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

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[Intervention Protocol]

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

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of interventions for treating people with the symptoms of bladder pain syndrome (BPS).

BACKGROUND

Description of the condition

Bladder pain syndrome (BPS), which includes the condition interstitial cystitis, is a chronic condition mostly affecting 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).

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) developed stringent diagnostic guidelines for interstitial cystitis based on objective cystoscopic and urodynamic evaluation (NIDDK 2017). Such evaluation involves putting the patient under local or general anaesthesia and catheterisation of 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) provided a new 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 of Incontinence in 2010 (Hanno 2010). In this Cochrane Review, we will refer to the condition as BPS, while we will also consider some older literature using the original terminology.

The 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 on 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 suggested by empirical studies (Hanno 2017). BPS may negatively impact the quality of life and 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 urothelium's mucosal glycosaminoglycans coating. 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 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 the conservative management is unlikely to succeed, pharmacological interventions including analgesics, antidepressants, antibiotics and immune modulators, may be used either 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).

How the intervention might work

Conservative interventions can be beneficial in reducing the symptoms associated with BPS, including dietary and lifestyle changes, behavioural modifications (e.g. patient education, bladder retraining) and psychological therapies (e.g. stress management techniques). 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 only be considered once all other treatments have failed (Hanno 2017). People should also be informed of all aspects of surgery and 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.

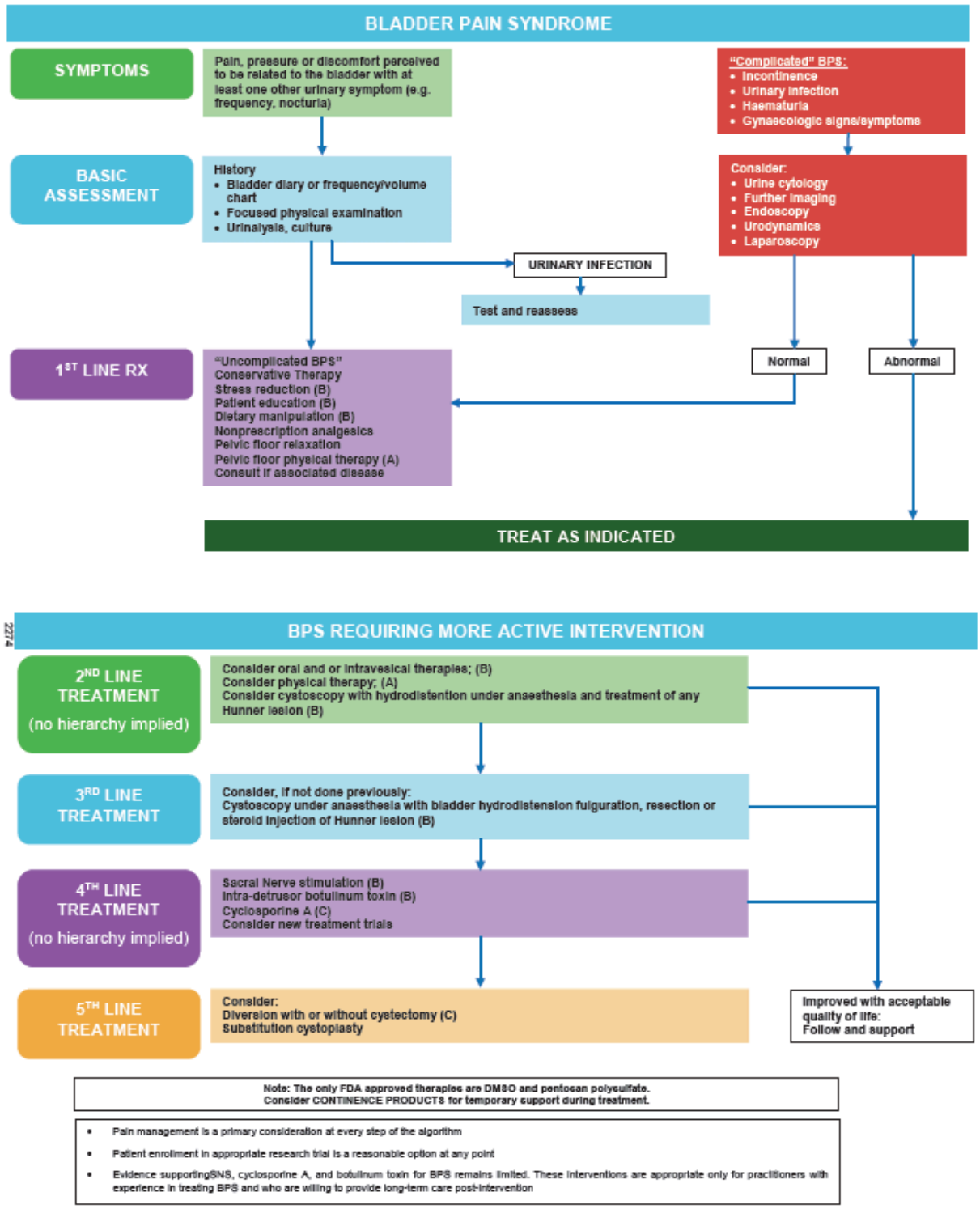
There are also some emerging therapies for treating BPS. These include:

- 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 and primarily subjective symptoms. More information is needed about the effects and safety of available treatment options and therapies. Currently, there are several small trials 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)). However, 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.

OBJECTIVES

To assess the effects of interventions for treating people with the symptoms of bladder pain syndrome (BPS).

METHODS

Criteria for considering studies for this review

Types of studies

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

Types of participants

Allowing for the many terminologies that have been used for the condition, we will include trials where adults are specified as having BPS, interstitial cystitis or painful bladder syndrome. We will accept the classification of diagnoses as defined by the trial investigators and a clinical diagnosis of BPS with or without meeting the NIDDK criteria will be eligible (NIDDK 2017). We will exclude studies of adults with urethral syndrome.

Types of interventions

We will include trials of any intervention that aim to cure or improve symptoms of BPS, covering both emerging and more traditional modes of treatments. All types of interventions are 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 and non-invasive electrical stimulation). We will consider pharmacological treatments regardless of their routes of administration (which are likely to be oral, subcutaneous, intramuscular, intravenous or intravesical).

Valid comparators are placebo, no treatment or another intervention.

We will exclude trials:

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

Types of outcome measures

We will use the following definitions of outcomes. If a particular outcome is reported using different definitions across different studies then, depending on the amount of data available, we will decide 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 where a study reports any other measure not included in our proposed list, we will add this at the bottom of the hierarchy and extract the data.

Primary outcomes

- Number of participants whose symptoms were cured or improved: self-reported measures are preferred, such as the Global Response Assessment. We will use objective measures (e.g. number of participants who experienced pain score reduction) as a proxy if self-reported measures are unavailable. We will use the number cured if this is reported. If cure is not reported, we will use the number improved, as defined by the trial investigators.
- Pain score: we will use 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); 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 consider the following terms to be equivalent to daytime frequency: frequency; daily frequency; frequency per day; and daytime frequency. We will exclude 24-hour frequency.
- Nocturia.

Secondary outcomes

- Subjective symptom measures (combining frequency, nocturia and pain): we will use 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 will use 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); 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 the review: functional bladder capacity; functional bladder volume; bladder capacity; maximum bladder capacity; and maximum tolerable bladder capacity. We will exclude volume at first or strong desire to void, (mean) voided volume, (maximum) cystometric bladder capacity, or urodynamic capacity.
- Adverse events: the category of adverse events will be accepted as reported by the study authors.

Timing of outcome assessment

The primary time point for outcome assessment is at 12 months or the nearest time point available to 12 months. For all continuous outcomes (e.g. pain scores), we will use observed final scores post-intervention if reported, with the change score from the baseline used as a proxy.

Main outcomes for 'Summary of findings' tables

- Number of participants whose symptoms were cured or improved
- Pain score
- Daytime frequency
- Nocturia

Search methods for identification of studies

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

Electronic searches

We will perform searches drawing on the search strategy developed for Cochrane Incontinence. We will identify relevant trials from the Cochrane Incontinence Specialised Register. For more 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), MEDLINE, MEDLINE In-Process, MEDLINE Epub Ahead of Print, ClinicalTrials.gov, WHO ICTRP, the UK Clinical Research Network Portfolio and handsearching of journals and conference proceedings. Many of the trials in the Cochrane Incontinence Specialised Register are also contained in CENTRAL.

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

Searching other resources

We will identify relevant studies from an existing Cochrane Review on intravesical treatments for BPS (Dawson 2007). We will also screen the reference lists from the included studies for other relevant trials.

Data collection and analysis

Selection of studies

One review author (SW) will establish the selection of studies from the relevant Cochrane Review on intravesical treatments for BPS (Dawson 2007), which a second review author (MI) will check. Two review authors (JO and AF) will independently screen the titles and abstracts of all citations identified by the literature searches. The same two review authors will evaluate full-text copies of all potentially relevant reports. We will resolve any discrepancy or inconsistency by recourse to a third review author (SW, MI, NS or MB).

We will obtain translations of eligible studies where resources allow, including any available translated information obtained by Dawson 2007. If translations are not obtained, we will add these studies to 'Studies awaiting classification' and discuss the implications of any missing information in the 'Overall completeness and applicability of the evidence' section of the completed review.

Data extraction and management

We will export study characteristics and outcome data of individual studies from the relevant Cochrane Review (Dawson 2007), and one review author (MI or YAD) will check them against individual trial reports. From additional studies identified by updated literature searches, one review author (MI or YAD) will perform data extraction using a prepiloted data form, which another review author (MI or YAD) will check. We will resolve any discrepancy or inconsistency by recourse to a third review author (SW, NS or MB).

We will collect information on study design and setting, participant characteristics (including disease diagnosis), study eligibility criteria, details of the intervention(s) given, the outcomes assessed and the source of study funding for each included study. We will map multiple publications of a primary study to unique studies and we will extract the most complete data across all known publications.

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

Assessment of risk of bias in included studies

We will use the original risk of bias assessments made by the review authors of the relevant Cochrane Review (Dawson 2007). Judgements were made for the following criteria.

- Adequacy of randomisation, description of allocated groups prior to 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.

Two review authors working independently (JO and AF) will update assessments using Cochrane's 'Risk of bias' assessment tool (Higgins 2011a). We will resolve any discrepancy or inconsistency by recourse to a third review author (SW, NS or MB). The new assessments will address 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

We will judge each included study to be at ‘low', 'high' or 'unclear' risk of bias.

Measures of treatment effect

For binary outcomes, we will use odds ratios (ORs) as the measure of treatment effect. For continuous outcomes, we will use the difference in means.

Unit of analysis issues

We will only include patient randomised trials in this review and the unit of analysis will be individual participants.

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

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

Dealing with missing data

We will employ a number of approaches to calculate or estimate SDs when these were not reported, though the standard methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* will be preferred (Higgins 2011c). If standard errors (SEs) are reported, we may derive 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 will calculate SDs from a 90% or 95% confidence interval (CI) for a mean difference, from the P value from a t-test (Higgins 2011b), or imputed using an average from other studies.

Assessment of heterogeneity

For pairwise meta-analyses, we will assess the presence of statistical heterogeneity by visual inspection of the forest plots and by calculating the I^2 statistic (Higgins 2003). For network meta-analyses, we will investigate consistency between direct and indirect evidence as outlined in the Data synthesis section below.

Assessment of reporting biases

If there are more than 10 trials per comparison in each outcome, we will examine funnel plots to assess reporting bias.

Data synthesis

We will divide interventions into treatment categories, classified as conservative, pharmacological or surgical interventions. The total number of treatment categories that could be included in each analysis will depend on the number of studies that provide useable data for the outcomes of interest. If considered clinically appropriate (e.g. if treatment B is considered a routine therapy), we will 'cancel' treatments (e.g. a trial of A + B versus B will become A versus control). If this is not appropriate, we will use a combination of therapies as a single treatment category (e.g. chondroitin sulfate plus hyaluronic acid). We will combine different doses of the same treatment as a single category, provided this is considered clinically appropriate.

We will perform two approaches to meta-analysis. The primary method will be network meta-analysis but we will also conduct standard pairwise meta-analyses and compare the results with those from the network meta-analysis.

Network meta-analysis

We will follow 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-analyses models will be fitted using WinBUGS 1.4 and used to conduct data synthesis of trials (Lunn 2000). We will use a binomial likelihood for binary outcomes and the normal likelihood for continuous outcomes. We will use random-effects models due to the expected heterogeneity between treatments and outcome measures. Three chains will be used and parameters fitted using vague normal prior distributions.

For binary outcomes, we will use Program 1(c) from the NICE DSU TSD 2 (Dias 2016). We will monitor ORs for all treatments in the network against control and present results using 95% credible intervals. ORs greater than one will be associated with a favourable effect of treatment versus control. We will only monitor the effect of active treatments versus control.

For continuous outcomes, the effect size will be the mean difference between groups but we will only monitor differences between active treatments and control. For each outcome, high scores will represent poorer outcomes than lower scores. Therefore, effect sizes of less than zero will mean that the treatment group is favoured. We will use a shared parameter model (Program 8(a) from the NICE DSU TSD 2) in order to simultaneously incorporate two data formats (Dias 2016):

- final score arm-based data; and
- contrast-based differences in change from baseline.

For the network meta-analysis, there is an additional assumption of transitivity, i.e. 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. We intend to use the methods described in the NICE DSU TSD 4 to compare closed loops within the network (Dias 2014).

We will produce 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 proportional to the number of included studies.

Pairwise meta-analyses

We will compare the results of the network meta-analysis with the direct evidence from head-to-head trials. For each outcome, we will perform a separate pairwise meta-analysis for each treatment category versus control. Meta-analyses will be conducted using the *metan* command in Stata (Stata 2017). We will not conduct meta-analyses between each pair of active treatments. The number of trials contributing to the pairwise meta-analyses may be smaller than those included in the network meta-analysis because only trials with a control group will be included.

For binary outcomes, we will pool ORs for each treatment versus control. We will use 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 will be the mean difference between treatment and control. We will use 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 will combine studies using the inverse variance weighted approach and present results using 95% confidence intervals (CIs).

Subgroup analysis and investigation of heterogeneity

We do not plan to conduct subgroup analyses.

Sensitivity analysis

We do not plan to conduct sensitivity analyses.

GRADE and 'Summary of findings' tables

We will prepare 'Summary of findings' tables for the main comparisons.

We will assess the overall quality of evidence for each of the outcomes listed in the 'Main outcomes for 'Summary of findings' table' using the GRADE approach (Guyatt 2008; Guyatt 2011; Schünemann 2011). We will rate each outcome as 'high', 'moderate', 'low', or 'very low', taking into account five criteria: study limitations, inconsistency, imprecision, indirectness and publication bias. We will apply the GRADE approach modified for network meta-analysis (Salanti 2014), and plan to explore the use of the CINeMA 2017 web application in order to implement this approach. If this application is not suitable for the purposes of this review, we will use Microsoft Excel 2016 instead. We will follow the guidance in the latest draft version of the *Cochrane Handbook for Systematic Reviews of Interventions* chapter on network meta-analysis to develop our own 'Summary of findings' tables (Chaimani 2017).

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REFERENCES

Additional references

Abrams 2002

Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourology and Urodynamics* 2002;**21**(2):167-78.

Abrams 2017

Abrams P, Cardozo L, Wagg A, Wein A, editor(s). Incontinence. 6th Edition. Bristol, UK: ICI-ICS. International Continence Society, 2017. [ISBN: 978-0956960733]

Chaimani 2017

Chaimani A, Caldwell DM, Li T, Higgins JP, Salanti G. Chapter 11: Undertaking network meta-analyses. In: Higgins JP, Churchill R, Chandler J, Cumpston MS, editor(s), Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017). The Cochrane Collaboration, 2017. Available from www.training.cochrane.org/handbook.

CINeMA 2017 [Computer program]

Institute of Social and Preventive Medicine, University of Bern. CINeMA: Confidence in Network Meta-Analysis. Version accessed 17 January 2019. Bern, Switzerland: Institute of Social and Preventive Medicine, University of Bern, 2017.

Cox 2016

Cox A, Golda N, Nadeau G, Curtis Nickel J, Carr L, Corcos J, et al. CUA guideline: Diagnosis and treatment of interstitial cystitis/bladder pain syndrome. *Canadian Urological Association Journal* 2016;**10**(5-6):E136-55.

Dawson 2007

Dawson TE, Jamison J. Intravesical treatments for painful bladder syndrome/interstitial cystitis. *Cochrane Database of Systematic Reviews* 2007, Issue 4. [DOI: 10.1002/14651858.CD006113.pub2]

Deeks 2011

Deeks JJ, Higgins JP, Altman DG editor(s). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Dias 2014

Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE, NICE Decision Support Unit. NICE DSU Technical Support Document 4: inconsistency in networks of evidence based on randomised controlled trials. www.nicedsu.org.uk (accessed 22 August 2017).

Dias 2016

Dias S, Welton NJ, Sutton AJ, Ades AE, NICE Decision Support Unit. NICE DSU Technical Support Document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. www.nicedsu.org.uk (accessed 22 August 2017).

EndNote 2018 [Computer program]

Clarivate Analytics. EndNote. Version X8.2. Philadelphia: Clarivate Analytics, 2018.

Goin 1998

Goin JE, Olaleye D, Peters KM, Steinert B, Habicht K, Wynant G. Psychometric analysis of the University of Wisconsin Interstitial Cystitis Scale: implications for use in randomized clinical trials. *Journal of Urology* 1998;**159**(3):1085-90.

Grover 2011

Grover S, Srivastava A, Lee R, Tewari AK, Te AE. Role of inflammation in bladder function and interstitial cystitis. *Therapeutic Advances in Urology* 2011;**3**(1):19-33.

Guyatt 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Schünemann HJ, et al. GRADE: what is "quality of evidence" and why is it important to clinicians?. *BMJ* 2008;**336**(7651):995-8.

Guyatt 2011

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94.

Hanno 1999

Hanno PM, Landis JR, Matthews-Cook Y, Kusek J, Nyberg L Jr. The diagnosis of interstitial cystitis revisited: lessons learned from the National Institutes of Health Interstitial Cystitis Database study. *Journal of Urology* 1999;**161**(2):553-7.

Hanno 2010

Hanno P, Lin A, Nordling J, Nyberg L, van Ophoven A, Ueda T, et al. Bladder Pain Syndrome Committee of the International Consultation on Incontinence. *Neurourology and Urodynamics* 2010;**29**(1):191-8.

Hanno 2017

Hanno P, Cervigni M, Dinis P, Lin A, Nickel JC, Nordling J, et al. Bladder pain syndrome. Incontinence: 6th International Consultation on Incontinence; 2016 September 12-14; Tokyo. Bristol: International Continence Society (ICS) and International Consultation on Urological Diseases (ICUD), 2017:2206-301. [ISBN: 978-0956960733]

Hays 1993

Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. *Health Economics* 1993;**2**(3):217-27.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

Higgins 2011a

Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928.

Higgins 2011b

Higgins JP, Deeks JJ, editor(s). Chapter 7: Selecting studies and collecting data. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011c

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration.

Kelleher 1997

Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A new questionnaire to assess the quality of life of urinary incontinent women. *British Journal of Obstetrics and Gynaecology* 1997;**104**(12):1374-9.

Logadottir 2014

Logadottir Y, Delbro D, Fall M, Gjertsson I, Jirholt P, Lindholm C, et al. Cytokine expression in patients with bladder pain syndrome/interstitial cystitis ESSIC type 3C. *Journal of Urology* 2014;**192**(5):1564-8.

Lunn 2000

Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS - a Bayesian modelling framework: concepts, structure, and extensibility. *Statistics and Computing* 2000;**10**(4):325-37.

McHorney 1993

McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Medical Care* 1993;**31**(3):247-63.

Melzack 1975

Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain* 1975;**1**(3):277-99.

Melzack 1987

Melzack R. The short-form McGill Pain Questionnaire. *Pain* 1987;**30**(2):191-7.

Microsoft Excel 2016 [Computer program]

Microsoft Corporation. Microsoft Excel for Windows. Version 16.0.6769.2017. Redmond, WA, USA: Microsoft Corporation, 2016.

NIDDK 2017

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Diagnosis of interstitial cystitis: how do health care professionals diagnose IC?. www.niddk.nih.gov/health-information/urologic-diseases/interstitial-cystitis-painful-bladder-syndrome/diagnosis (accessed 26 January 2018).

O'Leary 1997

O'Leary MP, Sant GR, Fowler FJ Jr, Whitmore KE, Spolarich-Kroll J. The interstitial cystitis symptom index and problem index. *Urology* 1997;**49**(5A Suppl):58-63.

Parsons 2002

Parsons CL, Dell J, Stanford EJ, Bullen M, Kahn BS, Waxell T, et al. Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynecologic cases identified using a new symptom questionnaire and intravesical potassium sensitivity. *Urology* 2002;**60**(4):573-8.

Salanti 2014

Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. *PLoS One* 2014;**9**(7):e99682.

Schünemann 2011

Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Stata 2017 [Computer program]

StataCorp. Stata. College Station, TX, USA: StataCorp, 2017.

van de Merwe 2008

van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. *European Urology* 2008;**53**(1):60-7.

Ware 1992

Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care* 1992;**30**(6):473-83.

Ware 1996

Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Medical Care* 1996;**34**(3):220-33.

APPENDICES

Appendix 1. Cochrane Incontinence Specialised Register - search terms

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

DESIGN.CCT* or DESIGN.RCT*

AND

TOPIC.URINE.INTERSTITIAL CYSTITIS.

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

CONTRIBUTIONS OF AUTHORS

MI: designed and wrote the protocol
NS: designed and wrote the protocol
JO: conceived, designed and wrote the protocol
AF: conceived, designed and wrote the protocol
SW: designed and wrote the protocol
YD: wrote the protocol
MB: designed and wrote the protocol. MB acts as the guarantor for the review.

DECLARATIONS OF INTEREST

MI: None known.
NS: None known.
JO: None known.
AF: Money received from Astellas towards travel to the IUGA conference in 2016. This has no impact on this current work.
SW: Sheila Wallace is the Cochrane Information Specialist for Cochrane Incontinence, whose single largest funder is the UK National Institute for Health Research (NIHR).
YD: None known.
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