WHAT ARE THE MOST EFFECTIVE INTERVENTIONS FOR TREATMENT OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS? A NETWORK META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS

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ABSTRACT
HYPOTHESIS / AIMS OF STUDY
Bladder pain syndrome (BPS) is a poorly understood bladder condition. According to the International Continence Society (ICS), BPS is defined as the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology.[1] BPS is also defined by the European Society for the Study of Interstitial Cystitis/Bladder Pain as pelvic pain, pressure or discomfort perceived to be related to the bladder, lasting for at least 6 months, and accompanied by at least one other urinary symptom.[2]

There is currently no definitive cure for BPS but a large number of treatments which aim to alleviate symptoms are employed with limited evidence. Previous research is hampered by its focus on numerous pairwise comparisons, which makes it difficult to identify the most effective treatments. This study aimed to bring together evidence for all available treatments that have been assessed in randomised controlled trials (RCT) by means of a network meta-analysis (NMA), which allow simultaneous comparisons of multiple interventions.

STUDY DESIGN, MATERIALS AND METHODS
We performed a NMA based on a systematic review of RCT of interventions for BPS in adults. RCTs were identified from existing Cochrane reviews and literature searches based on the Cochrane Incontinence Group Specialised Register, which contains trials identified from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE In-Process, MEDLINE Epub Ahead of Print, ClinicalTrials.gov, WHO ICTRP and hand-searching of journals and conference proceedings. Searches were performed on 3 October 2017. We also perused the reference lists of relevant identified articles. We sought any intervention (conservative, pharmacological or surgical) which aims to alleviate symptoms in adults with BPS, interstitial cystitis (IC) or painful bladder syndrome, accepting the various clinical terms used to identify this clinical condition in the literature. Urethral syndrome was excluded. Valid comparators were placebo, sham, control or another treatment. Primary outcomes were patient-reported improvement, pain, frequency and nocturia at 12 months. Secondary outcomes included Interstitial Cystitis Symptom Index (ICSI), Interstitial Cystitis Problem Index (ICPI), functional bladder capacity and adverse events. Risk of bias of the included studies was assessed using the Cochrane risk of bias tool for RCTs. For each outcome random effects NMA models were fitted using WinBUGS 1.4. Three chains were used and models were run with a burn-in of 20,000 iterations and then for a sample of 30,000 iterations. Results for each treatment category were monitored versus control.

RESULTS
The review included 81 RCTs. Most included studies had small sample sizes (<50) with a short follow-up. Only six studies had a follow-up of 12 months or longer. Sample sizes ranged from 10 to 369 participants, with a median of 38. Follow up time ranged from 0 to 27 months, with a median of 3 months.

Included studies assessed 65 different active treatments, either alone or in combination. To simplify, these were grouped into 31 active treatment categories by mode of action, following treatment descriptions for BPS/IC by the 6th International Consultation on Incontinence wherever possible.[3] Included studies were of moderate to low quality with three-quarters of included studies being assessed as having unclear or high risk of bias on most bias domains. Reporting quality of existing trials was also generally poor. For example, the number of patients with available data and the definition of outcome measures were not consistently reported across studies.

Full results of the NMA will be available shortly, but provisional results for the proportion of patients cured are available. A network of 42 RCTs and 20 treatment categories was evaluated, but 13 treatment categories were represented by just one or two RCTs and 95% credible intervals were generally wide. There was evidence that three pharmacological treatment categories (anti-depressants, immune modulators, PDE5 inhibitors), one surgical category (neuromuscular blockade) and one conservative therapy (behavioural therapy) were effective versus control. Adverse events appear uncommon in most interventions assessed. Data on long-term outcomes were limited.

INTERPRETATION OF RESULTS
Some interventions appear to be more effective than others. However, there is considerable uncertainty around the estimates of effect. Longevity of treatment is unclear.

CONCLUDING MESSAGE
To the best of our knowledge, this is the largest NMA conducted to assess the effects of different interventions for the treatment of BPS. The number and size of available RCTs for each treatment category was small and there was a lack of clear evidence for the majority of treatments assessed, which rendered it difficult to draw firm conclusions. Larger, more focused trials are needed to improve the current evidence base.