) **Trial registration number:** NCT02497976 **Publication type:** full journal article **Status in relation to this review:** new study

Carty 2019

Methods	**Study design:** RCT
Participants	**Sex:** female **Age:** 18 to 80 years **Condition:** "chronic urogenital pain" **Number randomised:** 70
Interventions	**Group A:** 90-minute life stress interview (stress and emotion interview) **Group B:** wait-list control (no interview)
Outcomes	**Follow-up:** 6 weeks **Outcomes:** pain severity and pain Interference (using Brief Pain Inventory); pelvic floor symptoms (using Pelvic Floor Distress Inventory – Short Form–20; depression and anxiety (using Brief Symptom Inventory - 18)
Notes	**Funding:** "Student Award from the Blue Cross Blue Shield of Michigan Foundation and grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (AR057808 and AR057047" **Trial registration number:** NCT02286115 **Publication type:** full journal article **Status in relation to this review:** additional report of the already included Carty 2017 (already with a PhD thesis, a conference abstract and a trial registration) **Treatment category in NMA:** behavioural therapy vs control

Cervigni 2018

Methods	**Study design:** cross-over RCT
Participants	**Sex:** female (no males recruited) **Age:** mean 52.6 years (SD ± 12.6) **Condition:** BPS/IC (ESSIC criteria) **Target sample size:** 15 (of which 2 dropouts)
Interventions	**Group A:** transcranial magnetic stimulation **Group B:** sham stimulation
Outcomes	Two weeks' treatment followed by 6 weeks' washout period followed by 2 weeks on alternative treatment. 6 weeks' follow-up at the end of the final treatment session Outcomes include pain (VAS); Overactive Bladder Questionnaire (OABq); O'Leary-Saint Questionnaire; QoL (36-Item Short Form Health Survey - SF-36)
Notes	**Funding:** Associazione Italiana Cistite Interstiziale (AICI) **Trial registration number:** not reported **Publication type:** full journal article **Status in relation to this review:** new study

El Refaye 2019

Methods	**Study design:** RCT
Participants	**Sex:** female **Age:** 25 to 40 years **Condition:** interstitial cystitis **Target sample size**: 40
Interventions	**Group A (n = 20):** interferential current (lower abdomen) + anticholinergic (propiverine hydrochloride) **Group B (n = 20):** anticholinergic (propiverine hydrochloride)
Outcomes	**Treatment period:** 8 weeks **Outcomes measured at the end of the treatment period:** pain (VAS); ICSI
Notes	**Funding:** unclear **Trial registration number:** NCT03844581 **Publication type:** trial registration **Status in relation to this review:** new ongoing study **Recruitment started:** 1 January 2019

El Refaye 2019 *(Continued)*

	Recruitment due to end: 13 February 2019

Hsieh 2018

Methods	**Study design:** RCT
Participants	**Sex:** any **Age:** 20 years and over **Condition:** IC/BPS; "patients with symptoms of unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six months duration, in the absence of infection or other identifiable causes" **Target sample size:** 96
Interventions	**Group A:** low-energy shock wave (LESW) (transcutaneous applied to the suprapubic bladder region with 2000 shocks, frequency of 3 pulses per second and maximum total energy flow density 0.25 millijoule/mm^2) **Group B:** sham LESW treatment (same condition but with no energy)
Outcomes	**Outcomes measured at "one month after the treatment day":** GRA; VAS; daytime voiding frequency; nighttime voiding frequency; ICSI; ICPI; functional bladder capacity
Notes	**Funding:** unclear **Trial registration number:** NCT03619486 **Publication type:** trial registration **Status in relation to this review:** new ongoing study **Recruitment started:** 4 July 2018 **Recruitment due to end:** 1 July 2020

Kenny 2016

Methods	**Study design:** RCT
Participants	**Sex:** female **Age:** 18 to 60 years **Condition:** chronic pelvic pain - study authors included BPS/IC due to the difficulties of excluding from chronic pelvic pain **Target sample size:** 79
Interventions	**Group A:** manual therapy **Group B:** trigger point dry needling
Outcomes	**Outcomes at each treatment session for up to 10 weeks:** 1 treatment session per week: pain (on 0 to 10 Pain Rating Scale); Pelvic Pain Questionnaire; Pain Treatment Satisfaction Scale

Kenny 2016 *(Continued)*

Notes	**Funding:** not reported **Trial registration number:** NCT02795026 **Publication type:** trial registration **Status in relation to this review:** new ongoing study **Recruitment started:** April 2016 **Recruitment due to end:** June 2018

Lee 2018

Methods	**Study design:** CCT
Participants	**Sample size:** 60 **Sex:** female **Age:** adult **Condition:** IC/BPS
Interventions	**Group I:** self-management telecare system (patient video education, mobile phone app, lifestyles) **Group II:** control (no detail - "only regular treatments")
Outcomes	**Outcomes measured at 8 weeks:** O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI); pain and urgency (both using VAS); QoL (SF-36)
Notes	**Funding:** "partly funded by Feng Yuan Hospital, Ministry of Health and Welfare (Grant no. FYH1030709-2) and Ministry of Science and Technology (Grant no. MOST106-2410-H-166-004) **Trial registration number:** not reported **Publication type:** full journal article **Status in relation to this review**: additional report of the already included Lee 2016 (currently only 2 conference abstracts are included in the full review) **Treatment category in NMA:** behavioural therapy vs control

Moldwin 2018

Methods	**Study design:** RCT
Participants	**Target sample size:** 433 **Sex:** any **Age:** 18 to 80 years **Condition:** IC/BPS
Interventions	**Group I:** AQX-1125 100 mg **Group II:** AQX-1125 200 mg

Moldwin 2018 *(Continued)*

	Group III: placebo Oral administration
Outcomes	**Outcomes to be measured at 12 weeks:** "average bladder pain based on an 11-point numerical rating scale (NRS); voiding over a 24-hour period; and symptom scores based on the following questionnaires: Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS), O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) and O'Leary-Sant Interstitial Cystitis Problem Index (ICPI)"
Notes	**Funding:** "Aquinox Pharmaceuticals Inc sponsored this clinical trial" **Trial registration number:** NCT02858453; EUCTR2016-000906-12 **Publication type:** conference abstract **Status in relation to this review:** additional report of the already included ongoing study Leadership 301 Trial 2016 - this abstract reports only baseline details of participants

Moon 2019

Methods	**Study design:** RCT
Participants	**Sex:** any **Age:** 45 years or over **Condition:** interstitial cystitis with an IPSS total score of 8 or higher **Target sample size:** 80
Interventions	**Group A (target n = 40):** pentosan polysulphate + alpha blocker **Group B (target n = 40):** alpha blocker alone
Outcomes	At end of 12 week treatment period, these outcomes will be measured: ICSI; ICPI; Pelvic Pain and Urgency/Frequency Patient Symptom Scale; functional bladder capacity
Notes	**Funding:** Chong Kun Dang (a pharmaceutical company) **Trial registration number:** KCT0003772 **Publication type:** trial registration **Status in relation to this review:** new ongoing study **Recruitment started:** 1 May 2019 **Recruitment due to end:** 30 November 2019

Oh-Oka 2017

Methods	**Study design:** RCT
Participants	**Sex:** female **Age:** 20 years or over **Condition:** IC/BPS

Oh-Oka 2017 *(Continued)*

	Target sample size: 40
Interventions	**Group A (n = 30):** intensive systematic dietary manipulation **Group B (n = 10):** did not receive intensive dietary manipulation
Outcomes	**Outcomes measured at 3 months and 1 year from baseline:** pain; urinary urgency; ICSI; ICPI; QoL
Notes	**Funding:** not reported **Trial registration number:** none given **Publication type:** 2 reports (1 full journal article and 1 conference abstract) **Status in relation to this review:** new study

Rahimi 2018

Methods	**Study design:** RCT
Participants	**Sex:** female **Age:** over 18 years **Condition:** interstitial cystitis **Target sample size:** 24
Interventions	**Group A (n = 12):** hydrodistension + hyaluronic acid **Group B (n = 12):** hydrodistension alone
Outcomes	At 3 months' follow-up, the following outcomes were measured using the O'Leary-Sant questionnaire: frequency; urgency; nocturia; dysuria
Notes	**Funding:** Mashhad University of Medical Sciences (states: public funding) **Trial registration number:** IRCT20130811014330N5 **Publication type:** trial registration **Status in relation to this review:** new ongoing study **Recruitment started:** 22 April 2017 **Recruitment due to end:** 26 July 2017

Yusefi 2018

Methods	**Study design:** RCT
Participants	**Sex:** any **Age:** over 18 years to 80 years **Condition:** interstitial cystitis

Yusefi 2018 *(Continued)*

	Target sample size: 50
Interventions	**Group A:** topical use of chamomile oil “in the bladder area” **Group B:** topical use of placebo oil “in the bladder area”
Outcomes	**Outcomes measured at the end of the treatment period (2 months):** ICSI
Notes	**Funding:** The Qom University of Medical Science (states: public funding) **Trial registration number:** IRCT20170112031893N2 **Publication type:** trial registration **Status in relation to this review:** new ongoing study **Recruitment started:** 6 December 2018 **Recruitment due to end:** 6 December 2019

BPIC-SS: Bladder Pain/Interstitial Cystitis Symptom Score.
BPS: bladder pain syndrome.
CCT: controlled clinical trial.
ESSIC: International Society for the Study of Bladder Pain Syndrome (BPS).
GRA: Global Response Assessment.
IC: interstitial cystitis.
ICPI: Interstitial Cystitis Problem Index.
ICSI: Interstitial Cystitis Symptom Index.
IPSS: International Prostate Symptom Score.
LESW: low-energy shock wave.
MCID: minimal clinically important difference.
NMA: network meta-analysis.
QoL: quality of life.
RCT: randomised controlled trial.
SD: standard deviation.
SF-36: 36-Item Short Form Health Survey.
TNF: tumour necrosis factor.
VAS: visual analogue scale.&&

Characteristics of ongoing studies *[ordered by study ID]*

Bhat 2018

Study name	Tadalafil for painful bladder
Methods	**Study design:** parallel-group RCT **Blinding:** participant and investigator
Participants	**Target sample size:** 100 **Country:** India **Sex:** any **Age:** 15 to 85 years **Condition:** "painful bladder syndrome" **Exclusion criteria:** "those with co-morbidities such as Diabetes Mellitus, Hypertension, IHD, Asthma, immune compromised status and proved urinary bladder diseases shall be excluded."

Bhat 2018 *(Continued)*

Interventions	**Group A:** tadalafil 5 mg **Group B:** placebo
Outcomes	At 3 months **Primary outcomes:** pain score (O'Leary-Sant and numerical rating scale); bladder capacity (USG) **Secondary outcomes:** dropout rate "due to adverse events or worsening of symptoms"
Starting date	1 April 2018
Contact information	Dr Gajanan Bhat Consultant Urologist and Andrologist TSS Shripad Hegde Kadave Institute of Medical Sciences, Sirsi Uttara Kannada KARNATAKA 581402 India Email: gajubhatru@gmail.com
End date	"Not yet recruiting"
Notes	**Funding:** "nil" **Clinical Trials Registry - India (CTRI) number:** CTRI/2018/03/012720

Bond 2016

Study name	A pilot study investigating the use of a therapeutic wand in addition to physiotherapy for bladder pain syndrome
Methods	**Study design:** parallel-group RCT **Blinding:** none
Participants	**Target sample size:** 10 **Country:** United Kingdom **Sex:** female **Age:** 18 to 65 years **Condition:** "diagnosis of Bladder Pain Syndrome or interstitial Cystitis as per the definition of the International Society for the Study of Bladder Pain Syndrome"
Interventions	**Group A:** therapeutic wand plus physiotherapy (PFMT, lifestyle and bladder training) **Group B:** physiotherapy
Outcomes	At 6 weeks and 12 weeks

Bond 2016 *(Continued)*

	Primary outcomes: O'Leary-Sant IC Symptom Index Score and Problem Index Score At 12 weeks **Secondary outcomes:** Genitourinary Pain Index; Pelvic Pain and Urinary Urgency Frequency Patient Symptom Scale; patient-reported urinary urgency; overall pain; ease of use of wand; adverse effects
Starting date	"April 2016"
Contact information	Jilly Bond, Clinical Specialist Physiotherapist, University of Bradford
End date	"October 2016"
Notes	**Funding:** not reported **ClinicalTrials.gov registration number:** NCT02743962 **Results posted on ClinicalTrials.gov 'Study Results' tab:** 3 May 2018 (not yet incorporated into this review)

Brucker 2016

Study name	Randomized controlled trial of PTNS versus sham efficacy in treatment of bladder pain syndrome
Methods	**Study design:** parallel-group RCT **Blinding:** participant and investigator
Participants	**Target sample size:** 100 **Country:** USA **Sex:** female **Age:** 18 years or older **Condition:** "Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC)"... "with visual analog scale > 5"
Interventions	**Group A:** percutaneous tibial nerve stimulation **Group B:** sham
Outcomes	At 12 weeks **Primary outcomes:** Patient Global Impression of Improvement (PGI-I) **Secondary outcomes:** quality of life scores (VAS); O'Leary-Sant Pain Scores ("pain intensity, location of pain and associated symptoms"); Overactive Bladder-Questionnaire; Short Form SF-12 Health Scale
Starting date	June 2016
Contact information	Dominique Malacarne New York University School of Medicine New York, New York, USA 10016

Brucker 2016 *(Continued)*

	Email: malacd01@nyumc.org
End date	March 2020
Notes	**Funding:** unclear **ClinicalTrials.gov registration number:** NCT02747420

Cardenas-Trowers 2018

Study name	Randomized controlled trial comparing two different bladder instillation treatments for interstitial cystitis/bladder pain syndrome
Methods	**Study design:** parallel-group RCT **Blinding:** participant and care provider
Participants	**Target sample size:** 80 **Country:** USA **Sex:** female **Age:** 18 years or older **Condition:** "with IC/BPS who have a score of ≥ 6 on either index (problem or symptom index) of the O'Leary-Sant questionnaire who have selected bladder instillations as part of their IC/BPS treatment"
Interventions	**Group A:** intravesical instillation of "standard cocktail" plus triamcinolone acetonide (40 mg/1 mL) **Group B:** intravesical instillation of "standard cocktail" alone. Standard cocktail = "heparin (10,000 units), 2% viscous lidocaine (10 mL), 8.4% sodium bicarbonate (15 mL of 1 mEq/mL) and 0.5% bupivacaine (10 mL of 5 mg/mL)"
Outcomes	At 3 weeks and 6 weeks **Primary outcomes:** O'Leary-Sant Questionnaire **Secondary outcomes:** Pelvic Pain and Urgency/Frequency Questionnaire; Overactive Bladder Questionnaire; Pelvic Floor Distress Inventory; Pelvic Organ Prolapse Incontinence Sexual Questionnaire; VAS for pain; adverse effects
Starting date	25 January 2019
Contact information	Alyce Goodman-Abraham University of Louisville Urogynecology at Springs Medical Center Louisville, Kentucky, United States, 40205 Email: contactus@ulp.org
End date	December 2020
Notes	**Funding:** not reported **ClinicalTrials.gov registration number:** NCT03463915

Cvach 2011

Study name	Efficacy of Clorpactin(R) in bladder pain syndrome/interstitial cystitis: a randomised placebo-controlled trial
Methods	**Study design:** parallel-group RCT **Blinding:** "blinded (masking used)". No further details
Participants	**Target sample size:** 54 **Final sample size:** 50 **Country:** Australia **Sex:** female **Age:** 18 to 70 years **Condition:** "diagnosed with bladder pain syndrome/interstitial cystitis". No further details
Interventions	**Group A:** intravesical: Clorpactin (sodium oxychlorosene) **Group B:** placebo (cystodistension)
Outcomes	At 3 months **Primary outcomes:** "subject improvement as reflected in the Global Response Assessment" **Secondary outcomes:** "nil"
Starting date	**Actual recruitment start date:** 1 March 2012
Contact information	Dr Kristina Cvach Mercy Hospital for Women 163 Studley Rd Heidelberg VIC 3084 Australia Email: kcvach@mercy.com.au
End date	**Actual recruitment end date:** 31 December 2016
Notes	**Funding:** "self-funded/unfunded" **Trial registration number:** ACTRN12611000717954

Drug Company 2005

Study name	A phase 2, randomized, double-blind, placebo-controlled study of YM672 in the treatment of painful bladder syndrome/interstitial cystitis
Methods	**Study design:** parallel-group RCT **Blinding:** double blind - no other details
Participants	**Target sample size:** 150

Drug Company 2005 *(Continued)*

	Country: multi-national **Sex:** any **Age:** 18 years or older **Condition:** "diagnosis of PBS/IC defined as suprapubic pain related to bladder filling, accompanied by other symptoms, such as increased daytime and nighttime frequency, in the absence of proven urinary infection or other obvious pathology, with symptoms for at least 12 consecutive weeks prior to the screening visit." A score of a least 1 on the PBS/IC Problem Index Question #4. PBS/IC Symptom Index Score of at least 7 (total score) at baseline
Interventions	**Group A:** oral: YM672 (IPD(R)) ("suplatast tosilate" on trial registration) **Group B:** placebo
Outcomes	At 12 weeks and/or at "end of treatment" **Primary outcome:** "...success, defined as "moderately improved" or "markedly improved" PBS/IC on the subject-rated 7-point Global Response Assessment (GRA)" **Secondary outcomes:** including GRA at weeks 4 and 8; IC Symptom Index; IC Problem Index; mean number of micturitions per day; mean number of micturitions per night; severity of urinary urgency on VAS; severity of bladder pain, pelvic pain and pain (including discomfort) accompanied by urinary urgency on VAS; adverse events, etc.
Starting date	Not reported (ethics committee opinion 05/01/2005)
Contact information	Astellas Pharma Europe B.V. No further details
End date	23 April 2007
Notes	**Funding:** Astellas Pharma Europe B.V. **Trials registration number:** EUCTR2005-003367-23-DE **Sponsor's Protocol Code Number:** 672-CL-035

Drug Company 2017a

Study name	Exploratory, randomized, double-blind, placebo-controlled evaluation of efficacy, tolerability, and safety of intravesical instillation of GRT6010 compared to placebo in subjects with bladder pain syndrome
Methods	**Study design:** parallel-group RCT **Blinding:** double blind - no other details
Participants	**Target sample size:** 120 (of which 15 will be 65 years of age or older) **Country:** multi-national **Sex:** female **Age:** 18 to 75 years **Condition:** "pain perceived to be related to the urinary bladder and consistent presence of at least 1 other urinary symptom such as persistent urge to void or frequency for at least 12 months. Princi-

Drug Company 2017a *(Continued)*

	pal exclusion criteria: presence of Hunner's lesion as demonstrated by a cystoscopy with hydrodistention"
Interventions	**Group A:** intravesical: GRT6010 **Group B:** placebo
Outcomes	**Treatment period/time points/length of follow-up:** unclear, total length of study in all countries reported as 1 year **Primary outcome:** average daily paIn scores on a 0 to 100 VAS **Secondary outcomes:** including O'Leary/Sant Questionnaire (Symptom and Problem Index) score; Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS); mean number of micturitions per day; adverse events, etc.
Starting date	Not reported (ethics committee opinion 22/05/2017)
Contact information	Grünenthal GmbH Email: Clinical-Trials@grunenthal.com
End date	**Date of the global end of the trial:** 2 May 2018
Notes	**Funding:** Grünenthal GmbH **Trial registration number:** EUCTR2016-003940-35 **WHO Trial Reference Number (UTRN):** U1111-1188-0214 **Sponsor's Protocol Code Number:** KF6010-02

Drug Company 2017b

Study name	A Phase III, multicenter, randomized, double-blind, placebo controlled, parallel group study to assess the efficacy and safety of KRP-116D in Japanese patients with interstitial cystitis
Methods	**Study design:** parallel-group RCT **Blinding:** double blind - no other details
Participants	**Target sample size:** 90 **Country:** Japan **Sex:** any **Age:** 20 years or older **Condition:** "diagnosed with IC"
Interventions	**Group A:** intravesical: KRP-116D ("dimethyl sulfoxide" according to the trial registration) **Group B:** placebo
Outcomes	**Treatment period/time points/length of follow-up:** not reported **Primary outcome:** O'Leary and Sant's IC Symptom Index

Drug Company 2017b *(Continued)*

	Secondary outcomes: "O'Leary and Sant's IC Problem Index; Urinary Symptom, Bladder Pain Score, etc.; Safety Questionnaire; Symptom Diary; adverse event and adverse drug reaction"
Starting date	25 May 2017
Contact information	Kyorin Pharmaceutical Co., Ltd Email: develop@mb.kyorin-pharm.co.jp
End date	Not reported (expected end date: 30 June 2019)
Notes	**Funding:** Kyorin Pharmaceutical Co., Ltd **Trial registration number:** JPRN-JapicCTI-173566

Drug Company 2017c

Study name	A study to investigate efficacy, safety, pharmacodynamics and pharmacokinetics of ASP6294 in the treatment of female subjects with bladder pain syndrome/interstitial cystitis
Methods	**Study design:** parallel-group RCT **Blinding:** participant and investigator
Participants	**Target sample size:** 117 **Country:** multi-national **Sex:** female **Age:** 18 years of age or older **Condition:** used the ESSIC definition for BPS/IC with document proof of at least 2 months' duration. In addition: "a score of ≥ 4 and ≤ 9 for pain as assessed by scoring the average pain of the week preceding Visit 1/Screening, using an 11-point NRS (0-10)"; "subject has an estimated voiding frequency of ≥ 8 and ≤ 30 voids per 24 hours"; "subject has a score of ≥ 7 on the Interstitial Cystitis Symptom Index (ICSI) Questionnaire"
Interventions	**Group A:** ASP6294 (administration: subcutaneous injection) **Group B:** placebo
Outcomes	At 12 weeks **Primary outcome:** average mean daily pain (MDP) **Secondary outcomes:** 13 listed, including Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS); average worst daily pain; GRA; adverse effects, etc.
Starting date	28 September 2017
Contact information	Astellas Pharma Europe B.V. No further details
End date	21 March 2019
Notes	**Funding:** Astellas Pharma Europe B.V. **ClinicalTrials.gov registration number:** NCT03282318

Drug Company 2017c *(Continued)*

	Trial registration number: EudraCT2016-004138-12 **Other study ID/name:** SERENITY **Protocol number:** 6294-CL-0101

Leadership 301 Trial 2016

Study name	The LEADERSHIP 301 Trial: a 12-week, randomized, multi-center, double-blind, placebo-controlled, 3-arm, parallel-group, phase 3 trial to evaluate the efficacy and safety of 2 doses of AQX-1125 targeting the Src homology 2-containing inositol-5'-phosphatase 1 (SHIP1) pathway in subjects with interstitial cystitis/bladder pain syndrome followed by 14- or 40-week extension periods
Methods	**Study design:** parallel-group RCT **Blinding:** "quadruple (participant, care provider, investigator, outcomes assessor)"
Participants	**Target sample size:** 433 **Country:** multi-national **Sex:** any **Age:** 18 to 80 years **Condition:** "symptoms of bladder pain in addition to urinary urgency and/or urinary frequency for more than 6 months"; "clinical diagnosis, or history consistent with the diagnosis, of interstitial cystitis/bladder pain syndrome for > 3 months but ≤ 20 years". Must have undergone a cystoscopy within the last 36 months before baseline
Interventions	**Group A:** AQX-1125 100 mg **Group B:** AQX-1125 200 mg **Group C:** placebo Oral administration
Outcomes	At 12 weeks **Primary outcome:** maximum daily bladder pain score "based on a standardized 11-point numerical rating scale (NRS) recorded by electronic diary (e-diary)" **Secondary outcomes:** IC Symptom Index Score; Bladder Pain/IC Symptom Score; GRA; voiding frequency over 24 hours; adverse effects
Starting date	July 2016
Contact information	Aquinox Pharmaceuticals (Canada), Inc.
End date	February 2020
Notes	**Funding:** Aquinox Pharmaceuticals (Canada), Inc. **ClinicalTrials.gov registration number:** NCT02858453 **Other trial registration number:** EUCTR2016-000906-12 **Other study ID numbers:** AQX-1125-301

Parsons 2015

Study name	A phase 2a, randomized, double-blind, placebo-controlled multi-center single dose study to evaluate the safety and effectiveness of URG101 compared with the individual components lidocaine and heparin in subjects with interstitial cystitis/bladder pain syndrome
Methods	**Study design:** parallel-group RCT **Blinding:** triple (participant, care provider, investigator)
Participants	**Target sample size:** 92 **Country:** USA **Sex:** any **Age:** 18 years of age or older **Condition:** diagnosed with BPS/IC and have "moderate-to-severe symptoms of bladder pain of bladder origin for at least 9 months prior to the study; may or may not have received a cystoscopy in association with their diagnosis of interstitial cystitis/bladder pain syndrome prior to or at time of screening; Have a score of ≥ 15 and < 30 on the PUF questionnaire, completed at screening; a minimum score of 5 is required on the VAS"
Interventions	**Group A:** lidocaine **Group B:** heparin **Group C:** lidocaine plus heparin **Group D:** placebo Intravesical administration
Outcomes	At 12 or 24 hours after administration **Primary outcome:** change in bladder pain on VAS **Secondary outcomes:** change in urgency on VAS; adverse effects
Starting date	September 2015
Contact information	Urigen
End date	18 June 2018
Notes	**Funding:** Urigen **ClinicalTrials.gov registration number:** NCT02591199 **On trial registration states:** "terminated (prematurely terminated based on interim study analysis)" **Other study ID numbers:** URG101-105

Peters 2016

Study name	Comparison of bladder directed and pelvic floor therapy in women with interstitial cystitis/bladder pain syndrome

Peters 2016 *(Continued)*

Methods	**Study design:** parallel-group RCT **Blinding:** single (outcome assessor)
Participants	**Target sample size:** 128 **Country:** USA **Sex:** female **Age:** 18 to 85 years of age **Condition:** "history of patient self-reported IC/BPS symptoms for at least 6 months"
Interventions	**Group A:** physical therapy (pelvic floor) **Group B:** intravesical (heparin sulphate, lidocaine, sodium bicarbonate and Kenalog) **Other names:** Xylocaine, triamcinolone
Outcomes	At week 9 (1 week after last treatment) **Primary outcome:** GRA **Secondary outcomes:** change in pelvic floor examination findings and symptoms as measured by questionnaires
Starting date	21 April 2017
Contact information	KM Peters, William Beaumont Hospitals. Baylor College of Medicine Email: kmpeters@beaumont.edu
End date	August 2020
Notes	**Funding:** unclear **ClinicalTrials.gov registration number:** NCT02870738 **Other study ID numbers:** 2016-253

Shah 2016

Study name	A pilot study of the effects of mirabegron on symptoms in patients with interstitial cystitis
Methods	**Study design:** parallel-group RCT **Blinding:** single (participant)
Participants	**Target sample size:** 60 **Country:** USA **Sex:** female **Age:** 18 to 95 years of age **Condition:** "participants must be diagnosed with BPS/IC with a minimum O'Leary-Sant score of 8 on the ICSI, as well as 8 on the ICPI. Participants should be stable on their regimen (no increase or change in medications, behavioral treatments or physical therapy in previous 4 weeks prior to

Shah 2016 *(Continued)*

	starting the study) and be willing to remain on this regimen during the duration of the study. Participant must be stable on current IC/BPS regimen. Participant must have subjective complaints of i. urinary urgency, relieved with voiding; ii. urinary frequency, ≥ 8 voids per day; or iii. pelvic pain, pressure, hypersensitivity or discomfort"
Interventions	**Group A:** mirabegron (beta-3-adrenergic agonist; tablets; presumably oral administration) **Group B:** placebo
Outcomes	At 12 weeks **Primary outcome:** IC symptom improvement on O'Leary Sant Questionnaire **Secondary outcomes:** incontinence episodes via bladder diary and UDI-6 Questionnaire; QoL via PFIQ-7 Questionnaire; participant satisfaction via GRA; sexual function via FSFI Questionnaire; adverse effects
Starting date	August 2016
Contact information	Philadelphia Urosurgical Associates Email: drexelurogyn@gmail.com
End date	December 2018
Notes	**Funding:** unclear. Sponsors and collaborators: Philadelphia Urosurgical Associates; Astellas Pharma Global Development, Inc. **ClinicalTrials.gov registration number:** NCT02787083 **Other study ID numbers:** MYRB-15G02

BPS: bladder pain syndrome.
BPIC-SS: Bladder Pain/Interstitial Cystitis Symptom Score.
ESSIC: International Society for the Study of Bladder Pain Syndrome (BPS).
FSFI: Female Sexual Function Index.
GRA: Global Response Assessment.
IC: interstitial cystitis.
ICPI: Interstitial Cystitis Problem Index.
ICSI: Interstitial Cystitis Symptom Index.
IHD: ischaemic heart disease.
MDP: mean daily pain.
NRS: numerical rating scale.
PBS: painful bladder syndrome.
PFIQ-7: Pelvic Floor Impact Questionnaire-7.
PFMT: pelvic floor muscle training.
PGI-I: Patient Global Impression of Improvement.
PTNS: percutaneous tibial nerve stimulation.
PUF: Pelvic Pain and Urgency/Frequency Patient Symptom Scale.
QoL: quality of life.
RCT: randomised controlled trial.
UDI-6: Urinary Distress Inventory-6.
USG: ultrasonography.
VAS: visual analogue scale.

ADDITIONAL TABLES

Table 1. Interventions for the treatment of BPS

Treatment category	Example of intervention
Conservative therapies	
Behavioural, psychological and complementary therapies	· Bladder training · Stress management techniques · Complementary therapy (e.g. acupuncture)
Physical therapy	· Pelvic floor muscle training (PFMT) · Non-invasive electrical stimulation (e.g. transcutaneous electrical nerve stimulation (TENS))
Pharmacological treatments (by mode of action, irrespective of route of administration)	
Amino acid	· L-Arginine
Analgesics	
Analgesics, local (local anaesthetics)	· Lidocaine
Antibiotics	· Antibiotic regimen
Anticholinergics	· Oxybutynin
Anticoagulants	· Heparin
Anticytokines	· Tacrolimus
Antidepressants	· Amitriptyline · Doxepin · Desipramine · Duloxetine
Antihistamines	· Cimetidine · Hydroxyzine
AQX-1125	
Buffer solutions	
Caffeine	
Calcium channel agonists	· Capsaicin · PD-0299685 · Resiniferatoxin (RTX)
(Sodium) chondroitin sulfate	
Dimethyl sulfoxide (DMSO)	

Table 1. Interventions for the treatment of BPS *(Continued)*

Hyaluronic acid	
Hyperbaric oxygen	
Hydrogen-rich water	
Immune modulators	· Azathioprine and chloroquine derivatives · Corticosteroids · Triamcinolone · Cyclosporine · Suplatast tosilate · Adalimumab · Bacillus Calmette-Guerin (BCG) · Curcumin · Fulranumab · Mycophenolate mofetil (MMF) · Tanezumab · Nerve growth factors (NGFs) · Recombinant human nerve growth factor
Methotrexate	
Misoprostol	
Nifedipine	
P2X3 antagonist	· AF-219
Parasympathomimetic (+ urinary antiseptics)	· Cystex
Phosphodiesterase-5 (PDE5) inhibitor	· Sildenafil
(Sodium) pentosan polysulfate (PPS)	
Quercetin	
Surgical interventions	
Hydrodistension	
Neuromuscular blockade	· Botulinum toxin · Lipotoxin (liposomal formulated onabotulinumtoxinA (onaBoNTA))
Fulguration	
Transurethral resection	

Table 1. Interventions for the treatment of BPS *(Continued)*

Neuromodulation (implanted)	
Denervation	· Neurolysis · Superior hypogastric plexus neurolysis · Surgical denervation · Cystolysis – peripheral denervation · Sympathetic denervation · Parasympathetic denervation
Bowel surgery	· Bladder augmentation - cystoplasty · Cystoplasty with supratrigonal resection · Cystoplasty with subtrigonal cystectomy - orthotopic continent bladder augmentation · Urinary diversion with or without total cystectomy and urethrectomy

Based on the intervention categories used by Hanno and colleagues for their work presented at the 6th International Consultation on Incontinence (Hanno 2017).

Table 2. Treatment category (by mode of action) for active interventions in the included studies

Treatment category A	Treatment category B	Study name	Intervention A	Intervention B
Conservative vs control				
Behavioural therapy	Control	Carrico 2008	Guided imagery	Control (rest)
		Carty 2017	Life-stress interview	Usual care
		Hsieh 2012	Hydrodistension + bladder training	Hydrodistension
		Kanter 2016	Mindfulness-based stress reduction + usual care	Usual care
		Lee 2014	E-health system	Control (include treatment)
		Lee 2016	Self-management telecare system (patient education, mobile phone app, lifestyles)	Control (no detail)
		O'Reilly 2004	Transdermal laser stimulation of the posterior tibial nerve	Sham
Physical therapy	Control	FitzGerald 2009	Myofascial physical therapy	Global therapeutic massage
		FitzGerald 2012	Pelvic floor myofascial physical therapy	Global therapeutic massage

Table 2. Treatment category (by mode of action) for active interventions in the included studies *(Continued)*

		Zakaria 2016	TENS + physical therapy + medical care	Sham TENS + physical therapy + medical care
Pharmacological vs control				
Amino acid	Control	Cartledge 2000	L-Arginine	Placebo
		Korting 1999	L-Arginine	Placebo
Antibiotics	Control	Warren 2000	Antibiotic regimen	Placebo
Anticholinergics	Control	Barbalias 2000	Oxybutinin	Saline
Anticoagulants + local anaesthetics	Control	Parsons 2012	Heparin + lidocaine + sodium bicarbonate in water	Sodium bicarbonate in water
Anticytokines	Control	Mirkin 2015	Hyaluronic acid + anticytokine substance	Hyaluronic acid
Antidepressants	Control	Foster 2010	Amitriptyline + EBMP	Placebo + EBMP
		van Ophoven 2004	Amitriptyline	Placebo
Antihistamines	Control	Thilagarajah 2001	Cimetidine	Placebo
AQX-1125	Control	Leadership 201 Trial 2016	AQX-1125	Placebo
Buffer solutions	Control	Nguan 2005	Acidic buffered solution	Neutral buffered solution
Caffeine	Control	Herati 2011	Caffeine	Placebo
Calcium channel agonists	Control	Chen 2005	RTX, 2 arms with varying dose	Placebo
		Ham 2012	RTX + hydrodistension	Hydrodistension
		Kim 2012	RTX + hydrodistension	Hydrodistension
		Lazzeri 1996	Capsaicin	NaCl
		Lazzeri 2000	RTX	NaCl
		Nickel 2012b	PD-0299685	Placebo
		Payne 2005	RTX, 3 arms with varying dose	Placebo
Chondroitin sulfate	Control	Gulpinar 2013	Sodium chondroitin sulfate + hyaluronic acid	Hyaluronic acid
		Nickel 2010	Sodium chondroitin sulfate	NaCl
		Nickel 2012a	Sodium chondroitin sulfate	NaCl
DMSO	Control	Perez-Marrero 1988	DMSO	Saline

Table 2. Treatment category (by mode of action) for active interventions in the included studies *(Continued)*

Hyperbaric oxygen	Control	van Ophoven 2006	Hyperbaric oxygen	Placebo
Hydrogen-rich water	Control	Matsumoto 2013	Hydrogen-rich water	Placebo
Immune modulators	Control	Bosch 2014	Adalimumab	Placebo
		Dimitrakov 2001	Recombinant human nerve growth factor	Placebo
		Evans 2011	Tanezumab	Placebo
		Irani 2004	BCG	NaCl
		Mayer 2005	Live Tice BCG	Saline
		Nickel 2016	Tanezumab	Placebo
		Peters 1997	Tice strain BCG	Saline
		Shirvan 2015	Hydrodistension + curcumin	Hydrodistension in normal saline
		Wang 2017a	Fulranumab	Placebo
		Yang 2011	Mycophenolate mofetil	Placebo
Local anaesthetic	Control	Nickel 2009	PSD597	Saline
		Nomiya 2017	Heparin + lidocaine	Heparin
P2X3 antagonist	Control	Hanno 2015	AF-219	Placebo
		Moldwin 2015	AF-219	Placebo
Parasympathomimetic (+ urinary antiseptics)	Control	Souza 2012	Cystex	Placebo
PDE5 inhibitor	Control	Chen 2014	Sildenafil	Placebo
PPS	Control	Bade 1997	PPS	Placebo
		Davis 2008	Intravesical PPS + oral PPS	Intravesical placebo + oral PPS
		Mulholland 1990	PPS	Placebo
		Nickel 2015	PPS	Placebo
Surgical vs control				
Neuromuscular blockade	Control	Ahmadnia 2011	Botulinum toxin A	NaCl

Table 2. Treatment category (by mode of action) for active interventions in the included studies *(Continued)*

		Chuang 2017	2 arms: onabotulinumtoxinA (i) with liposomes (lipotoxin) and (ii) in normal saline	Saline
		Gottsch 2011	Botulinum toxin A	Saline
		Ismail 2016	Botulinum toxin A	Saline
		Kuo 2009	Botulinum toxin A + hydrodistension	Hydrodistension
		Kuo 2016	Botulinum toxin A + hydrodistension	NaCl + Hydrodistension
		Manning 2014	Botulinum toxin A + hydrodistension	Saline + hydrodistension
		Payne 2014	Botulinum toxin A	Saline
		Pinto 2016	Botulinum toxin A	Saline
		Yassin 2011	Botulinum toxin A + hydrodistension	NaCl + hydrodistension
Neuromuscular blockade + DMSO	Control	Mirkin 2012	Incobotulinumtoxin A + DMSO	NaCl
Comparison of different treatments				
Behavioural therapy	Physical therapy	Geirsson 1993	Acupuncture	TENS
(Sodium) chondroitin sulfate	DMSO	De Ridder 2013	Sodium chondroitin sulfate	DMSO
Hyaluronic acid	DMSO	Singh 2003	Hyaluronic acid	DMSO
Immune modulators	DMSO	Peeker 2000	BCG	DMSO
		Sairanen 2009	BCG	DMSO
(Sodium) chondroitin sulfate + hyaluronic acid	DMSO	Cervigni 2014	Sodium chondroitin sulfate + hyaluronic acid	DMSO
Anticoagulants + local anaesthetics	Hyaluronic acid	Lu 2015	Heparin + lidocaine	Hyaluronic acid
(Sodium) chondroitin sulfate	Hyaluronic acid	Gulpinar 2015	Sodium chondroitin sulfate	Hyaluronic acid
Immune modulators	PPS	Sairanen 2005	Cyclosporin A	PPS
Immune modulators	Neuromus-	Taha 2007	BCG	Botulinum toxin A

Table 2. Treatment category (by mode of action) for active interventions in the included studies *(Continued)*

	cular block-ade					
Immune modula-tor	Fulgu-ration	Oliver 2013	Triamcinolone		Fulguration	
Neuromuscular blockade	Hy-drodis-tension	Kasyan 2012	Botulinum toxin A		Hydrodistension	
Fulguration	Hy-drodis-tension	Kim 2015	Fulguration		Hydrodistension	
Denervation	Hy-drodis-tension	El-Hefnawy 2015	Superior hypogastric plexus neurolysis		Hydrodistension	
4-Arm trial						
Antihistamines vs PPS vs PPS + antihistamines vs control		Sant 2003	Hydroxyzine	PPS	PPS + hy-droxyzine	Placebo

BCG: bacillus Calmette-Guérin.
DMSO: dimethyl sulfoxide.
EBMP: educational and behavioural modification programme.
NaCl: sodium chloride.
PDE5: phosphodiesterase-5.
PPS: pentosan polysulfate.
RTX: resiniferatoxin.
TENS: transcutaneous electrical nerve stimulation.

Table 3. List of interventions for which no studies were identified in the review

Treatment category	Example of intervention
Pharmacological therapy (irrespective of route of administration)	
Analgesics	
Antidepressants	· Doxepin · Desipramine · Duloxetine
Immune modulators	· Azathioprine and chloroquine derivatives · Suplatast tosilate
Methotrexate	
Misoprostol	

Table 3. List of interventions for which no studies were identified in the review *(Continued)*

Nifedipine	
Quercetin	
Surgical therapy	
Transurethral resection	
Neuromodulation (implanted)	
Denervation	· Surgical denervation · Cystolysis – peripheral denervation · Sympathetic denervation · Parasympathetic denervation
Bowel surgery	· Bladder augmentation - cystoplasty · Cystoplasty with supratrigonal resection · Cystoplasty with subtrigonal cystectomy - orthotopic continent bladder augmentation · Urinary diversion with or without total cystectomy and urethrectomy

Table 4. Results of the meta-analyses for proportion cured or improved

		Network meta-analysis		Pairwise meta-analyses		
Treatment category	**Intervention**	**No. of trials in network**	**OR vs control (median (95% CrI)) (random effects)**	**No. of trials vs control**	**OR vs control (95% CI) (random effects)**	**GRADE certainty of evidence**
Behavioural therapy	Con	2	**9.64 (1.13 to 99.38)**	2	**7.04 (1.57 to 31.61)**	Very low
Physical therapy	Con	2	**6.78 (1.08 to 46.85)**	2	**4.77 (2.00 to 11.38)**	Very low
Amino acid	Pharm	1	3.36 (0.24 to 53.09)	1	3.07 (0.66 to 14.18)	Low
Local anaesthetics	Pharm	2	1.94 (0.28 to 13.78)	2	2.20 (0.84 to 5.80)	Very low
Antibiotics	Pharm	1	4.71 (0.36 to 63.5)	1	**4.33 (1.09 to 17.17)**	Very low
Antidepressants	Pharm	2	**5.91 (1.12 to 37.56)**	2	7.02 (0.35 to 141.48)	Very low
Antihistamines	Pharm	1	1.43 (0.15 to 14.01)	1	1.96 (0.49 to 7.87)	Very low
Calcium channel agonists	Pharm	3	1.51 (0.38 to 6.22)	3	1.40 (0.57 to 3.43)	Very low
Chondroitin sulfate	Pharm	3	3.82 (0.86 to 19.18)	2	1.70 (0.85 to 3.41)	Very low
DMSO	Pharm	4	3.05 (0.55 to 16.58)	1	4.55 (0.77 to 26.84)	Very low

Table 4. Results of the meta-analyses for proportion cured or improved *(Continued)*

Hyaluronic acid	Pharm	2	2.10 (0.12 to 44.26)	0	N/A	Very low
Hyperbaric oxygen	Pharm	1	11.73 (0.27 to 8324.85)	1	5.53 (0.25 to 124.4)	Very low
Immune modulators	Pharm	10	**2.74 (1.16 to 6.57)**	7	**2.19 (1.24 to 3.89)**	Very low
PDE5 inhibitor	Pharm	1	**24.53 (1.21 to 1255.14)**	1	**16.43 (1.89, 142.50)**	Very low
PPS	Pharm	6	1.14 (0.40 to 3.35)	5	1.41 (0.95 to 2.08)	Very low
Neuromuscular blockade	Surg	6	**5.80 (2.08 to 18.30)**	6	**4.19 (1.44 to 12.25)**	Very low
Anticoagulants + local anaesthetics	Comb	1	0.93 (0.01 to 65.89)	0	N/A	Very low
PPS + antihistamines	Comb	1	3.94 (0.42 to 37.37)	1	**5.18 (1.34 to 20.06)**	Very low
Chondroitin sulfate + hyaluronic acid	Comb	1	7.04 (0.37 to 128.77)	0	N/A	Very low

Credible intervals excluding 1 are highlighted in bold.
CI: confidence interval.
Comb: combination therapy.
Con: conservative therapy.
CrI: credible interval.
DMSO: dimethyl sulfoxide.
N/A: not applicable.
OR: odds ratio.
PDE5: phosphodiesterase-5.
Pharm: pharmacological therapy.
PPS: pentosan polysulfate.
Surg: surgical therapy.

Table 5. Results of the meta-analyses for pain

		Network meta-analysis		Pairwise meta-analyses		
Treatment category	**Intervention**	**No. of trials in network**	**Mean difference vs control (median (95% CrI)) (random effects)**	**No. of trials vs control**	**Mean difference vs control (95% CI) (random effects)**	**GRADE certainty of evidence**
Behavioural therapy	Con	6	-0.60 (-1.79 to 0.62)	6	**-1.50 (-2.93 to -0.06)**	Very low
Physical therapy	Con	2	**-3.92 (-5.80 to -1.94)**	2	-3.69 (-9.90 to 2.52)	Moderate
Local anaesthetics	Pharm	2	-0.31 (-2.58 to 2.00)	2	-0.51 (-1.93 to 0.91)	Very low
Calcium channel agonists	Pharm	6	-0.53 (-1.72 to 0.68)	6	**-0.68 (-0.94 to -0.42)**	Very low
Chondroitin sulfate	Pharm	4	0.36 (-1.31 to 2.05)	3	0.30 (-0.40 to 1.00)	Very low
Hyperbaric oxygen	Pharm	1	-2.45 (-5.95 to 1.04)	1	**-2.45 (-4.76 to -0.15)**	Low

Table 5. Results of the meta-analyses for pain *(Continued)*

Hydrogen-rich water	Pharm	1	-0.20 (-3.50 to 3.12)	1	-0.20 (-2.17 to 1.77)	Very low
Immune modulators	Pharm	8	-0.77 (-1.81 to 0.24)	7	-0.54 (-1.27 to 0.20)	Low
PDE5 inhibitor	Pharm	1	-0.60 (-3.77 to 2.56)	1	-0.60 (-2.30 to 1.10)	Very low
Neuromuscular blockade	Surg	6	-0.33 (-1.71 to 1.03)	5	-0.21 (-1.01 to 0.60)	Very low
Hydrodistension	Surg	3	-0.01 (-3.48 to 3.44)	0	N/A	Very low
Fulguration	Surg	1	-1.93 (-6.53 to 2.70)	0	N/A	Very low
Anticytokines	Pharm	1	-1.20 (-3.92 to 1.51)	1	**-1.20 (-1.85 to -0.55)**	Very low
Denervation	Surg	1	1.97 (-2.44 to 6.44)	0	N/A	Very low
AQX-1125	Pharm	1	-1.01 (-3.83 to 1.82)	1	-1.00 (-2.03 to 0.03)	Very low
Neuromuscular blockade + DMSO	Comb	1	-2.81 (-5.87 to 0.24)	1	**-2.80 (-4.36 to -1.24)**	Low
Antidepressants	Pharm	2	-1.27 (-3.25 to 0.71)	2	-1.28 (-3.31 to 0.76)	Low
Antihistamines	Pharm	1	0.65 (-1.96 to 3.27)	1	0.56 (-0.44 to 1.55)	Very low
Buffer solutions	Pharm	1	0.23 (-3.89 to 4.33)	1	0.21 (-2.94 to 3.36)	Very low
DMSO	Pharm	2	1.46 (-1.22 to 4.13)	0	N/A	Very low
P2X3 antagonist	Pharm	1	-1.20 (-4.13 to 1.73)	1	-1.20 (-2.54 to 0.14)	Very low
Parasympathomimetic (+ urinary antiseptics)	Pharm	1	-2.75 (-5.83 to 0.34)	1	**-2.76 (-4.36 to -1.16)**	Low
PPS	Pharm	4	0.42 (-1.04 to 1.91)	3	-0.03 (-0.65 to 0.60)	Very low
PPS + antihistamines	Comb	1	-0.58 (-3.20 to 2.04)	1	-0.67 (-1.70 to 0.37)	Very low
Chondroitin sulfate + hyaluronic acid	Comb	1	-0.05 (-197.8 to 195.2)	0	N/A	Very low
Treatments not part of the connected network						
Hyaluronic acid	Pharm	1	N/A	0	N/A	N/A
Anticoagulants + local anaesthetics	Comb	1	N/A	0	N/A	N/A

Pain is measured on a 0 to 10 scale where 0 is no pain and 10 is maximum pain.
Credible intervals excluding zero are highlighted in bold.
CI: confidence interval.
Comb: combination therapy.
Con: conservative therapy.
CrI: credible interval.
DMSO: dimethyl sulfoxide.
N/A: not applicable.

OR: odds ratio.
PDE5: phosphodiesterase-5.
Pharm: pharmacological therapy.
PPS: pentosan polysulfate.
Surg: surgical therapy.

Table 6. Results of the meta-analyses for daytime frequency (number of daytime voids)

		Network meta-analysis		Pairwise meta-analyses		
Treatment category	**Intervention**	**No. of trials in network**	**Mean difference vs control (median (95% CrI)) (random effects)**	**No. of trials vs control**	**Mean difference vs control (95% CI) (random effects)**	**GRADE certainty of evidence**
Behavioural therapy	Con	1	-2.01 (-6.44 to 2.47)	1	**-2.00 (-3.41 to -0.59)**	Very low
Amino acid	Pharm	1	4.14 (-2.47 to 10.80)	1	4.10 (-1.18 to 9.38)	Low
Local anaesthetics	Pharm	1	0.35 (-6.12 to 6.69)	1	0.30 (-4.67 to 5.27)	Very low
Anticholinergics	Pharm	1	-0.73 (-6.34 to 4.95)	1	-0.75 (-4.62 to 3.13)	Very low
Anticytokines	Pharm	1	-4.69 (-9.70 to 0.29)	1	**-4.70 (-7.38 to -2.02)**	Very low
Calcium channel agonists	Pharm	4	-0.79 (-3.61 to 2.23)	4	-1.09 (-2.72 to 0.55)	Very low
Chondroitin sulfate	Pharm	2	0.05 (-3.35 to 3.46)	2	0.03 (-1.44 to 1.49)	Very low
Immune modulators	Pharm	4	-1.95 (-4.78 to 0.73)	3	-0.82 (-2.51 to 0.88)	Very low
PDE5 inhibitor	Pharm	1	-2.46 (-7.54 to 2.53)	1	-2.50 (-5.32 to 0.33)	Very low
PPS	Pharm	2	-0.37 (-5.00 to 3.44)	1	**-6.00 (-10.34 to -1.66)**	Very low
Neuromuscular blockade	Surg	5	-0.91 (-3.24 to 1.29)	5	-0.84 (-2.28 to 0.56)	Very low
Neuromuscular blockade + DMSO	Comb	1	**-8.97 (-15.23 to -2.81)**	1	**-9.00 (-13.62 to -4.38)**	Moderate
Antidepressants	Pharm	1	-2.41 (-6.85 to 2.05)	1	**-2.40 (-3.75 to -1.05)**	Very low
Treatments not part of the connected network						
Anticoagulants + local anaesthetics	Comb	1	N/A	0	N/A	N/A
Hydrodistension	Surg	1	N/A	0	N/A	N/A
Hyaluronic acid	Pharm	1	N/A	0	N/A	N/A
Denervation	Surg	1	N/A	0	N/A	N/A
DMSO	Pharm	1	N/A	0	N/A	N/A
Chondroitin sulfate + hyaluronic acid	Comb	1	N/A	0	N/A	N/A

Credible intervals excluding zero are highlighted in bold.
CI: confidence interval.
Comb: combination therapy.
Con: conservative therapy.
CrI: credible interval.
DMSO: dimethyl sulfoxide.
N/A: not applicable.
OR: odds ratio.
PDE5: phosphodiesterase-5.
Pharm: pharmacological therapy.
PPS: pentosan polysulfate.
Surg: surgical therapy.

Table 7. Results of the meta-analyses for nocturia (number of nighttime voids)

		Network meta-analysis		Pairwise meta-analyses		
Treatment category	**Intervention**	**No. of trials in network**	**Mean difference vs control (median (95% CrI)) (random effects)**	**No. of trials vs control**	**Mean difference vs control (95% CI) (random effects)**	**GRADE certainty of evidence**
Behavioural therapy	Con	1	-0.71 (-3.21 to 1.82)	1	**-0.70 (-1.26 to -0.14)**	Very low
Amino acid	Pharm	1	0.12 (-2.65 to 2.87)	1	0.10 (-1.29 to 1.49)	Low
Local anaesthetics	Pharm	1	0.29 (-3.05 to 3.67)	1	0.30 (-2.14 to 2.74)	Very low
Calcium channel agonists	Pharm	3	-0.24 (-2.04 to 1.52)	3	-0.30 (-0.99 to 0.38)	Very low
Chondroitin sulfate	Pharm	1	-0.01 (-2.63 to 2.65)	1	0.00 (-1.10 to 1.10)	Very low
PDE5 inhibitor	Pharm	1	-1.40 (-4.07 to 1.22)	1	**-1.40 (-2.47 to -0.33)**	Very low
PPS	Pharm	2	-1.20 (-3.62 to 1.28)	1	**-2.20 (-4.03 to -0.37)**	Very low
Neuromuscular blockade	Surg	4	-0.04 (-1.35 to 1.27)	4	-0.04 (-0.84 to 0.76)	Very low
Antidepressants	Pharm	1	0.01 (-2.53 to 2.50)	1	0.00 (-0.69 to 0.69)	Very low
Immune modulators	Pharm	2	-2.65 (-5.04 to 0.20)	1	-1.00 (-3.63 to 1.63)	Low
Treatments not part of the connected network						
Denervation	Surg	1	N/A	0	N/A	N/A
Hydrodistension	Surg	1	N/A	0	N/A	N/A

Credible intervals excluding zero are highlighted in bold.
CI: confidence interval.
Con: conservative therapy.
CrI: credible interval.
N/A: not applicable.
PDE5: phosphodiesterase-5.
Pharm: pharmacological therapy.

PPS: pentosan polysulfate.
Surg: surgical therapy.

Table 8. Results of the meta-analyses for ICSI (Interstitial Cystitis Symptom Index) score

		Network meta-analysis		Pairwise meta-analyses	
Treatment category	**Inter-vention**	**No. of trials in network**	**Mean difference vs control (median (95% CrI)) (random effects)**	**No. of trials vs control**	**Mean difference vs control (95% CI) (random effects)**
Behavioural therapy	Con	5	-0.89 (-2.57 to 0.81)	5	-0.94 (-2.05 to 0.18)
Physical therapy	Con	1	-0.70 (-4.07 to 2.68)	1	-0.70 (-2.61 to 1.21)
Local anaesthetics	Pharm	2	-1.25 (-3.95 to 1.44)	2	-1.30 (-2.73 to 0.13)
Calcium channel ago-nists	Pharm	2	-1.25 (-4.01 to 1.49)	2	-1.22 (-3.14 to 0.70)
Chondroitin sulfate	Pharm	4	0.34 (-1.63 to 2.32)	3	0.32 (-0.84 to 1.49)
Hydrogen-rich water	Pharm	1	0.16 (-4.1 to 4.45)	1	0.20 (-3.10 to 3.50)
Immune modulators	Pharm	5	-1.06 (-2.87 to 0.77)	3	-0.76 (-1.65 to 0.15)
PDE5 inhibitor	Pharm	1	**-6.02 (-9.05 to -2.93)**	1	**-6.00 (-7.28 to -4.72)**
Neuromuscular blockade	Pharm	5	-0.65 (-2.49 to 1.10)	4	-0.58 (-1.96 to 0.80)
Hydrodistension	Surg	2	-1.26 (-5.22 to 2.62)	0	N/A
Denervation	Surg	1	1.64 (-3.41 to 6.56)	0	N/A
Antidepressants	Surg	1	-1.51 (-4.47 to 1.48)	1	**-1.50 (-2.48 to -0.52)**
Antihistamines	Pharm	3	1.16 (-1.95 to 4.36)	1	1.00 (-0.77 to 2.77)
AQX-1125	Pharm	1	-2.39 (-5.62 to 0.80)	1	**-2.40 (-4.02 to -0.78)**
DMSO	Pharm	1	1.02 (-3.08 to 5.20)	0	N/A
PPS	Pharm	5	1.18 (-1.10 to 3.45)	1	0.60 (-1.15 to 2.35)
PPS + antihistamines	Comb	3	-1.14 (-4.31 to 2.06)	1	-1.30 (-3.09 to 0.49)

Credible intervals excluding zero are highlighted in bold.
CI: confidence interval.
Comb: combination therapy.
Con: conservative therapy.
CrI: credible interval.
DMSO: dimethyl sulfoxide.
N/A: not applicable.
PDE5: phosphodiesterase-5.
Pharm: pharmacological therapy.
PPS: pentosan polysulfate.
Surg: surgical therapy.

Table 9. Results of the meta-analyses for ICPI (Interstitial Cystitis Problem Index) score

		Network meta-analysis		Pairwise meta-analyses	
Treatment category	**Inter-vention**	**No. of trials in network**	**Mean difference vs control (median (95% CrI)) (random effects)**	**No. of trials vs control**	**Mean difference vs control (95% CI) (random effects)**
Behavioural therapy	Con	4	0.31 (-1.80 to 2.38)	4	0.27 (-2.08 to 2.62)
Physical therapy	Con	1	-1.40 (-5.09 to 2.33)	1	-1.40 (-2.98 to 0.18)
Local anaesthetics	Pharm	2	-1.15 (-4.09 to 1.97)	2	**-1.45 (-2.84 to -0.06)**
Calcium channel ago-nists	Pharm	1	-2.94 (-7.41 to 1.55)	1	-2.92 (-5.93 to 0.09)
Chondroitin sulfate	Pharm	4	-0.18 (-2.41 to 2.09)	3	-0.19 (-1.30 to 0.92)
Hydrogen-rich water	Pharm	1	-0.20 (-4.36 to 4.00)	1	-0.20 (-2.73 to 2.33)
Immune modulators	Pharm	4	-0.59 (-2.61 to 1.54)	3	-0.07 (-1.12 to 0.98)
PDE5 inhibitor	Pharm	1	-3.50 (-7.71 to 0.69)	1	**-3.50 (-6.05 to -0.95)**
Neuromuscular blockade	Surg	6	-1.37 (-3.28 to 0.48)	5	-1.28 (-2.61 to 0.05)
Hydrodistension	Surg	2	-1.87 (-6.02 to 2.25)	0	N/A
Denervation	Surg	1	1.04 (-4.39 to 6.40)	0	N/A
Antidepressants	Pharm	1	-1.28 (-4.83 to 2.25)	1	**-1.30 (-2.32 to -0.28)**
Antihistamines	Pharm	1	1.63 (-1.78 to 5.31)	1	0.80 (-0.63 to 2.23)
AQX-1125	Pharm	1	-1.99 (-5.72 to 1.72)	1	**-2.00 (-3.55 to -0.45)**
DMSO	Pharm	1	0.43 (-4.22 to 5.15)	0	N/A
PPS	Pharm	2	2.66 (-0.16 to 5.59)	1	0.40 (-1.22 to 2.02)
PPS + antihistamines	Comb	1	-0.27 (-3.82 to 3.50)	1	-1.10 (-2.79 to 0.59)

Credible intervals excluding zero are highlighted in bold.
CI: confidence interval.
Comb: combination therapy.
Con: conservative therapy.
CrI: credible interval.
DMSO: dimethyl sulfoxide.
N/A: not applicable.
PDE5: phosphodiesterase-5.
Pharm: pharmacological therapy.
PPS: pentosan polysulfate.
Surg: surgical therapy.

Table 10. Functional bladder capacity

Treatment category 1	Treatment category 2	Study ID	Outcome	Time point (month)	Intervention 1		Intervention 2	
					Mean (SD)	N	Mean (SD)	N
Antidepressants	Control	van Ophoven 2004	Functional bladder volume (mL), change from baseline	4	19 (54.62)	24	-7.7 (47.5)	24
Calcium channel agonists	Control	Ham 2012	Functional bladder capacity (mL), final value	3	222.9 (36.9)	8	242 (50.2)	10
Chondroitin sulfate + hyaluronic acid	DMSO	Cervigni 2014	Bladder capacity (mL), change from baseline	3	38.07 (71.53)	44	20.6 (61.62)	25
Hyperbaric oxygen	Control	van Ophoven 2006	Functional bladder capacity (mL), final value	3	147 (49)	14	118 (36)	7
Immune modulators	Control	Mayer 2005	Functional bladder capacity (mL), change from baseline	8.5	-26 (156)	109	-17 (112)	113
Immune modulators	Control	Irani 2004	Maximum tolerable bladder capacity (mL), final value	24	240.5 (93.7)	15	196.5 (61.8)	15
Neuromuscular blockade	Control	Chuang 2017	Functional bladder capacity (mL), final value: a. lipotoxin; b. onabotulinumtoxinA	1	a. 307 (110) b. 315 (118)	a. 31 b. 28	332 (169)	31
		Kuo 2016	Functional bladder capacity (mL), final value	2	219.6 (103.6)	40	189 (99.4)	20

Table 10. Functional bladder capacity *(Continued)*

	Kuo 2009	Functional bladder capacity (mL), final value: a. Botulinum toxin A 100 units; b. Botulinum toxin A 200 units	3	a. 189 (78.8) b. 190.8 (80.6)	a. 29 b. 15	145.5 (77.4)	23
	Manning 2014	Maximum functional bladder capacity (mL), final value	3	273 (152)	26	210 (84)	27
Parasympathomimetic (+ urinary antiseptics)	Control	Souza 2012	Functional bladder volume (mL), change from baseline	0.7	27.8 (49.3)	11	17.8 (47.6)	11

SD: standard deviation.

Table 11. Number of patients experiencing adverse events

Treatment category 1	Treatment category 2	Time point (month)	n1	N1	%	n2	N2	%	Notes
Conservative									
Physical therapy	Control	3	25	39	64	25	42	60	Pain was the most common category (FitzGerald 2012)
Behavioural therapy	Physical therapy	0 (unclear)	0	9 (unclear)	0	0	8 (unclear)	0	Geirsson 1993
Pharmacological									

Table 11. Number of patients experiencing adverse events *(Continued)*

Amino acid	Control	3	12	21	57	12	25	48	Korting 1999
Antibiotics	Control	4.5	20	25	80	10	25	40	AEs included nausea and/or vomiting 23 vs 6; diarrhoea 12 vs 2; headache 5 vs 2; dizziness 2 vs 0; rash 1 vs 3; vaginal symptoms 3 vs 2; other 5 vs 10 (Warren 2000)
Anticoagulants + local anaesthetics	Hyaluronic acid	12 (unclear)	0	13	0	0	11	0	Lu 2015
Antidepressants	Control	3	119	135	88	98	136	72	AEs included constitutional symptoms (primarily fatigue, malaise) 61 vs 42; dermatological/skin 9 vs 10; gastrointestinal (primarily dry mouth, constipation) 57 vs 32; infection, fever 9 vs 14; musculoskeletal 7 vs 3; neurological (primarily dizziness, somnolence) 45 vs 29; ocular, visual 3 vs 7; pain (primarily headache) 43 vs 48; pulmonary 15 vs 13; renal/genitourinary 22 vs 10 (Foster 2010)
		4	22	24	92	5	24	21	AEs included mouth dryness 19 vs 2; weight gain 15 vs 2; sedation 9 vs 3; constipation 11 vs 2; nausea/vertigo 3 vs 3; blurred vision/diplopia 4 vs 0; erectile dysfunction 1 vs 0. "A dry mouth was the most frequent side effect in the amitriptyline group. No adverse effects of grade 3 or higher were reported" (van Ophoven 2004)
AQX-1125	Control	1	19	37	51	25	32	78	Any treatment-emergent adverse events. "The most frequently reported TEAEs (greater than 5%) and those that developed at a higher frequency in the AQX-1125 group were dyspepsia, gastroesophageal reflux disease and sinusitis" (Leadership 201 Trial 2016)
Calcium channel agonists	Control	3	16	18	89	3	4	75	AEs included pain during instillation, abdominal pain, cystitis, dizziness, pallor and urinary tract disorders (number per event not reported) (Chen 2005)

Table 11. Number of patients experiencing adverse events *(Continued)*

		3	N/R	8	N/A	N/R	10	N/A	AEs included haematuria 2 vs 0; bladder pain 0 vs 1. "These side effects disappeared within 2 days" (Ham 2012)
		6	N/R	17	N/A	N/R	18	N/A	AEs included pain during instillation: 17 vs 15 (Lazzeri 1996)
		3	N/R	9	N/A	N/R	9	N/A	AEs included pain during instillation: 4 vs 0 (Lazzeri 2000)
		1	N/R	119	N/A	N/R	44	N/A	AEs included pain during instillation: 90 vs 23 (Payne 2005)
Chondroitin sulfate	Control	3	22	33	67	28	32	88	AEs included gastrointestinal disorders 0 vs 1; nausea 0 vs 1; infections and infestations 0 vs 1; urethritis 0 vs 1; renal and urinary disorders 0 vs 1; urethral pain 0 vs 1; reproductive system and breast disorders 1 vs 0; pelvic pain 1 vs 0; skin and subcutaneous tissue disorders 0 vs 1; rash macular 0 vs 1; urinary tract signs and symptoms 1 vs 1; dysuria 1 vs 1. Most AEs were reported as mild (Nickel 2010)
		2.8	34	49	69	35	49	71	Treatment-related AEs occurred in 3 vs 5 participants (Nickel 2012a)
Chondroitin sulfate + hyaluronic acid	DMSO	6	11	74	15	11	36	31	Treatment-related AEs were seen in 1 participant in the 'chondroitin sulfate + hyaluronic acid' group and 8 participants in the DMSO group. The most common treatment-related AEs were related to renal and urinary disorders (1 vs 8), in particular, bladder irritation (0 vs 1) or bladder pain (1 vs 1), cystitis (0 vs 2), dysuria (0 vs 4) and strangury 0 vs 1 (Cervigni 2014)
Hydrogen-rich water	Control	2	0	18	0	0	10	0	Matsumoto 2013
Immune modulators	Control	4	23	29	79	18	20	90	AEs included UTI 1 vs 2; voiding dysfunction (retention) 0 vs 0. "Headache was the most frequently reported AE in the tanezumab group (20.6% vs placebo 16.7%). Paresthe-

Table 11. Number of patients experiencing adverse events *(Continued)*

							sia (tanezumab 17.6%, placebo 3.3%) and hyperesthesia (tanezumab 8.8%, placebo 0.0%) were the most common AEs of abnormal peripheral sensation reported for tanezumab. All of the abnormal peripheral sensation AEs were mild to moderate in severity, and most had resolved by the end of the study. There were 3 patients on tanezumab and 2 on placebo who had a clinically significant worsening from baseline in the neurological examination" (Evans 2011)
8.5	123	129	95	126	132	95	AEs included allergy/immunology 21 vs 19; cardiovascular, general 7 vs 15; constitutional symptoms 75 vs 67; fever 5 vs 13; gastrointestinal 70 vs 72; bladder symptoms 101 vs 101; haematuria 27 vs 45; infection, catheter related 1 vs 1; other infection 16 vs 11; musculoskeletal 29 vs 23; neurological 31 vs 25; pain (pelvic) 18 vs 26; pain (headache) 17 vs 10; pain (arthralgias, myalgias 31 vs 16); pain (other) 39 vs 39; pulmonary 35 vs 34; sexual, reproductive 15 vs 9; skin 42 vs 38 (Mayer 2005)
2	23	40	58	24	42	57	AEs occurring in ≥ 3 patients in any treatment included headache 4 vs 4; arthralgia 4 vs 4; myalgia 3 vs 0; hyperaesthesia 3 vs 0; paraesthesia 2 vs 3; UTI 2 vs 1; pain in extremity 2 vs 2; peripheral oedema 2 vs 0; injection site reaction 2 vs 4; back pain 1 vs 1; hypoaesthesia 1 vs 1; nausea 1 vs 0; fatigue 1 vs 1; abdominal pain 1 vs 0; bladder pain 0 vs 0; dizziness 0 vs 0; urinary retention 0 vs 0. AEs of abnormal peripheral sensation included hyperaesthesia 3 vs 0; paraesthesia 2 vs 3; hypoaesthesia 1 vs 1; allodynia 1 vs 0; sensory disturbance 1 vs 0; burning sensation 0 vs 0; decreased vibratory sense 0 vs 2 (Nickel 2016)
6	N/R	17	N/A	N/R	15	N/A	AEs included arthralgia 3 vs 1; fatigue 2 vs 0; low back pain 3 vs 4; burning 3 vs 5; nausea 1 vs 2; bronchitis 1 vs 0; diarrhoea 1 vs 2; fever less than 38.5°C 0 vs 1; incontinence 1 vs 1; urinary tract infection 2 vs 1; rash 0 vs 1;

Table 11. Number of patients experiencing adverse events *(Continued)*

									shoulder/neck pain 1 vs 1; abdominal distension 1 vs 0 (Peters 1997)
		6.5	8	14	57	11	17	65	AEs included diarrhoea 3 vs 2; carpal tunnel syndrome 2 vs 0; UTI 2 vs 2; pain 0 vs 2; pain in extremity 0 vs 2; paraesthesia 0 vs 2; sinusitis 0 vs 2 (Wang 2017a)
		4	34	39	87	13	19	68	AEs included blood/bone marrow 2 vs 1; constitutional symptoms (primarily fatigue, malaise) 14 vs 6; dermatological/skin 7 vs 3; gastrointestinal (primarily nausea, constipation, diarrhoea) 27 vs 8; haemorrhage 2 vs 0; infectious/febrile 7 vs 2; lymphatic 0 vs 1; metabolic/laboratory 4 vs 0; musculoskeletal 1 vs 2; neurological (primarily dizziness, anxiety) 8 vs 4; ocular, visual 2 vs 1; pain, primarily headache 21 vs 11; pulmonary 2 vs 2; renal/genitourinary 9 vs 2; sexual/reproductive function 1 vs 1; benign viral syndromes 2 vs 1; vascular 0 vs 1 (Yang 2011)
Immune modulators	PPS	6	30	32	94	18	32	56	"In the immune modulator group, increased blood pressure and serum creatinine were considered significant AE as was gross hematuria in the PPS arm" (Sairanen 2005)
Local anaesthetics	Control	0.5	N/R	50	N/A	N/R	52	N/A	AEs included general disorders and administration site conditions: any 8 vs 5; fatigue 4 vs 3. Infections and infestations: any 3 vs 6; UTI 1 vs 4. Musculoskeletal and connective tissue disorders: any 2 vs 4; back pain 1 vs 3. Nervous system disorders: any 6 vs 8; dizziness 4 vs 3; headache 2 vs 4. Renal and urinary disorders: any 13 vs 10; bladder pain 7 vs 3; dysuria 2 vs 3; urethral pain 1 vs 3 (Nickel 2009)
		1	0	10	0	0	10	0	Nomiya 2017
P2X3 antagonist	Control	1	N/R	36	N/A	N/R	38	N/A	"AEs were generally mild. The P2X3 antagonist group reported significantly more dysgeusia/hyoogeusia than the placebo group". Number per event not reported (Hanno 2015)

Table 11. Number of patients experiencing adverse events *(Continued)*

		1	N/R	36	N/A	N/R	38	N/A	"AEs were generally mild. The most frequently reported AE in AF-219 treated patients (=P2X3 antagonist) was dysgeusia/hypogeusia" (Moldwin 2015)
Parasympathomimetic (+ urinary antiseptics)	Control	0.7	10	11	91	9	11	82	"Dry mouth was the most frequent side effect in the Cystex group" (Souza 2012)
PDE5 inhibitor	Control	6	N/R	24	N/A	N/R	24	N/A	AEs included mild headache in 1 and flushing in 4 in the sildenafil group. "The symptoms remitted after 2-4 days" (Chen 2014)
PPS	Control	4.5	N/R	21	N/A	N/R	20	N/A	AEs included UTI 2 vs 0; headache 14 vs 12; bruise in arms due to blood draw 11 vs 11; mild hair loss 3 vs 1 (Davis 2008)
		3	3	54	6%	7	56	13	AEs included headache 1 vs 2; nausea 1 vs 0; indigestion 1 vs 0; increased perspiration 1 vs 0; severe mood swings 1 vs 0; suicidal ideation 1 vs 0; diarrhoea 0 vs 2; explosive diarrhoea 0 vs 1; severe joint pain 0 vs 1; skin rash on arms 0 vs 1; itching 0 vs 1 (Mulholland 1990)
		6	205	251	82	96	118	81	AEs include bladder pain 82 vs 38, nausea 31 vs 9, headache 30 vs 16, nasopharyngitis 21 vs 2, diarrhoea 19 vs 7, UTI 18 vs 4, back pain 12 vs 2, sinusitis 12 vs 7, dizziness 10 vs 3, influenza 7 vs 6 (Nickel 2015)
Surgical									
Neuromuscular blockade	Control	1	N/R	59	N/A	N/R	31	N/A	AEs included dysuria after treatment 3 vs 1; haematuria 0 vs 0; UTI 0 vs 0 (Chuang 2017)
		3	0	9	0	0	11	0	Gottsch 2011

Table 11. Number of patients experiencing adverse events *(Continued)*

		> 6	N/R	44	N/A	N/R	23	N/A	AEs included UTI 3 vs 0; voiding dysfunction 12 vs 0; haematuria 2 vs 0; dysuria 10 vs 1 (Kuo 2009)
		2	20	40	50	1	20	5	AEs included UTI 2 vs 0; voiding dysfunction (retention) 1 vs 0; dysuria 16 vs 1; haematuria 1 vs 0 (Kuo 2016)
		3	N/R	26	0	N/R	27	%	AEs included UTI 7 vs 5 (Manning 2014)
		6 (unclear)	N/R	14	0	N/R	2	%	AEs included voiding dysfunction (retention) 5 vs 0 (Payne 2014)
		3	N/R	10	0	N/R	9	%	AEs included UTI 3 vs 2 (Pinto 2016)
		6	0	18	0	0	10	0	Yassin 2011
Neuromuscular blockade + DMSO	Control	0.2	0	15	0	0	8	0	Mirkin 2012
Neuromuscular blockade	Hydrodistension	3	N/R	15	N/A	N/R	17	N/A	AEs included upper urinary tract retention 0 vs 0 (Kasyan 2012)
Denervation	Hydrodistension	1	N/R	12	N/A	N/R	12	N/A	AEs included self-limited transient haematuria 0 vs 1; left lower limb numbness 1 vs 0; lower back ache 2 vs 0 (El-Hefnawy 2015)
Hyperbaric oxygen (HBO)	Control	3	4	12	33	1	7	14	"Four patients in the treatment arm reported transient problems with accommodation during treatment that were not further reported at 3-month follow-up. One woman reported mild eustachian tube dysfunction during treatment sessions, resulting in a transient hearing impairment within the chamber. The events were solved by intense chewing of some candy or gum, resulting in the opening of the tube with subsequent pressure balance between the middle ear and the environment. A decongestant nasal spray was occasionally administered some minutes before start of and/or during treatment. Oral med-

Table 11. Number of patients experiencing adverse events *(Continued)*

									ication was given to control temporary claustrophobia in another patient at the start of the study" (van Ophoven 2006)
4-Arm study									
Placebo + PPS alone (2 arms)	PPS + combination PPS and antihistamine (2 arms)	6	51	62	82	50	59	85	4-Arm trial using factorial design (Sant 2003)
Placebo + antihistamine (2 arms)	Antihistamine + combination PPS and antihistamine (2 arms)	6	51	60	85	50	61	82	4-Arm trial using factorial design (Sant 2003)

AE: adverse event.
DMSO: dimethyl sulfoxide.
N/A: not applicable.
N/R: not reported.
PDE5: phosphodiesterase-5.
PPS: pentosan polysulfate.
TEAE: treatment-emergent adverse event.
UTI: urinary tract infection.

Table 12. Number of patients with serious adverse events (SAE)

Treatment category 1	Treatment category 2	Time point (month)	n1	N1	%	n2	N2	%	Outcome definition/Notes
Pharmacological									
Calcium channel agonists	Control	3	0	18	0	0	4	0	SAE (details not reported; Chen 2005)
		3	0	8	0	0	10	0	SAE (bladder puncture and sepsis; Ham 2012)

Table 12. Number of patients with serious adverse events (SAE) *(Continued)*

		6	0	17	0	0	18	0	Significant AE (details not reported; Lazzeri 1996)
		3	0	9	0	0	9	0	Important AE (details not reported; Lazzeri 2000)
		3	2	108	2	0	52	0	SAE, including 1 event each of deep vein thrombosis and a suicide attempt. Both cases were deemed treatment-related SAEs and were resolved. The patients were discontinued from the study (Nickel 2012b)
		1	0	119	0	1	44	2	SAEs included abdominal pain requiring hospitalisation, judged to be related to the treatment (Payne 2005)
Chondroitin sulfate	Control	6	0	30	0	0	23	0	Severe AE (details not reported; Gulpinar 2013)
Chondroitin sulfate + hyaluronic acid	DMSO	6	0	74	0	0	36	0	SAE (details not reported; Cervigni 2014)
Hyaluronic acid	Chondroitin sulfate	6	0	21	0	0	21	0	Severe AE (details not reported; Gulpinar 2015)
Immune modulators	Control	3 (unclear)	0	21 (unclear)	0	0	22 (unclear)	0	Significant AE (details not reported; Bosch 2014)
		4	2	29	7	4	20	20	SAEs, including "vertigo" and "drug exposure during pregnancy" for tanezumab; "cholelithiasis", "ovarian mass", "urosepsis and urinary tract infection", "transient ischaemic attack" for placebo (Evans 2011)
		8.5	64	129	50	63	132	48	Severe AE, defined as Grade 3 AE on the Common Toxicity Criteria A total of 32 serious (rather than severe) AEs were reported among 21 participants (num-

Table 12. Number of patients with serious adverse events (SAE) *(Continued)*

									ber in each group unclear), with 2 ascribed to treatment (BCG hypersensitivity reaction in 1 patient in the BCG group; prostatitis and UTI in 1 patient in the placebo group) (Mayer 2005)
		2	1	40	3	0	42	0	SAE (details not reported; Nickel 2016)
Local anaesthetics	Control	0.5	4	50	8	5	52	10	Severe AE. The most common event was bladder pain, which usually resolved within a day of instillation (Nickel 2009)
P2X3 antagonist	Control	1	0	36	0	0	38	0	SAE (details not reported; Hanno 2015)
		1	0	36	0	0	38	0	SAE (details not reported; Moldwin 2015)
PDE5 inhibitor	Control	6	0	24	0	0	24	0	SAE (details not reported; Chen 2014)
PPS	Control	6	4	251	2	4	118	3	SAEs, including 1 event each of abdominal pain, anxiety, chest pain, gastroesophageal reflux disease, pyrexia, renal mass and urinary tract infection in the PPS group; 1 event each of cholelithiasis, cholesterolosis, homicidal ideation and urinary retention in the placebo group (Nickel 2015)
Surgical									
Neuromuscular blockade	Control	1	0	61	0	0	31	0	Treatment-related SAE (Chuang 2017)
		2	0	15	0	0	15	0	Major AE (details not reported; Ismail 2016)
		6 (unclear)	0	14	0	0	2	0	SAE (details not reported; Payne 2014)
Denervation	Hydrodistension	1	0	12	0	0	12	0	SAE (details not reported; El-Hefnawy 2015)

AE: adverse event.
BCG: bacille Calmette-Guérin.
DMSO: dimethyl sulfoxide.
N/A: not applicable.
N/R: not reported.

PDE5: phosphodiesterase-5.
PPS: pentosan polysulfate.
SAE: serious adverse event.
UTI: urinary tract infection.

APPENDICES

Appendix 1. Cochrane Incontinence Specialised Register - search terms

We searched the Cochrane Incontinence Specialised Register using the following search terms:

DESIGN.CCT* or DESIGN.RCT*

AND

TOPIC.URINE.INTERSTITIAL CYSTITIS.

All searches were of the 'Keyword' field in EndNote 2018.

Please note: the UK Clinical Research Network Portfolio was replaced by UK Clinical Trials Gateway, which in turn has been replaced by Be Part of Research. At 11 July 2019, the site is still in development and is available at https://bepartofresearch.nihr.ac.uk/

HISTORY

Protocol first published: Issue 5, 2019
Review first published: Issue 7, 2020

CONTRIBUTIONS OF AUTHORS

MI: designed and wrote the protocol; conducted risk of bias assessment, data extraction and data checking; and drafted the methods and results section.
NS: designed and wrote the protocol; contributed to data extraction and data checking; conducted all statistical analyses; contributed to interpretation and presentation of results; and drafted methods and results sections.
JO: conceived, designed and wrote the protocol; provided expert advice; conducted study screening and selection, risk of bias assessment and data extraction; and contributed to interpretation of results.
AF: conceived, designed and wrote the protocol; provided expert advice; conducted study screening and selection, risk of bias assessment and data extraction; and contributed to interpretation of results.
SW: designed and wrote the protocol; conducted literature searches and compiled the reference list of the review; led study screening and selection; conducted risk of bias assessment; and drafted sections of the report related to the search strategies and search results.
YD: contributed to protocol development; conducted data extraction; and drafted the background section.
MB: designed and wrote the protocol; contributed to study screening and selection; interpreted data; and provided expert advice on review methods.

DECLARATIONS OF INTEREST

MI: none known.
NS: none known.
JO: none known.
AF: received money from Astellas towards travel to the IUGA Conference in 2016; this had no impact on this current work.
SW: serves as Cochrane Information Specialist for Cochrane Incontinence, whose single largest funder is the UK National Institute for Health Research (NIHR).
YD: none known.
MB: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Methods used for the GRADE assessment of evidence certainty and the 'Summary of findings' table were amended after the review commenced. These include the use of CINeMA software, modification of the 'Risk of bias' assessment to make it outcome specific and specification of minimal clinically important differences for primary outcomes.