INVESTIGATING THE DIAGNOSIS AND MANAGEMENT OF BLADDER PAIN SYNDROME (BPS) IN WOMEN WITH CHRONIC PELVIC PAIN (CPP).

A study of prevalence, diagnostic tests, the effectiveness of neuromodulation, the quality of information available to patients and the discrepancies in rating the level of evidence for the management of BPS.

Seema Anushka Tirlapur

A thesis submitted to the School of Medicine and Dentistry at Queen Mary, University of London in partial fulfillment of the requirements for the Degree of Doctor of Medicine (Research) [MD (Res)]

Women's health research unit
Centre for primary care and public health
Barts and The London School of Medicine and Dentistry
Queen Mary, University of London

December 2014

Declaration on the availability of the thesis

1. I authorise that the thesis I present for examination for the MD (Res) degree shall, if a degree is awarded, be deposited in the library of Queen Mary, University of London and the electronic institutional repository and that, subject to the conditions set out below, it may be made available for public reference, inter-library loan and copying.

2. I authorise the College or University authorities as appropriate to supply a copy of the abstract of my thesis for inclusion in any published list of theses offered for higher degrees in British universities or in any supplement thereto, or for consultation in any central file of abstracts of such theses.

3. I authorise the College libraries, or their designated agents, to make a microform or digital copy of my thesis for the purposes of electronic public access, inter-library loan and the supply of copies.

4. I understand that before my thesis is made available for public reference, inter-library loan and copying, the following statement will have been included at the beginning of my thesis or clearly associated with any electronic version: The copyright of this thesis rests with the author and no quotation from it or information

derived from it may be published without the prior written consent of the author.

5. I authorise the College to make a microform or digital copy of my thesis in due course as the archival copy for permanent retention in substitution for the original copy.

6. I warrant that this authorisation does not, to the best of my belief, infringe the rights of any third party.

7. I understand that if my thesis is not approved by the examiners, this declaration will become void.

Statement of originality

I, *Seema Anushka Tirlapur*, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by others, that this is duly acknowledged below and my contribution indicated. Previously published material is also acknowledged below.

I attest that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge break any UK law, infringe any third party's copyright or other Intellectual Property Right, or contain any confidential material.

I accept that the College has the right to use plagiarism detection software to check the electronic version of the thesis.

I confirm that this thesis has not been previously submitted for the award of a degree by this or any other university.

Signature: [can be digital signature]

Date: 30th November 2014

Details of collaboration and publications:

1. The 'evil twin syndrome' in chronic pelvic pain: a systematic review of the prevalence studies of bladder pain syndrome and endometriosis

SA Tirlapur, K Kuhrt, C Chaliha, E Ball, C Meads, KS Khan

Int J Surg. 2013 Feb; 233-237

2. Quality of information on the internet related to bladder pain syndrome: a systematic review of the evidence

SA Tirlapur, C Leiu, KS Khan

Int J Urogyn. 2013 Aug;24(8):1257-62

3. Bladder pain syndrome: Validation of simple tests for Diagnosis in women with chronic pelvic pain: BRaVADO study protocol

SA Tirlapur, L Priest, D Wojdyla, KS Khan

Reprod Health. 2013 Dec 4;10(1):61.

4. The role of laparoscopy and cystoscopy in the diagnosis and management of chronic pelvic and bladder pain.

SA Tirlapur, KS Khan, E Ball

Recent advances in obstetrics and gynaecology 25 (chapter 1, July 2014

(Edited by William Ledger and Justin Clark)

5. Nerve stimulation for chronic pelvic pain and bladder pain syndrome: a systematic review

SA Tirlapur, A Vlismas, E Ball, KS Khan

Acta Obstet Gynecol Scand 2013 Aug;92(8):881-7

6. Discrepancies in the grading of evidence for bladder pain syndrome: A comparative review of quality assessment methods

SA Tirlapur, KS Khan

Int Urogynecol J. 2014 Aug;25(8):1005-13

7. Variations in the reporting of outcomes used in systematic reviews of treatment effectiveness research in bladder pain syndrome

SA Tirlapur, R Ni Riordain, KS Khan

Eur J Obstet Gynecol Reprod Biol. 2014 Jun 13;180C:61-67

Contributions to each paper are stated in appendix 1. All appropriate licensing copyrights have been obtained and copies of all original manuscripts are enclosed at the end of the appendix section.

Abstract Summary (299 words)

The aim of this thesis is to investigate the prevalence and management of bladder pain syndrome (BPS) amongst women with chronic pelvic pain (CPP) through a series of systematic reviews, a structured survey and primary study.

It has been acknowledged that the diagnosis and management of BPS is a contentious subject. The mean prevalence of BPS in women with CPP is 61%. I initially carried out a patient and clinician survey to understand how BPS was being managed in the UK. I found wide variation in diagnostic methods and treatments of BPS used by clinicians and experienced by patients with no obvious consensus. Since we know the predominant complaint in these patients is pain (bladder or pelvic) I used patients with pelvic pain as my cohort.

Cystoscopy is no longer used as a diagnostic test for BPS. It is possible to diagnose BPS through a consensus expert panel using symptom-based criteria. This method of deriving a reference standard is demonstrated in the primary study, since no gold standard diagnostic test exists for BPS. A case-control feasibility study was undertaken to investigate the accuracy of a group of urinary symptoms to diagnose BPS. While, neither index test of bladder filling pain or bladder wall tenderness can sensitively diagnose BPS alone, the symptoms of bladder filling pain, urinary frequency, pain on urination and pain on full bladder are a good predictor of the condition. A systematic review assessing the reporting outcomes identified five measures that should be included in studies; pain, urinary symptoms, general

wellbeing, quality of life and bladder capacity. Of the 19 treatments used for BPS, the level and strength of evidence ratings overestimated quality compared to the GRADE ratings. BPS can be diagnosed symptomatically but there is variable reporting of outcome measures and poor evidence for treatment effectiveness.

Aims

1. To investigate the prevalence of bladder pain syndrome (BPS) amongst patients with chronic pelvic pain

2. To assess the information available to patients regarding BPS on the internet

3. To assess patients and clinicians experiences managing BPS

4. To evaluate the test accuracy of bladder wall tenderness and bladder filling pain for diagnosing BPS in patients with chronic pelvic pain

5. To assess the role of laparoscopy and cystoscopy in the diagnosis and management of pelvic and bladder pain

6. To assess the effectiveness of nerve stimulation in the treatment of pelvic and bladder pain

7. To assess the relationship between quality of outcomes reported, study quality and journal impact factor in systematic reviews and trials of bladder pain syndrome.

8. To assess the discrepancies in grading of evidence for the management of bladder pain syndrome

Methods

- Systematic reviews to meet objectives 1,2,6,7
- Structured questionnaire survey to meet objective 3
- Prospective observational study to meet objective 4

Results

1. Nine studies were included with 1016 patients. Study quality and diagnostic assessment varied. The mean prevalence of BPS was 61% (range 11-97%, CI 58-64%, I^2 = 98%). Co-existing BPS and endometriosis was seen in 48% (range 16-78%, CI 44-51%, I^2 = 96%).

2. Eighteen websites were identified. The combined quality mean scores (for accuracy, quality, credibility and readability) ranged from 83 to 144 for specialist websites and 76 to 137 for non-specialist ones (a maximum possible score of 208). There was good inter-observer agreement for the assessments performed.

3. 133 patients and 69 clinicians participated in the survey. Patients reported their main symptom to be pain when their bladder was full in 80% (n=107) and the most bothersome symptom was pelvic pain (22%, n= 29). 93% (n=64) of clinicians made their diagnosis by history and cystoscopy and 81% (n=108) of patients, reported to be diagnosed in this way. 78% (n=54) of clinicians treated patients with amitriptyline and 75% (n=52) by dietary modification while 77% (n=102) of patients reported using simple analgesia, 74% (n=98) dietary modification and 62% (n=83) low-dose long-term antibiotics.

4. 46 eligible patients were recruited with a mean age of 32.8 years old. Three patients suffered from bladder wall tenderness and 16 from bladder filling pain, with 21 patients being diagnosed with BPS by expert panel diagnosis. The inter-observer intra-class coefficient agreement was 0.46. The sensitivity of bladder wall tenderness as a predictor of BPS compared to a symptom-based diagnosis was 0.10 and the sensitivity of bladder filling pain was 0.57.

5. Chronic pelvic pain can be due to structural or non-structural causes and maybe due to multiple co-existing pathologies. Cystoscopy can be used as a therapeutic treatment for bladder pain syndrome.

6. Three studies were included with 169 patients; two for CPP and one for BPS. There were improvements in pain, urinary and quality of life scores using both forms of neuromodulation.

7. Five reporting outcomes were identified (pain, urinary symptoms, general wellbeing, quality of life and bladder capacity) using 19 different measurement scales. The correlation between reporting outcomes and study quality for systematic reviews was 0.73 (95% CI 0.06 - 0.95, p = 0.02) and 0.19 (95% CI -0.22 – 0.55, p = 0.18) for RCTs. The Spearman's rank correlation between impact factor and quality of reporting outcomes for RCTs was 0.38 (95% CI -0.06 – 0.70, p = 0.04) compared to 0.38 (95% CI -0.88 – 0.52, p = 0.82) for systematic reviews.

8. Of the 19 treatments for BPS that had GRADE ratings assigned, comparison with level of evidence ratings showed that on average the latter overestimated quality by 1.8 points (1.1 v 2.9; 95% CI of mean difference 1.2 to 2.3; p= <0.0001). Comparison of GRADE ratings with strength of evidence ratings showed that on average the latter overestimated quality by 1.7 points (1.1 v 2.8; 95% CI of mean difference 1.3 to 2.1; p= <0.0001).

Conclusion

1. Almost two thirds of women presenting with CPP have BPS. Clinicians need to actively investigate patients for BPS, a condition that appears to co-exist with endometriosis.

2. There were for websites that filled the criteria for good quality information.
3. There is wide variation in diagnostic methods and treatments of BPS used by clinicians and experienced by patients with no obvious consensus. There is a need for national guidance to standardise care.
4. The absence of bladder wall tenderness can be associated with a high specificity and bladder filling pain with a reasonable sensitivity with high specificity in diagnosing BPS. A consensus expert panel was found to be a suitable method to achieve a symptom-based diagnosis as a reference standard.

5. In view of the high incidence of co-existing pathology amongst patients with chronic pelvic pain (CPP), clinicians should consider performing laparoscopy and cystoscopy routinely to investigate CPP in order to rule out gynaecological or bladder causes of pain.
6. Variable success of posterior tibial nerve stimulation (PTNS) in improving pain, urinary symptoms and quality of life in CPP and BPS was reported. There was no reported data for sacral nerve stimulation (SNS). A large multi-centered clinical trial investigating the effectiveness of electrical nerve stimulation to treat BPS and CPP along with the cost-analysis of this treatment is recommended.
7. Good quality RCTs tend to have better quality of outcome reporting. There is a need to generate consensus over a set of core outcomes in bladder pain syndrome.
8. GRADE, a refined method of assigning quality to evidence, provided a more conservative gauge of quality of evidence, giving a realistic assessment of the value of recommendations for consideration in practice.

Table of contents

Preface

This thesis is based on work carried out during my employment at the Women's health research unit, at Queen Mary, University of London between 2011 to 2014, in collaboration with the department of gynaecology at The Royal London Hospital.

The supervisors of the MD study were:

- Khalid S Khan, Professor of Clinical Epidemiology and Women's health, Queen Mary, University of London.
- Miss Elizabeth Ball, Consultant obstetrician and gynaecologist, The Royal London Hospital, Barts Health NHS Trust.

Synopsis

This thesis assesses the prevalence and impact of bladder pain syndrome (BPS) amongst women with chronic pelvic pain (CPP), the effectiveness of neuromodulation, along with patients and clinicians prior beliefs about treatment and the levels of evidence for different treatment recommendations. It evaluates the diagnostic value of two index tests; bladder wall tenderness and bladder filling pain to diagnose BPS, as well as which outcome measures are important when reporting studies on BPS, along with examining the information available to patients with BPS and the experiences of patients and clinicians managing the disease.

Dedication

To my family – thank you for your endless support.

Acknowledgments

My heartfelt gratitude to my supervisor, Professor Khalid Khan, for his patience in guiding me through my research, for teaching me how to run a clinical trial and for encouraging my ideas. I truly enjoyed every moment of my time as a research fellow and thank him for the opportunity to work in such a nurturing unit.

To my clinical supervisor, Miss Ball, thank you for your words of wisdom and teaching me all about managing pelvic pain.

Thank you to all those who acted as second reviewers, helped data extract and co-author the systematic reviews: Katy Kuhrt, Christopher Leiu, Antonis Vlismas and Richeal Ni Riordain. I would like to thank Ana Gutierrez for her help with translation of a foreign manuscript.

This work was supported by my position as clinical research fellow on the MEDAL study funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme (grant number: 09/22/50). I would like to thank the MEDAL study management team for all their help gathering and collating data for my primary study and for teaching me about the running of a clinical trial: Khalid Khan, Jane Daniels, Jon Deeks, Elizabeth Ball, Teresita Beeston, Lee Middleton, Lee Priest, Julia Seeley and Julie Dodds. I learnt so much working on this trial and it opened my eyes to all the work that still needs to be done to improve managing pelvic pain. A special thank you to the MEDAL study research nurse,

Teresita, for your friendship, help, pep talks and constant supply of caramel lattes.

To all the consultants at the Royal London Hospital, I wish to thank them for helping me recruit patients into the study and for being so supportive while I trained and worked as a research fellow there.

Thank you to Pallavi Latthe for her advice, help and encouragement throughout my journey as a research fellow.

Thank you to the consultants who acted as part of the Bravado study expert panel: Pallavi Latthe, Anupreet Dua and Dudley Robinson for patiently reviewing data and contributing to our paper. Your suggestions and expert advice was much appreciated.

Thank you to the pelvic pain network (www.pelvicpainnetwork.org.uk), cystitis and overactive bladder foundation UK (www.cobfoundation.org) and international painful bladder foundation (www.painful-bladder.org) for posting the patient survey on their website and to the British Society of Urogynaecology (BSUG) for distributing the survey of clinicians to their members.

To the fantastic team in the Women's Health Research Unit, thank you to all for your support and friendship: Khalid, Shakila, Tracy, Julie, John, Aoife, Anna, Ewelina, Fiona, Elaine, James and Jahnavi. It is to all of you that I attribute my passion for

research and global health. Everything achieved over my years as a research fellow was made possible with your help and support and for that I am truly grateful.

To my wonderful family, Mum, Dad and Nikhil, thank you for the ambition you instilled in me, for your constant encouragement and words of support. Thank you for patiently allowing me to spend many hours writing and researching over the years.

To anyone else who has been forgotten from this list whom I encountered on my research adventure, your words of advice and encouragement were very much appreciated.

Abbreviations

AMSTAR: Assessment of multiple systematic reviews

AUA: American Urological Association

BCG: Bacillus Calmette-Guerin

BMI: Body mass index

BPS: Bladder Pain Syndrome

BSUG: British Society of Urogynaecology

CI: Confidence interval

COMET: Core Outcome Measures in Effectiveness Trials

COS: Core outcome sets

CPP: Chronic Pelvic Pain

CPPS: Chronic pelvic pain syndromes

DMSO: Dimethyl sulfoxide

EAU: European Urology Association

ESSIC: International Society for the Study of BPS

FRE: Flesch reading ease

FSFI: Female sexual function index

GAG: Glycosaminoglycan

GRADE: Grading of Recommendations, Assessment, Development and Evaluations

IASP: International Association for the Study of Pain

IC: Interstitial Cystitis

ICC: Intra-class co-efficient

ICS: International Continence Society

ICSI: Interstitial cystitis symptom index

ITT: Intention to treat

MEDAL: MRI to Establish Diagnosis Against Laparoscopy

MeSH: Medical subject headings

MRI: Magnetic resonance imaging

NIDDK: National Institute of Diabetes, Digestive and Kidney Diseases

NIH CPSI: Chronic prostatitis symptom index

NIHR: National Institute of Health Research

OLS: O'Leary-Sant

PBS: Painful bladder syndrome

PPS: Pentosan polysulfate sodium

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

PROSPERO: International prospective register for systematic reviews

PTNS: Posterior tibial nerve stimulation

PUF: Pain, urgency, frequency symptom scale

RCOG: Royal College of Obstetricians and Gynaecologists

RCT: Randomised control study

SD: Standard deviation

SNS: Sacral nerve stimulation

TENS: Transcutaneous electrical stimulation

UK: United Kingdom

USA: United States of America

UTI: Urinary tract infection

VAS: Visual analogue scale

List of figures in thesis

List of tables in thesis

CHAPTER 1:
INTRODUCTION

Bladder Pain Syndrome

1.1 *Definition*

Interstitial cystitis (IC) with ulcers was first described in 1915 by Hunner (1). By 1978 IC had been sub-divided into disease groups with the presence of glomerulations and reduced bladder capacity and the 'classical' condition with Hunner's ulcers (2). In 1987 The National Institute of Digestive, Diabetes and Kidney Diseases (NIDDK) criteria for IC were first proposed (Appendix 2) (3). The strict inclusion criteria meant that many patients were under-diagnosed and the need for revisions to the definition were identified (4).

The term 'painful bladder syndrome' (PBS) was introduced by the International Continence Society (ICS) in 2002. The condition is a differential diagnosis of chronic pelvic pain (CPP) with imprecise clinical characterisation, based on symptoms of urgency or frequency and pain in the pelvic region. PBS was defined as suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency in the absence of any identifiable pathology or infection (5). The ICS defined IC as a condition associated with the typical cystoscopic and histological features previously described (6).

In 2008, The European Society for the Study of Interstitial Cystitis/Painful Bladder Syndrome (ESSIC), now known as the International Society for the Study of BPS, proposed a change in the nomenclature from IC/PBS to bladder pain syndrome (BPS)

describing chronic pelvic pain, bladder pressure or discomfort along with at least one other urinary symptom (7). The type of BPS can be further classified according to the cystoscopy and biopsy grading of glomerulations and the presence of Hunner's lesions (Table 1).

Table 1: The classification of bladder pain syndrome (BPS) according to cystoscopy and biopsy findings (7)

	Cystoscopy with hydrodistension			
	Not done	Normal	Glomerulations [b]	Hunner's lesions [c]
Biopsy				
Not done	XX	1X	2X	3X
Normal	XA	1A	2A	3A
Inconclusive	XB	1B	2B	3B
Positive [a]	XC	1C	2C	3C

[a] *Histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafasicular fibrosis.*

[b] *Glomerulations: grades 2-3 (grade 2 = severe areas of submucosal bleeding, grade 3 = diffuse bleeding of bladder mucosa)*

[c] *With or without glomerulations*

In 2009 the Japanese introduced the term hypersensitive bladder syndrome (HBS), which was defined as bladder hypersensitivity, usually associated with urinary frequency, with or without bladder pain (8). This included patients complaining of the IC/PBS symptoms without cystoscopic findings.

In 2011 the International Society for the Study of Pain (IASP) proposed a revised definition for BPS, acknowledging the multi-factorial nature of the disease and the impact on the patient's quality of life. It defined BPS as the occurrence of persistent or recurrent pain perceived in the urinary bladder region, accompanied by at least one other symptom, such as pain worsening with bladder filling and daytime and/or night-time urinary frequency, with no proven infection or other obvious local pathology. BPS can often be associated with negative cognitive, behavioural, sexual, or emotional consequences as well as with symptoms suggestive of lower urinary tract and sexual dysfunction (9). IC and BPS are now used synonymously to describe this disease.

1.2 *Epidemiology*

A variety of signs, symptoms and tests may be performed to establish a possible diagnosis of BPS. In view of these differences in practice, it is difficult to accurately calculate the prevalence of the disease. An early Finnish study in 1975 estimated the prevalence of BPS as 18 cases per 100,000 (0.02%) based on positive symptoms, negative urine infection screen and positive bladder biopsy results (10). By 2007 the prevalence of patients with BPS was 0.3% in Austria (11). Whereas in Japan, in 1998 the prevalence was reported to be 2 per 100,000 and affected an older group of patients with a mean age of 52.9 years old, although more recently data showed that 1.0% of the general population experienced daily symptoms of bladder pain (12-14). An American epidemiological survey estimated the prevalence of disease to be between 2.7- 6.5% of women in the United States of America (USA) who suffered from urinary symptoms consistent with BPS, which highlights the burden of disease

(15). As the definition and diagnostic criteria for BPS has changed though the years, it is difficult to accurately calculate prevalence rates.

1.3 *Aetiology*

BPS is a chronic condition with an unknown aetiology, which is poorly understood pathophysiology (16). There are many theories regarding the causes of BPS. The glycosaminoglycan (GAG) layer protects the bladder mucosa. When this protective layer breaks down, the bladder mucosa is exposed to toxic substances in urine, leading to inflammation, which may cause symptoms such as urinary frequency and pain (17). The cause of this epithelial dysfunction is unknown. During the inflammatory process, mast cells are activated and release potent mediators, such as serotonin and histamine. An increased number of mast cells have been found in the bladder mucosa of patients (18). Studies have shown the presence of auto-antibodies in patients although specific ones have not been detected (19). A reduced bladder vascular perfusion has been noted in patients, with a decrease in the microvascular density of the submucosal layer and for this reason hyperbaric oxygen is believed to improve symptoms in affected patients (8, 20).

1.4 *Diagnosis*

IC was traditionally diagnosed according to the NIDDK criteria described in appendix 2 as a clinical condition comprising of patient reported symptoms, cystoscopy findings of glomerulations (pinpoint petechial haemorrhages) and/or Hunner's ulcers and bladder biopsies which would show inflammatory infiltrates and detrusor mastocytosis. Studies have shown poor correlation between cystoscopy findings and

diagnosis as glomerulations may be seen in asymptomatic patients and bladder biopsies may not confirm disease in the presence of glomerulations (8, 21). Cystoscopy was previously used as the 'gold standard' diagnostic tool but in view of these findings glomerulations are no longer considered diagnostic for BPS. While bladder biopsies are important to exclude pathology, for example carcinoma, they are often not performed as routine diagnostic work-up due to poor correlation with disease (22). Recent American guidelines regarding the management of BPS have overcome these diagnostic uncertainties by recommending a symptom-based diagnosis, after exclusion of other confusable diseases, with cystoscopy and hydrodistension performed as an aid in complex presentations (8, 23, 24). It is important to confirm absence of a urinary tract infection. Some of the symptoms of BPS and overactive bladder overlap, for example, the sensation of urinary urgency so a careful history needs to be obtained (25). These recommendations have led to an over-diagnosis of symptom-based disease and under-diagnosis of Hunner's lesions (formerly known as Hunner's ulcers). It is important to identify patients with Hunner's lesions as they do not respond to conservative management and need a different treatment course.

1.5 *Questionnaire tools*

Over the years, several questionnaires have been used as an aid to diagnosing affected patients. The two most commonly used are the O'Leary Sant (OLS) symptom and problem index scores and the Pelvic Pain and Urgency/Frequency (PUF) questionnaire (Appendix 3 and 4). In 1997 O'Leary and Sant created the OLS questionnaire, which was validated on 112 patients, taking into account the duration

of urinary and pain symptoms, and the personal impact of these symptoms on the patient (26). This questionnaire was shown to be a reliable measure of treatment outcome when comparing pre and post-treatment scores (27). In 2002, Parsons devised the PUF questionnaire, which was tested on 382 patients, validated against the outdated potassium sensitivity test (28). Unfortunately, in the PUF questionnaire three out of the eight questions relate to pain and are not specific for urinary symptoms, which cause patients to be assigned high scores. In a prospective study of 97 patients, the PUF questionnaire was not found to be a reliable predictor of disease or disease severity (29). Both questionnaires tend to report a higher prevalence of BPS than confirmed by the clinician, therefore should not be used in isolation as a diagnostic tool (30).

1.6 *Management*

Due to the difficulty diagnosing BPS and the variety of methods used by clinicians, patients have often been subjected to a 'trial and error' approach to treatments with no clear evidence or guidelines regarding the effectiveness of treatment modalities. Through the results of systematic reviews the American Urological Association (AUA) published their guidelines for the diagnosis and management of BPS in 2011. First-line treatments comprise of conservative self-care, behavioural modification (eg pain management and dietary and lifestyle modification) and stress management. Second-line treatments include manual physical therapy (eg physiotherapy with internal vaginal massage), oral and intra-vesical therapies, while cystoscopy with low-pressure hydrodistension is recommended as a third-line treatment option. The fourth-line option is neurostimulation and fifth-line treatments include cyclosporin A and Botulinum toxin A while major surgery is sixth-line (Appendix 5). There are huge

variations in the management of BPS both locally and internationally so it is hoped that these guidelines will standardise diagnosis and treatment. The symptom cluster in BPS makes diagnosis challenging and is associated with high levels of anxiety and sexual dysfunction with low levels of self-esteem and quality of life amongst patients (11, 31).

1.7 *Areas of uncertainty*

There is much uncertainty around BPS from the causative bladder pathology to methods of diagnosis. Although the AUA guidelines have guided clinicians to diagnose patients and commence treatment on symptoms alone, there is still a huge degree of variation in practice across the UK and worldwide. The wide spectrum of symptoms and lack of a 'gold standard' diagnostic test for BPS compounds these difficulties. Discrepancies exist in the different international guidelines over efficacy of treatment and the methods of presenting this information with limited randomised control studies (RCTs) for many treatment options (8, 23). Many of the first-line treatments are conservative, such as stress and pain management and behavioural modifications. These can be patient driven, so disease awareness and patient empowerment are an important part of management.

1.8 *Aims of the Study*

1. To investigate the prevalence of bladder pain syndrome amongst patients with chronic pelvic pain through a systematic review (chapter 2)

2. To assess the information available to patients regarding bladder pain syndrome on the internet through a systematic review (chapter 3)

3. To assess patients and clinicians experiences managing bladder pain syndrome (chapter 4)

4. To evaluate the sensitivity of bladder wall tenderness and bladder filling pain in patients with chronic pelvic pain (chapter 5)

5. To assess the role of laparoscopy and cystoscopy in the diagnosis and management of pelvic and bladder pain (chapter 6)

6. To assess the effectiveness of nerve stimulation in the treatment of pelvic and bladder pain through a systematic review (chapter 7)

7. To assess the relationship between quality of outcomes reported, study quality and journal impact factor in systematic reviews and trials of bladder pain syndrome (chapter 8)

8. To assess the discrepancies in grading of evidence for the management of bladder pain syndrome (chapter 9)

1.9 *Framing the research questions*

Table 2: Structured questions for each chapter of this thesis

Chapter number	**Population**	**Intervention/test**	**Outcome**	**Study design**
2	Women with CPP	Laparoscopy and cystoscopy	Endometriosis BPS Both	Systematic review of observational studies
3	Websites with information about BPS	Quality Readability Accuracy Credibility	Quality assessment of information	Systematic review
4	Patients with BPS	Symptoms Cystoscopy	Diagnostic tests Treatment options	Electronic structured questionnaires
5	Women with CPP	Bladder wall tenderness Bladder filling pain	Diagnosis of BPS	Prospective observational
6	Patients with CPP and/or BPS	Laparoscopy Cystoscopy	Gynaecology pathology Bladder pathology	Literature review
7	Patients with CPP and/or BPS	Sacral nerve stimulation Posterior tibial nerve stimulation	Symptomatic improvement	Systematic review of randomised studies
8	Patients with BPS	Outcome measures for treatments of BPS	Quality of reporting outcomes	Systematic review of systematic reviews
9	Treatment options for BPS	GRADE rating	Discrepancy in quality of evidence score	Literature and quality review of evidence

CHAPTER 2:

PREVALENCE OF BLADDER PAIN SYNDROME AMONGST PATIENTS WITH CHRONIC PELVIC PAIN:

A SYSTEMATIC REVIEW

This chapter focuses on assessing the prevalence of bladder pain syndrome amongst women with chronic pelvic pain (CPP). CPP is multi-factorial and the main gynaecology pathology is endometriosis. I have investigated the co-existence of BPS and endometriosis.

2.1 Abstract

Objectives: To estimate the prevalence of BPS and the co-existence of BPS and endometriosis in women with CPP.

Data sources: The following databases were searched from inception until March 2012: The Cochrane Library, DARE (1997-2012), EMBASE (1980-2012), Medline (1950-2012), PSYCHINFO (1806-2012), Web of knowledge (1900-2012), LILACS (1982-2012) and SIGLE (1990-2012). There were no language restrictions. Bibliographies and conference proceedings of the International Continence Society were manually hand-searched.

Study selection: Observational studies of women suffering from CPP, who underwent a laparoscopy and cystoscopy to investigate their symptoms, were included. Exclusion criteria were pregnancy and a diagnosis of cancer. Study selection, data extraction and quality assessment was performed independently in duplicate. Estimates of prevalence and confidence intervals (CI) were calculated.

Results: There were nine studies (1016 patients) with women with CPP. Quality and diagnostic assessment varied across studies. The mean prevalence of BPS was 61% (range 11-97%, CI 58-64%, I^2 = 98%). The mean prevalence of endometriosis was

70% (range 28-93%, CI 67-73%, I^2 = 93%) and co-existing BPS and endometriosis was 48% (range 16-78%, CI 44-51%, I^2 = 96%).

Conclusion: Almost two thirds of women presenting with CPP have BPS. There are large variations in prevalence, which may be due to variable study selection and quality. We recommend that clinicians actively investigate patients for BPS, a condition that appears to co-exist with endometriosis.

2.2 Background

BPS has an unknown aetiology. The reported prevalence is between 5 and 16 per 100,000 of the population (15, 32). Its prevalence amongst women with CPP is unknown. CPP can be multi-factorial in nature and the co-existence of pathology is not uncommonly found. Conditions such as BPS and endometriosis, described by Chung et al as the 'evil twins syndrome' can make management very difficult (33-35). The 'evil twin syndrome' is not a medical definition but it this name is able to convey the misery of the co-existence of these two chronic pain conditions amongst patients.

The aim of this systematic review was to estimate the prevalence of BPS in women suffering from CPP. The secondary objective was to estimate the prevalence of endometriosis and the co-existence of BPS and endometriosis within this group of women.

2.3 Methods

Our systematic review was prospectively conducted and reported in accordance with the PRISMA statement (36).

Data sources

Searches through the following databases from inception until March 2012 were performed: The Cochrane Library, DARE (1997-2012), EMBASE (1980-2012), Medline (1950-2012), PSYCHINFO (1806-2012), Web of knowledge (1900-2012)

and LILACS (1982-2012). Grey literature was searched through SIGLE (1990-2012) and there were no language restrictions imposed.

Search strategy

Medical subject headings (MeSH) and keywords for 'chronic pelvic pain' and 'chronic pain' were combined using the Boolean operator 'and' with the terms 'interstitial cystitis' or 'painful bladder syndrome' or 'bladder pain syndrome' or 'urinary frequency' or 'urinary urgency'. The search criteria was restricted to those studies involving female patients. Bibliographies from relevant articles and conference proceedings of the International Continence Society were manually hand-searched in order to identify articles not electronically cited because prevalence studies are not well indexed in database searches.

Study selection

Relevant observational studies on CPP were identified which met the following eligibility criteria:

Participants

Women suffering from chronic pelvic pain with, or without, urinary symptoms suggestive of IC, PBS or BPS, who underwent a laparoscopy and cystoscopy to investigate their symptoms, were included. Exclusion criteria were pregnancy, a woman suffering from cancer and patients diagnosed solely on intravesical potassium sensitivity test (PST). CPP was defined according to the Royal College of Obstetricians and Gynaecologists of the United Kingdom (RCOG), as an intermittent

or constant pain in the lower abdomen or pelvis of at least 6 months duration that is not exclusively associated with menstruation, intercourse or pregnancy (37).

Outcome

As most of the studies were performed prior to the introduction of the BPS nomenclature, for the purpose of this review all those with IC were considered to have a symptom based diagnosis of BPS, as this would logically happen under the new disease classification. BPS was defined according to the NIDDK criteria with glomerulations on cystoscopy or a classic Hunner's ulcer, and either pain associated with the bladder or urinary urgency. Glomerulations are punctuate petechial hemorrhages on the bladder wall which were diagnosed after two minutes of bladder distension under anaesthesia (2). At least ten glomerulations were needed in at least three quadrants of the bladder in order to diagnose BPS (4).

Study selection

Cross-sectional studies were included, which are neither prospective nor retrospective but measure the given condition at one point in time, as well as cohort studies, which provide prevalence figures from the baseline data collection phase.

Data extraction and quality assessment

The data were extracted independently in duplicate by two reviewers (SAT, KK). Patient characteristics (number of participants, age and ethnicity), study details (study design, location, setting, and participant recruitment as part of the study quality assessment to assess possible selection bias) and outcomes assessed (diagnostic tools

and rates of BPS, endometriosis and co-existing pathology) were collected on a pre-designed data extraction form.

Quality assessment was performed by one reviewer and checked by a second reviewer in order to assess the overall quality of the studies used in this systematic review. There were no language restrictions so studies not published in English were translated by individuals with command of the relevant language (38). Data from one study was extracted from a conference abstract where the full article could not be obtained (39). Quality assessment was performed using a checklist to evaluate internal validity using the following characteristics (40) (41): (a) Study design to determine if BPS assessment had been performed prospectively to minimise recall bias; (b) Adequacy of sampling by assessing whether participant recruitment was random or consecutive; (c) Sufficiently high response rate (>80%); (d) Use of diagnostic criteria to diagnose BPS to ensure participants response rates are a true representation of the underlying condition; (e) Sample size calculation so as to ascertain prevalence reliably. An study that complied with 3/5 quality criteria was considered 'high quality' (42). External validity was considered separately as the representativeness of the sample for the general population (source of sample) (35).

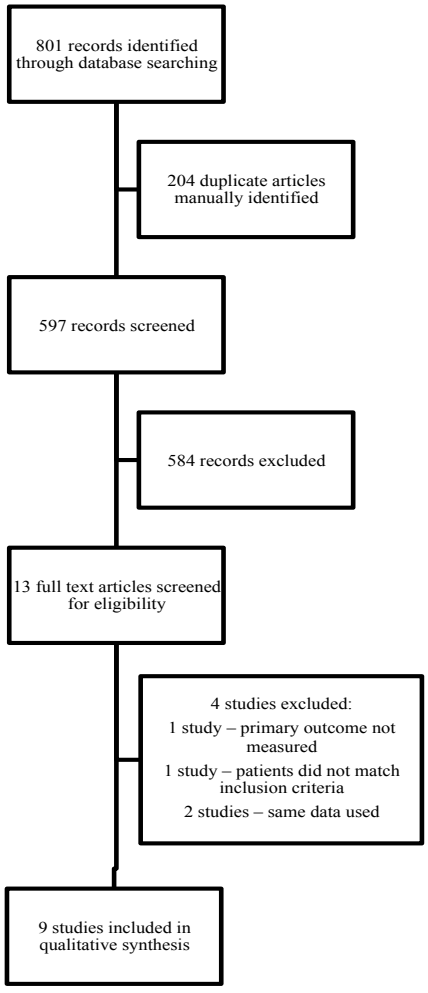
Data synthesis

The prevalence and 95% confidence interval (CI) was calculated for each study, along with heterogeniety which was assessed using I^2 using the Metadisc statistical software package (43). Individual studies could not be combined as they were too heterogenous so pooled results were given for information only. Results with $I^2 > 50\%$ are considered highly heterogenous.

2.4 Results

801 citations were identified (figure 1). 597 citations were found after all duplicate citations were removed and 13 of these were deemed relevant and their full papers were retrieved. Four studies had to be excluded for the following reasons: in one study only the secondary outcome of co-existing BPS and endometriosis was measured, one had the presenting condition of BPS rather than CPP and in two studies the same patient population was reported, and this was confirmed by the corresponding author. This systematic review included nine studies (21, 34, 38, 39, 44-48).

Figure 1: A flow chart to represent the study selection for the prevalence of bladder pain syndrome amongst women with chronic pelvic pain.



Study characteristics

The nine observational studies included 1016 patients. These studies were performed between 1990 to 2011. Table three summarises the study characteristics.

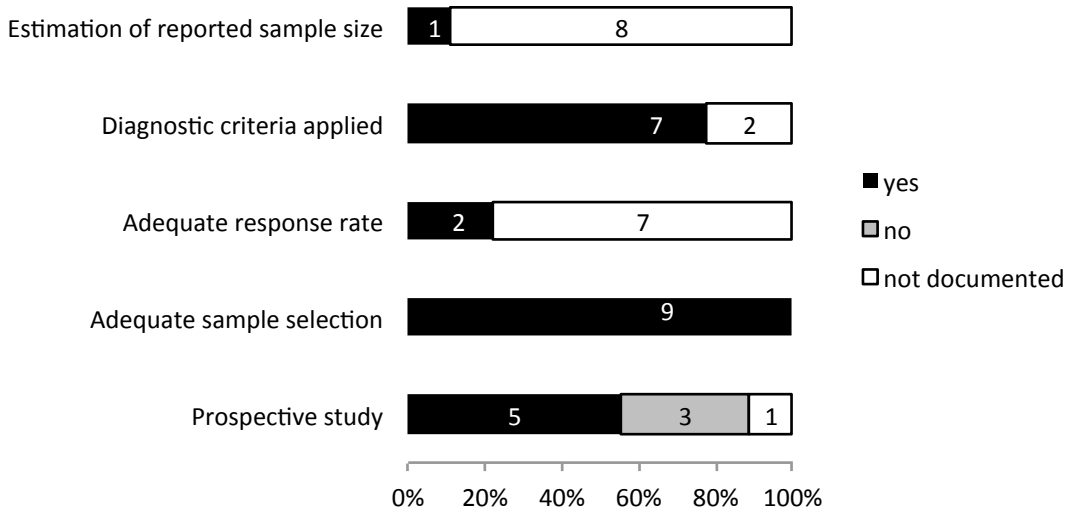
Table 3: Study characteristics for papers included in the systematic review of bladdder pain syndrome and endometriosis.

Study	Country	Mean age in years (age range)	Ethnicity	Number of patients	Duration of study (months)	Source of recruitment
Cheng 2012	Australia	30	Not documented	150	29	Specialist clinic
Chung 2002	USA	19-62	Not documented	60	12	Specialist clinic
Chung 2005	USA	18-60	Not documented	178	24	Specialist clinic
Clemons 2002	USA	35.2 (20-53)	73% Caucasian, 16% Hispanic, 2% African-American, 9% other	45	7	Operating list
Paulson 2011	USA	Not documented	Not documented	284	72	Operating list
Rackow 2009	USA	13-25	96% Caucasian, 4% African-American	28	168	Operating list
Shahmohamady 2005	USA	36 (20-60)	Not documented	92	Not documented	Specialist clinic
Stanford 2005	USA	32.7	Not documented	64	12	Community gynaecology clinic
Villegas 2011	Columbia	32.6 (17-53)	Not documented	115	26	Specialist clinic

All the studies diagnosed BPS using the NIDDK criteria, despite variations in the disease nomenclature. Between 11% (48) to 97% (34) of patients were diagnosed with BPS, with a mean prevalence of 61% (58-64%). Assessing study design, five studies were prospective. Sample size calculations were performed in one study, using Piface software (17). The lack of reporting on whether participants were randomly or purposefully recruited, made assessing external validity difficult. However, in three studies retrospective recruitment of women was performed from theatre operating

lists. Figure two shows quality assessment for all included studies with seven considered 'high quality'.

Figure 2: Quality assessment of included studies



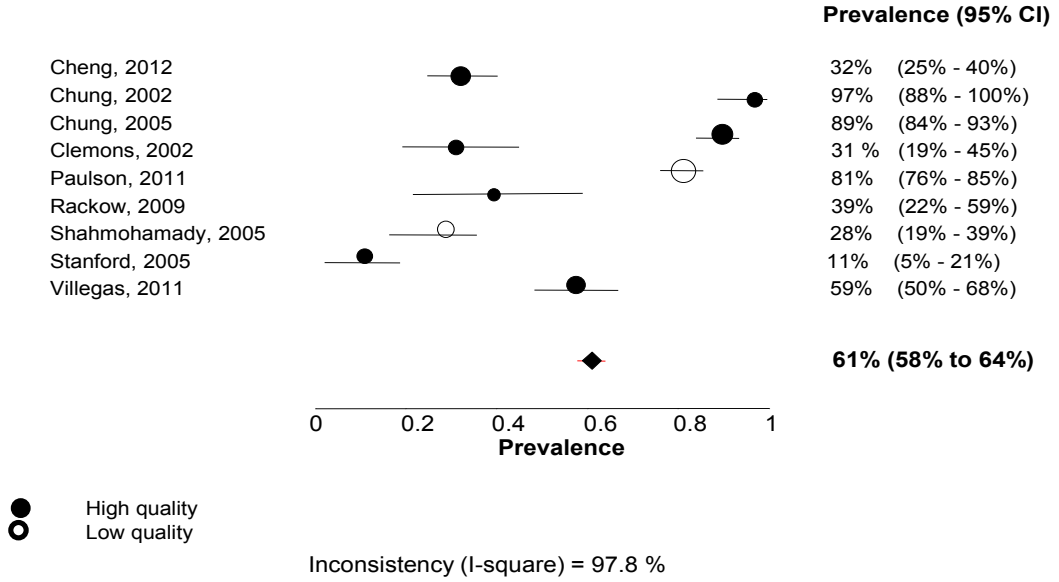
One study reported that routine bladder biopsies were only performed when glomerulations were noted at cystoscopy (21). 44% of patients had normal histopathology results. There were two studies in which bladder biopsies were performed; one to rule out carcinoma and another where no cause was identified during cystoscopy.

All nine studies reported the prevalence of endometriosis. This ranged from 28% (48) to 93% (34), with a mean prevalence of 70% (CI 67-73%) (Figure three). Endometriosis was diagnosed by visual inspection on laparoscopy with confirmatory biopsies performed in 3 studies (33, 34, 48). Two studies reported that biopsies were taken to confirm diagnosis where possible (21, 46). Seven studies documented the co-

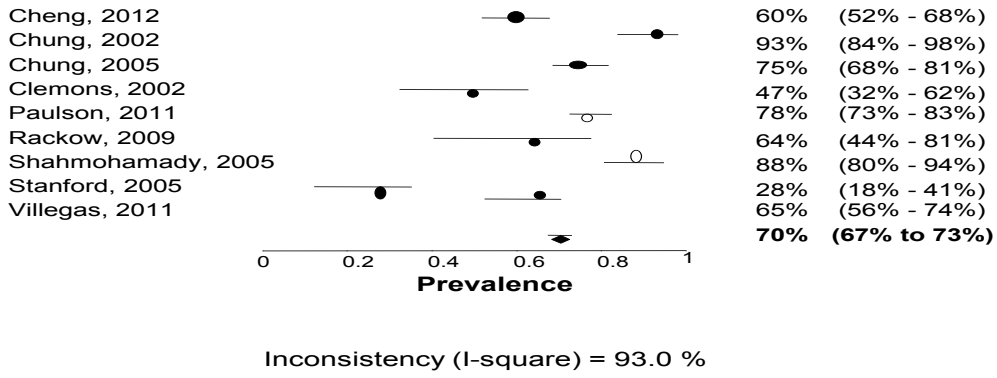
existence of pathology. This ranged from 16% (49) to 78% (34), with a mean prevalence of 48% (CI 44-51%) (Figure three).

Figure 3: Prevalences of bladder pain syndrome (BPS), endometriosis and co-existing BPS and endometriosis amongst women with chronic pelvic pain (CPP).

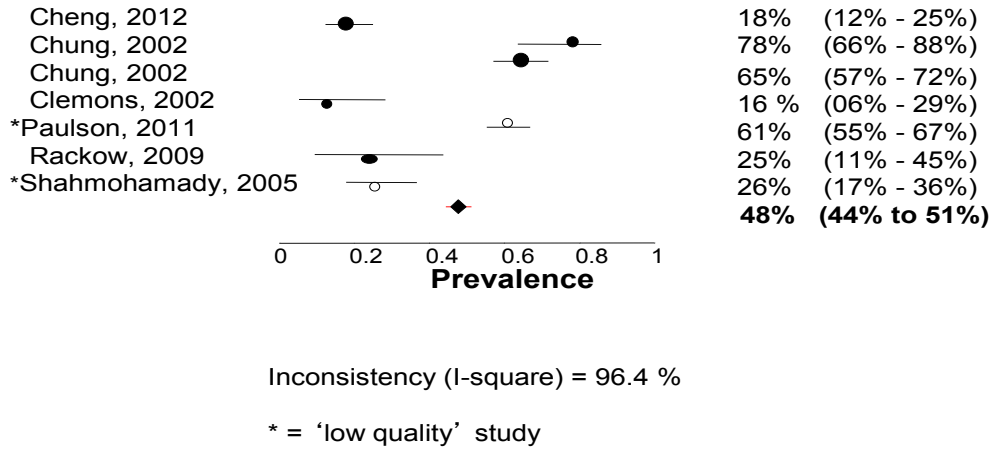
3a: Prevalence of BPS amongst women with CPP



3b: Prevalence of endometriosis amongst women with CPP



3c: Prevalence of BPS and endometriosis amongst women with CPP



In five (45%) studies the affected patient group was identified through their symptoms and clinical examination. In the other four studies (44%) validated questionnaires were used; one used the IC symptom index problem index (O'Leary Sant questionnaire, OLS) which correlated with the diagnosis of BPS in 94% of patients, two used the pelvic pain urgency/frequency (PUF) questionnaire, showing higher PUF scores in the BPS patients, and one used both questionnaires to assess the degree of BPS, showing higher scores in the BPS patients (mean PUF score of 8.6 and OLS score of 7.5) (21). Three studies (33%) used the visual analogue scale questionnaire to assess pain. The mean pain score for CPP ranged from 5.3 - 8, and 5.4 – 7 for BPS (21, 46, 49).

2.5 Conclusion

The literature reports a range of prevalence rates for BPS. There is large variation in rates which may be explained by variable study quality and sample selection. Patients recruited from specialist clinics and operating lists had the highest prevalence of BPS. In four out nine studies, patients suffered from CPP and urinary symptoms and some

of the highest prevalences of BPS (33, 34, 39, 46, 50). 67% (n=6) of studies had an authorship team with a special interest in urogynaecology.

This systematic review was performed in accordance with PRISMA (appendix 6), with comprehensive data searches, selection of studies and duplicate data extraction, and appropriate synthesis of results. This chapter highlights the fact that almost two thirds of patients presenting with CPP have BPS. The diagnosis was made by the presence of urinary symptoms and positive cystoscopy findings in all included studies. However, as previously discussed, cystoscopic normality and bladder lesions are poorly correlated with histopathology, which is a limitation to disease classification (23), leading to the possibility of misdiagnosing patients. Commonly used questionnaires like OLS and PUF do not record symptoms such as bladder pain or bladder filling pain and the clinical value of such questionnaires as a diagnostic tool is debatable (51). The included studies had limited information about ethnicity, although literature shows that the prevalence of BPS does not vary with ethnicity but minority women appear to be symptomatic for longer than Caucasian women. However, the prevalence of endometriosis appears to be higher in Asian women than other ethnicities (52-54).

The clinical presentation of BPS is similar to many other urinary conditions, making diagnosis challenging and can lead to delays in treatment. BPS is associated with chronic non-urological conditions, such as fibromyalgia, irritable bowel syndrome, vulvodynia and pelvic floor dysfunction, highlighting the importance of multi-disciplinary care (55, 56). The introduction of the American Urological Association guidelines for the diagnosis and management of IC and BPS in 2011 recommends that

cystoscopy only used as a diagnostic tool in complex presentations. Thus allowing initiation of conservative treatments, such as pain relief, behavioural modification and stress management (23). Clinicians need to be aware of the existence of co-existing pathology and actively investigate urinary symptoms and BPS as a cause of CPP, allowing treatments to be initiated early.

This chapter is based on the following peer-reviewed publication (57):

The 'evil twin syndrome' in chronic pelvic pain: a systematic review of the prevalence studies of bladder pain syndrome and endometriosis.

SA Tirlapur, K Kuhrt, C Chaliha, E Ball, C Meads, KS Khan

Int J Surg. 2013 Feb; 233-237

CHAPTER 3:

ASSESSING THE INFORMATION AVAILABLE TO PATIENTS REGARDING BLADDER PAIN SYNDROME ON THE INTERNET: A SYSTEMATIC REVIEW

This chapter discusses how information on the internet can be assessed, specifically looking at the quality of information related to BPS.

3.1 Abstract

Objectives: To assess sources of medical information on bladder pain syndrome available on the internet for quality, accuracy, credibility and readability.

Methods: The meta-search engine Copernic agent was used to perform searches with the terms 'pelvic pain, interstitial cystitis, painful bladder syndrome and bladder pain syndrome'. This meta-search engine captured websites from a range of commonly used search engines. We used English language websites, which were open-access. There were four quality assessments parameters; credibility which was based on a 10-point scale, accuracy that was based on the American Urological Association guidelines, quality which used the DISCERN questionnaire and readability which was evaluated using Flesch reading ease scores. Intra-class coefficient (ICC) was used to test for inter-rater agreement.

Results: We identified eighteen suitable websites; seven (39%) were specific to BPS. There was a wide variation in combined mean scores for the four quality parameters ranging from 83 to 144 for specialist BPS or urology websites and 76 to 137 for general or non-specialist ones. The maximum possible score was 208. We found good inter-observer agreement with an ICC ranging from the highest score of 0.80 for DISCERN to the lowest of 0.53 for readability. Specialty specific websites were found to have higher quality scores with a median difference of 10, p=0.07, and

readability scores had a median difference 5.4, p=0.05, compared to non-specialty websites whereas there was no difference in credibility and accuracy scores.

Conclusion: Four websites were found that fulfilled our criteria for good quality information related to BPS.

3.2 Background

Patients often use the internet as a source of information and for medical advice. It can be a useful tool, allowing patients to share experiences with others, acting as a support network. Unfortunately, the medical information found on the internet can be variable in quality and is often unregulated (58, 59). Conditions such as BPS have a huge impact on a patients quality of life and treatments may not adequately control symptoms, therefore support networks can be a valuable source of education and support (60). In this systematic review we assessed the quality of medical information related to BPS found on the internet.

3.3 Methods

A prospective protocol was registered with the international prospective register of systematic reviews (PROSPERO)(61). This included information about the search strategy, inclusion criteria, methodology and analysis, which was performed in accordance with PRISMA guidelines (62).

Identification of websites

We constructed a list of search terms most commonly used for BPS through the Google search engine. We used the terms 'interstitial cystitis', 'painful bladder syndrome' and 'bladder pain syndrome'. In order to develop a comprehensive search strategy, website links for the first ten websites were evaluated. On 15th November 2012 we performed the search using the meta-search engine Copernic agent. This engine combines several commonly used search engines to remove duplicate results,

store and manage the results obtained (http://www.copernic.com). The following search engines were used: Alta vista, ask.com, bing, blekko, Copernic, dogpile, duck duck go, enhance interactive, exalead, fast search, google, incywincy, lycos, mamma.com, open directory project, yahoo! and yippee, with the search terms 'bladder pain syndrome, interstitial cystitis, painful bladder syndrome, pelvic pain'. Only English language websites were included. Any websites that required a password or were not open access were excluded, as well as citations of scholarly scientific articles.

Data extraction and quality assessment

Two reviewers (SAT, CL) independently assessed information on the websites for four parameters: quality, credibility, accuracy and readability. Credibility was defined as the ability to inspire belief. It was scored on a ten-point criteria scale: source, content, currency, utility, editorial review process, hierarchy of evidence, statement of original source, disclaimer which included ownership, sponsorship, funding and advertising, omissions and a feedback mechanism (63-69). A score of 0 or 1 was assigned to each criterion with 0 for absence and 1 for presence, which gave a score ranging from 0-10. Table 4 describes the criteria for accuracy, which consisted of nine items that were based on the American Urological Association guidelines for the management of BPS (23, 30). Each item was assigned a score 0, 1, 2; 0 if there was absence or incorrect information, 1 if the item was mentioned and 2 if the item was mentioned adequately. This gave a score, which ranged from 0-18.

Table 4: The accuracy criteria used to assess the quality of information about bladder pain syndrome found on the internet (23).

Criteria	Descriptor*
1	Definition: 'Chronic pelvic pain, pressure or discomfort of greater than 6 weeks duration perceived to be related to the urinary bladder accompanied by at least one other urinary symptom in the absence of any identifiable cause'
2	Assessment: history, symptom questionnaire, pain evaluation, physical examination and urine dipstick
3	First line treatment: behavioural (stress management, relaxation, dietary modification, patient education)
4	Second line treatment: physical (pelvic floor biofeedback, soft tissue massage)
5	Oral: analgesia, antihistamine, antidepressants. Intravesical: DMSO (Dimethyl sulfoxide), heparin, lidocaine
6	Cystoscopy with hydrodistension under anaesthesia
7	Neuromodulation: posterior tibial nerve and sacral nerve stimulation
8	Botulinum toxin or cyclosporin
9	Surgical management: Diversion with possible cystectomy

* Each of the 18 websites were evaluated for accuracy using the 9-point scoring system above which was derived from the 2010 American Urological Association guidelines for the diagnosis and management of interstitial cystitis/bladder pain syndrome.

The Flesch Reading Ease and Flesch-Kincaid grade level were used to assess readability. Scores for the Flesch reading ease ranged from 0-100 where the higher the score, the more readable the website. The Flesch-Kincaid grade level scores ranged from 1-12. The target was a score of <8, which meant it could be understood by an 8th grade school child, aged around 13-14 years old (70, 71). In order to calculate readability the text on the first page of the website, which usually gave a summary of the condition, was used. This was done using an online readability

calculator (www.readability-score.com). The DISCERN questionnaire was used to test for quality. This tool analysed the quality of information about treatment choices for any given condition. There are 16 questions which were rated 1- 5; where 1 = no (incorrect response), 3 = partial and 5 = yes (correct response), with the highest achievable score being 80. This DISCERN questionnaire is a validated tool which is used to evaluate consumer health information to critically appraise the information in a standardised manner by assessing the reliability and quality of information (72, 73).

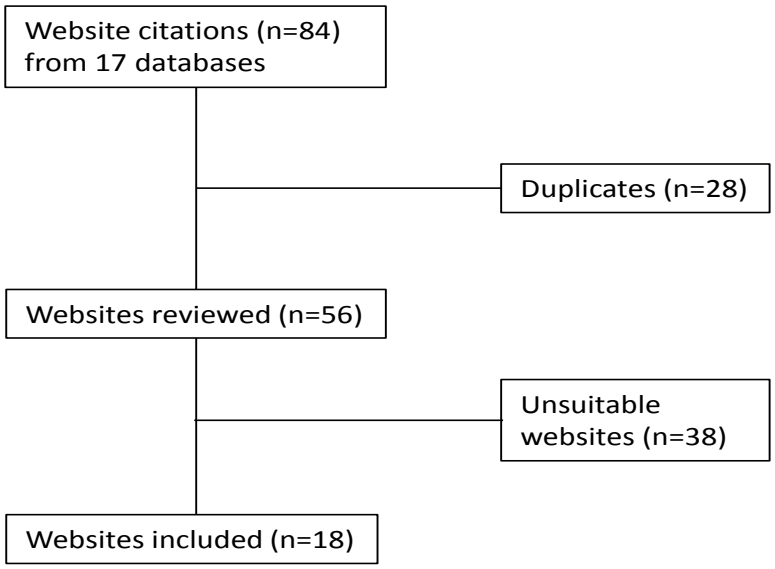
Data analysis

Intra-class co-efficient (ICC) was used to test for agreement between inter-rater reliability of assessments (72). The scoring system for agreement was made in the following manner: less than 0.2 (poor agreement); 0.6 to 0.8 (good agreement); greater than 0.8 (very good agreement) (74). Analysis was performed using the two observers mean scores. The stats direct software package (version 2.7.9) was used to perform the Mann-Whitney U test in order to compare measures for specialty and non-specialty websites. Websites specific to BPS and bladder related conditions were deemed to be specialty websites, compared to non-specialty websites.

3.4 Results

Figure 4 shows that from 84 citations in 17 different databases, 18 websites were identified to be included in this review.

Figure 4: Study selection for assessment of information on the internet related to bladder pain syndrome.



ICC was used to calculate the agreement between the two reviewers assessing the websites. For DISCERN the ICC was 0.75 (95% limits of agreement -14.8 to 21.8), 0.63 for credibility (95% limits of agreement -2.48 to 4.04), 0.80 for accuracy (95% limits of agreement -5.86 to 2.41) and 0.53 for readability (95% limits of agreement = -18.3 to 21.2).

The website characteristics are represented in table 5. There were 12 (67%) websites that were based in America; seven (39%) were specific to BPS/IC; six (33%) websites had a patient forum or participation function and 11 (61%) websites were linked to social media platforms such as Facebook and twitter.

Table 5: A summary of characteristics for the included websites.

Website address	Country	Disease specific	Patient focused	Listed authors	Patient forum	Privacy statement
www.niddk.nih.gov	USA	No	Yes	No	No	Yes
www.wikipedia.org	International	No	No	No	No	Yes
www.essic.eu	International	Yes	No	Yes	No	Yes
www.associatedcontent.com	USA	No	Yes	Yes	No	Yes
www.womenshealth.gov	USA	No	Yes	No	No	Yes
www.webmd.com	USA	No	Yes	No	Yes	Yes
www.painful-bladder.org	International	Yes	Yes	Yes	No	Yes
www.mayoclinic.com	USA	No	Yes	Yes	No	Yes
www.ehow.com	USA	No	Yes	Yes	No	Yes
www.bladderandbowelfoundation.org	UK	Yes	Yes	No	Yes	Yes
www.medicinenet.com	USA	No	Yes	Yes	Yes	Yes
www.ichelp.org	USA	Yes	Yes	Yes	No	Yes
my.clevelandclinic.org	USA	No	Yes	No	No	Yes
www.ic-network.com	USA	Yes	Yes	Yes	Yes	Yes
www.localhealth.com	USA	No	Yes	Yes	Yes	Yes
www.intelihealth.com	USA	No	Yes	Yes	No	Yes
www.cobfoundation.org	UK	Yes	Yes	Yes	Yes	Yes
www.urologyhealth.org	UK	Yes	Yes	Yes	No	Yes

Table 6: A summary of the outcome measures used to assess the included studies on bladder pain syndrome.

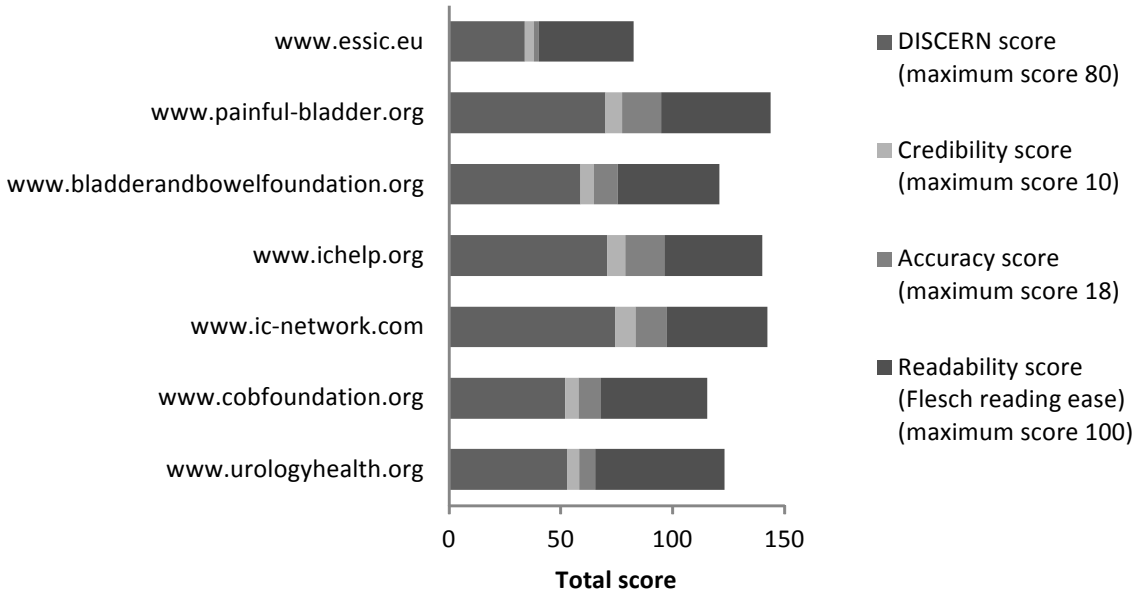
Website address	DISCERN*		Accuracy*		Credibility*		Readability*	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
www.niddk.nih.gov	68.5	0.5	12.0	0	8.0	1.0	48.2	1.75
Wikipedia.org	53.2	5.0	17.0	0	2.0	0	31.7	0.35
www.essic.eu	34.0	8.0	2.5	0.5	4.0	2.0	42.3	11.0
www.associatedcontent.com	27.5	2.5	5.0	1.0	3.5	0.25	40.2	3.55
www.womenshealth.gov	55.0	3.0	10.5	0.5	6.5	0.5	69.1	0.05
www.webmd.com	46.5	0.5	10.5	2.5	5.5	1.5	56.3	1.0
www.painful-bladder.org	70.0	4.0	17.5	0.5	7.5	0.5	48.9	8.95
www.mayoclinic.com	63.5	11.5	15.0	0	7.0	0	3.2	0.8
www.ehow.com	40.5	4.5	8.0	1.0	3.0	0	44.2	0.6
www.bladderandbowelfoundation.org	59.0	3.0	10.5	0.5	6.0	1.0	45.6	1.25
www.medicinenet.com	61.0	2.0	11.5	3.5	8.0	0	32.8	4.3
www.ichelp.org	71.0	7.0	17.5	0.5	8.0	1.0	43.7	9.8
my.clevelandclinic.org	40.0	4.0	8.0	1.0	4.5	0.5	35.5	2.65
www.ic-network.com	74.5	4.5	14.0	0	9.0	0	45.0	6.2
www.localhealth.com	45.0	2.0	10.5	1.5	7.0	0	37.5	7.85
www.intelihealth.com	43.5	2.5	8.5	1.5	7.0	0	39.6	0.6
www.cobfoundation.org	52.0	3.0	10.0	2.0	6.0	2.0	47.4	0.6
www.urologyhealth.org	53.0	6.0	7.0	1.0	5.5	0.5	57.8	0

*DISCERN tool for quality assessment (maximum score 80), accuracy assessment based on American Urological Association 2011 guidelines (maximum score 18), credibility based on10 criteria (maximum score 10) and readability using the Flesch reading ease assessment (maximum score 100).

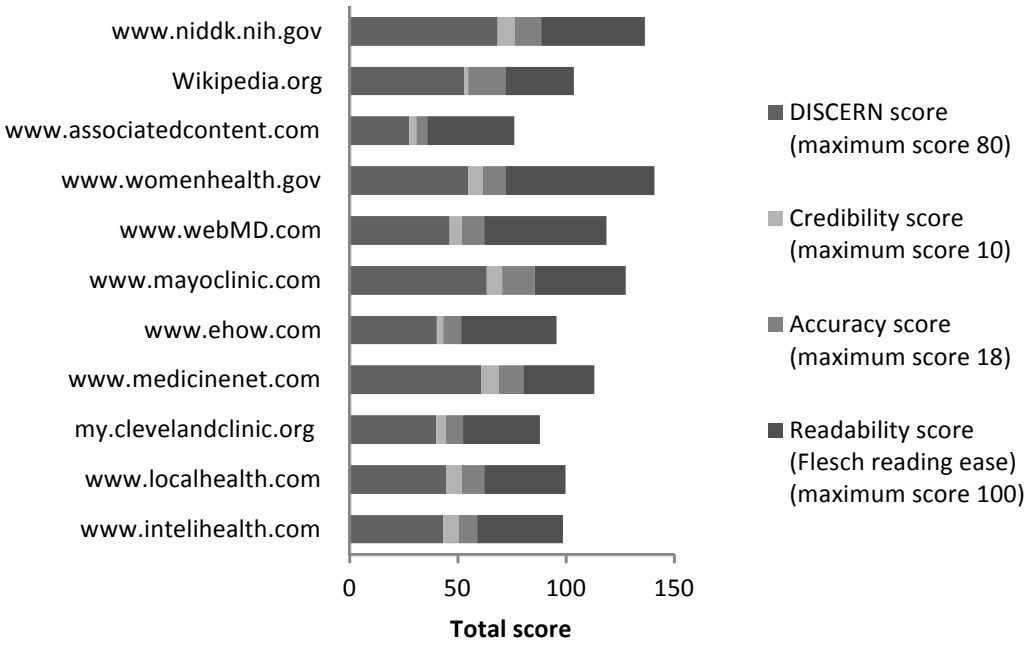
The quality outcome measures for the included websites are summarised in table 6 and figure 5.

Figure 5: Graphical summary of the outcome measures for the included websites.

5a: Websites specific to bladder pain syndrome



5b: Websites not specific to bladder pain syndrome



Total mean scores were calculated for the following criteria: DISCERN had a mean score of 60 (maximum score 80), accuracy had a mean score of 11 (maximum score 18), credibility had a mean score of 6 (maximum score 10) and readability had a mean score of 45 (maximum score 100). Readability scores were lower than other outcome measures. The complexity of medical terminology used by many websites may account for this as it did not make the website pages easy to read for the general public. Several websites performed well with high combined quality scores, which may have been due to their high readability scores. The readability of a website is important but general quality, accuracy and credibility measures are also necessary when providing information for patients. In this systematic review I found the best information was provided by the following websites: www.ic-network.com, www.ichelp.org, www.painful-bladder.org, www.niddk.nih.gov, of which three were specific to BPS. It was noted that specialty-specific websites tended to have higher DISCERN score (median difference 10, p=0.07) and readability scores (median difference 5.4, p=0.05) with no difference in credibility (median difference = 1, p= 0.22) and accuracy scores (median difference = 0.5, p=0.40) compared to non-specialist websites.

3.5 Conclusion

This appears to be the first formal publication assessing the information available on the internet related to BPS. It was a robust review of all identified websites associated with BPS and IC. There were four websites identified as easy to navigate, which performed well across the outcome measurements of accuracy, quality, credibility and readability that could be recommended to patients as useful sources of information. Good inter-rater agreement was recorded for DISCERN and credibility with very good agreement for accuracy. We had to

exclude websites that were not written in English or where a translation tool was unavailable, which was a weakness of this review.

Chronic pain syndromes like BPS, greatly impact on a patient's quality of life and their interactions with family members so it is important, that as clinicians, we can empower patients to better understand their conditions in order to improve disease awareness and self-management (75). There are guidelines for the postings on websites developed by the American Medical Association but their usefulness is extremely variable. For this reason it is important that clinicians enquire about the source and type of information patients receive from the internet in order to clarify any inaccuracies (65, 76-78).

Self-help and conservative lifestyle modifications can have a beneficial effect on patients symptoms (79). Social media and the internet can help patients contact other sufferers, acting as a support system, as well as a constant source of information and communication. Clinicians should be aware of the valuable resource these websites can provide and recommend the good ones as an educational and support aid (80).

This chapter is based on the following peer-reviewed publication (81):

Quality of information on the internet related to bladder pain syndrome: a systematic review of the evidence

SA Tirlapur, C Leiu, KS Khan

Int J Urogyn. 2013 Aug;24(8):1257-62

CHAPTER 4:

ASSESSING PATIENTS AND CLINICIANS EXPERIENCES MANAGING BLADDER PAIN SYNDROME AND THEIR PRIOR BELIEFS ON POSTERIOR TIBIAL NERVE STIMULATION

In this chapter I explore the attitudes of urogynaecologists based in the UK towards diagnosing and treating BPS, as well as evaluating their thoughts on the value of PTNS as a therapy. I investigate patient experiences in order to compare them to clinician's ideas to allow assessment of current practice.

4.1 Abstract

Background: The management of BPS varies throughout the UK with no current national guidance. This variation is reflected in the patient's experience, often with delays in diagnosis and initiation of treatments.

Objectives: To determine current practice regarding diagnosis and management of bladder pain syndrome (BPS) and assessment of prior beliefs on the effectiveness of percutaneous tibial nerve stimulation (PTNS) through a prospective electronic questionnaire based survey of patients and clinicians.

Methods: A patient questionnaire was posted on three international patient support groups. The clinician survey was sent to all members on the British Society of Urogynaecology (BSUG) database. Methods of diagnosis, treatment options, opinions and prior beliefs on neuromodulation and useful internet sources were assessed, along with patient and clinician characteristics.

Results: The survey questionnaire was completed by 133 patients and 69 clinicians. The main patient-reported symptom was pain when the bladder was full in 80% (n=107) with the

most bothersome symptom of pelvic pain in (22%, n= 29) of women. 93% (n=64) of clinicians relied on making their diagnosis by history and cystoscopy. 78% (n=54) of clinicians reported to use amitriptyline as a treatment option and 75% (n=52) used dietary modification. 77% (n=102) of patients reported using simple analgesia as a treatment, 74% (n=98) dietary modification and 62% (n=83) low-dose long-term antibiotics. 46% of clinicians were unsure whether PTNS was beneficial, but thought it was not harmful, while 16% of patients were unsure whether PTNS was harmful or beneficial.

Conclusion: This survey showed that there appears to be no obvious consensus in the management of BPS with wide variation in diagnostic methods and treatments used by clinicians and experienced by patients. There is a need for national guidance in order to standardise care.

4.2 Introduction

BPS is a diagnosis of exclusion, usually derived after ruling out other possible disease processes, which leads to challenges in the diagnosis and management of the condition (7). From clinical experience and observation, I noticed an apparent variation in clinician's approaches to managing this condition, which is hampered by the fact there are currently no national guidelines in the United Kingdom to standardise practice. The American Urological Association (AUA) guidelines of 2011 (23) may have helped stream-line management as this has encouraged clinicians to employ a symptom based diagnosis and commence treatment without waiting for a definite diagnosis, but this is often very hard to achieve.

When a condition has imprecise clinical characterisation and its aetiology is poorly understood, it can be insightful to gain an understanding of the patient's experience in the diagnosis and methods of treatment undertaken, along with appreciating the clinician's individual beliefs and therapeutic preferences. In these situations, surveys can provide up to date information about current ideas and practice, which can help identify areas in need of improvements (82).

Neuromodulation or nerve stimulation, for example percutaneous tibial nerve stimulation (PTNS), is used as a fourth-line treatment for BPS, which may be considered when other therapies have failed to offer symptomatic relief (23). There appears to be limited data on treatment effectiveness, and the observational studies present have low strength of evidence, with no randomised trials comparing PTNS and placebo (81, 83). As an individual, our prior beliefs in treatment effectiveness may often be guided by colleague's experiences, study results and personal experience or perceived assumptions. While it is possible to alter these

beliefs with the results from new evidence, it can be difficult to have a 'degree of confidence' in certain treatments where uncertainty about its effectiveness exists. (84).

The aim of this study was to determine current practice regarding diagnosis and management of BPS through patient and clinician surveys. I also explored the prior beliefs of patients and clinicians on the effectiveness of PTNS as a possible treatment for BPS. In chapter 7, I explore the evidence for the effectiveness of PTNS in the treatment of BPS. It is a treatment modality not often used in the UK and rarely used for this condition, hence my interest in patients and clinicians experiences of it.

4.3 Methodology

The patient based questionnaire was posted as an online *SurveyMonkey*® survey on the websites of two UK based patient support groups; the pelvic pain network since one of the main symptoms of BPS is pelvic pain (http://www.pelvicpain.org.uk/) and the cystitis and overactive bladder foundation who support patients with cystitis, bladder pain syndrome and overactive active bladder (http://www.cobfoundation.org/), between December 2012 to November 2013, and the International Painful Bladder Foundation (www.painful-bladder.org) in October 2013. Patients who suffer from symptoms suggestive of BPS were invited to participate in this survey via these three websites.

The authors and institute involved in the survey were kept anonymous from the participants. The questionnaires explored patient's disease symptoms, the investigations they had been exposed to and the treatments offered, where more than one option was possible, as many patients will have tried several therapies over the years. In recent years, the use of the internet

and social media as a source of information and support for patients and their families has been recognised. In order to assess this, the survey specifically asked patients about their use of the internet as a source of information and support.

In order to establish the most useful questions, I created the clinician survey and piloted it on a small group of gynaecology and urogynaecology consultants and trainees to allow me to refine the research questions (85). Once modified these questions were reviewed by the audit committee for the British Society of Urogynaecology (BSUG). After approval, they were sent to all members on their database. The clinician survey assessed the grade and specialty of the clinician along with methods of diagnosing and managing BPS. I wanted to establish individual clinicians opinions on the value or usefulness of two simple tests for BPS; bladder filling pain and bladder wall tenderness, which are further assessed in chapter 5. These opinions were collected using a 10-point likert scale, ranging from 1 (not useful) to 10 (useful), with responses greater than an arbitrary level of five indicating value in the test; and five and below indicating no value in the test.

In order to explore clinician's prior beliefs on the effectiveness of percutaneous tibial nerve stimulation (PTNS) a structured question was formulated (86). The same question was asked to patients in order to assess their prior beliefs with graphical representation of responses. Further questions about PTNS and assessment on patient's willingness to participate in a study with this treatment were evaluated.

4.4 Results

Patient survey

There were 133 participants in the patient survey. The denominator could not be calculated, as the survey was not sent to individual patients. The survey was posted on the three support group's websites, allowing patients with BPS to participate. The data are summarised in table 7.

Table 7: Patient survey results for the management of bladder pain syndrome (BPS)

	Number (n= 133)	%
1. Do you suffer from any of the following symptoms?		
o Lower abdominal/pelvic pain	103	77%
o Pain when your bladder is full	107	80%
o Pain on passing urine	73	55%
o Loin pain	41	31%
o Partial relief on passing urine	71	53%
o Iliac fossa pain	13	10%
o Pain radiation to genitals	49	37%
o Pain after passing urine	62	47%
o Urethral pain	77	58%
o Pain radiation to legs	35	26%
o Full relief on passing urine	18	14%
o No relief on passing urine	27	20%
o Nocturia (waking up more than once at night to pass urine)	92	69%
o Increased frequency (passing urine more than usual)	102	77%
o Urinary urgency (the sensation of incontinence if unable to urinate in time)	66	50%
o Incomplete voiding (the feeling of incompletely emptying your bladder when you urinate)	79	59%
2. Which symptoms do you find most problematic?		
o Lower abdominal/pelvic pain	29	22%
o Pain when your bladder is full	15	11%
o Pain on passing urine	4	3.0%
o Loin pain	1	0.8%
o Partial relief on passing urine	3	2.2%
o Iliac fossa pain	0	0.0%
o Pain radiation to genitals	4	3.0%
o Pain after passing urine	6	4.5%
o Urethral pain	18	14%
o Pain radiation to legs	1	0.8%
o Full relief on passing urine	0	0.0%
o No relief on passing urine	3	2.2%
o Nocturia (waking up more than once at night to pass urine)	9	6.8%
o Increased frequency (passing urine more than usual)	23	17%
o Urinary urgency (the sensation of incontinence if unable to urinate in time)	12	9.0%
o Incomplete voiding (the feeling of incompletely emptying your bladder when you urinate)	6	4.5%
3. Which of the following investigations were used to diagnose your BPS?		
o Symptoms alone	32	24%
o Symptoms and cystoscopy	19	14%

o	Symptoms, cystoscopy and bladder biopsy	35	26%
o	Symptoms, cystoscopy and hydrodistension	20	15%
o	Symptoms, cystoscopy, hydrodistension and bladder biopsy	35	26%
o	Cystoscopy alone	1	0.8%
o	Cystoscopy and bladder biopsies	0	0.0%
o	Cystoscopy with hydrodistension	3	2.2%
o	Cystoscopy with hydrodistension and bladder biopsies	2	1.5%

4. Which of the following treatments have you used?

o	Behavioural modification eg timed voids, decrease fluid intake	49	37%
o	Physical therapy eg pelvic floor biofeedback, soft tissue massage	28	21%
o	Stress reduction	37	28%
o	Dietary modification (avoiding caffeine, acidic foods)	99	74%
o	Simple analgesia	103	77%
o	Low-term, low-dose antibiotics	82	62%
o	Antidepressants eg. Oral amitriptyline	55	41%
o	Antihistamines eg. Oral cimetidine	47	35%
o	Immunosuppressants eg. Oral cyclosporine	6	4.5%
o	Intravesical glycoaminoglycans	5	3.8%
o	Intravesical dimethyl sulfoxide (DMSO)	20	15%
o	Intravesical hyaluronic acid	22	17%
o	Anticholinergics eg. Intravesical oxybutynin	10	7.5%
o	Botulinum toxin under cystoscopic guidance	3	2.3%
o	Cystoscopic hydrodistension	66	50%

5. Have you ever tried to obtain information about BPS on the internet?

o	Yes	91	68%
o	No	42	32%

6. Have you found any good websites that you would recommend to other patients?

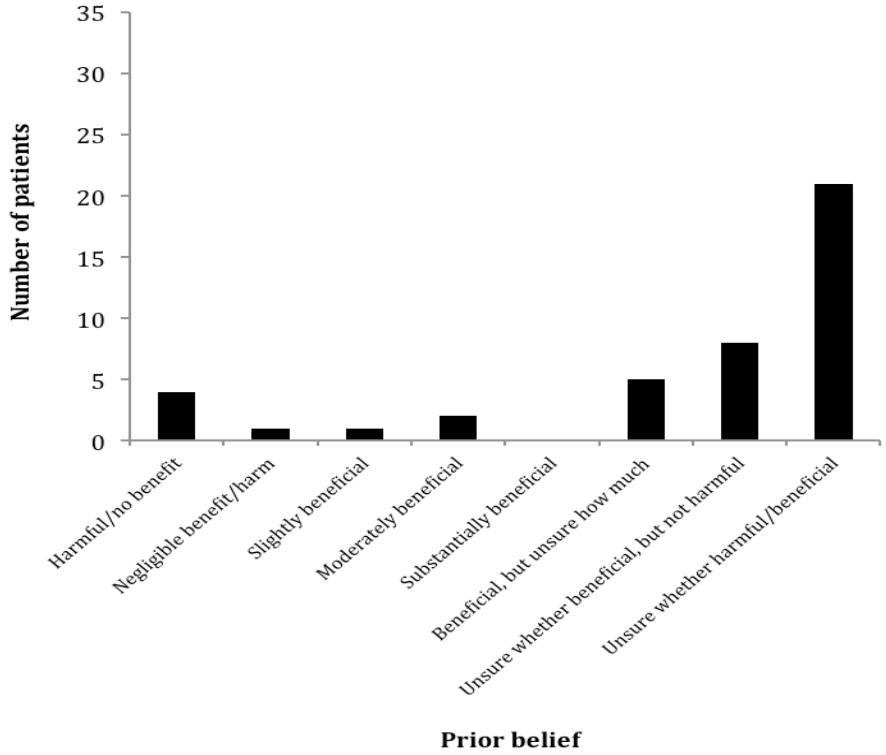
o	Yes	70	53%
o	No	63	47%

The patient's main symptom complaints were pain when the bladder is full (80%, n=107), lower abdominal/pelvic pain (77%, n= 103), and increased urinary frequency (77%, n= 102). The symptoms that caused the most bother were lower abdominal pain (21%, n=29) and nocturia (17%, n=23). In order to investigate their symptoms 26% (n=35) of patients were diagnosed by symptoms, cystoscopy and bladder biopsies, with or without hydrodistension. The most popular reported therapies included simple analgesia (77%, n= 103), dietary modifications (74%, n=99) and low dose long-term antibiotics (62%, n=82).

On enquiring about the internet as a source of information, 68% (n = 90) of patients reported that they had tried to obtain information about BPS on the internet, while 53% (n = 71) felt there were useful websites that they would recommend to other sufferers.

29% (n = 39) of patients had previously heard of PTNS and 0.8% (n = 1) of patients had previously used it. Figure 6 graphically represents patient's prior beliefs on the effectiveness of PTNS to treat refractory BPS with 16% (n = 21) unsure whether the treatment is beneficial or harmful. 65% (n = 86) expressed their interest in participating in a clinical trial to evaluate the effectiveness of PTNS in the treatment of refractory BPS.

Figure 6: Graphical elicitation on the patient beliefs of the effectiveness of percutaneous tibial nerve stimulation (PTNS).



Clinician survey

There were 69 clinicians who responded to this survey (17%, n= 399; 302 consultants and 97 trainees), 75% (n= 52) of whom were urogynaecologists and 88% (n= 61) were consultant grade. Table 8 summarises the clinician's responses. The clinicians were well spread across the UK with 15% from both London and East of England. 93% (n = 64) of clinicians claimed to diagnose BPS by symptoms and cystoscopy, compared to only 12% (n = 8) who diagnosed the condition by symptoms alone and 48% (n = 33) of them used cystoscopy and bladder biopsies as a diagnostic tool. When assessing bladder filling pain as a diagnostic test, 81% (n = 56) of clinicians rated this as useful while 26% (n = 18) of them gave a score of 8/10 for its usefulness. When the sign of bladder wall tenderness was assessed, 52% (n = 36) of clinicians rated it as a useful test and 16% (n = 11) of them gave a usefulness score 6/10 and

7/10. The most commonly used treatment were antidepressants, such as amitriptyline (78%) and dietary modification (75%) but all treatment options had been tried by at least one clinician.

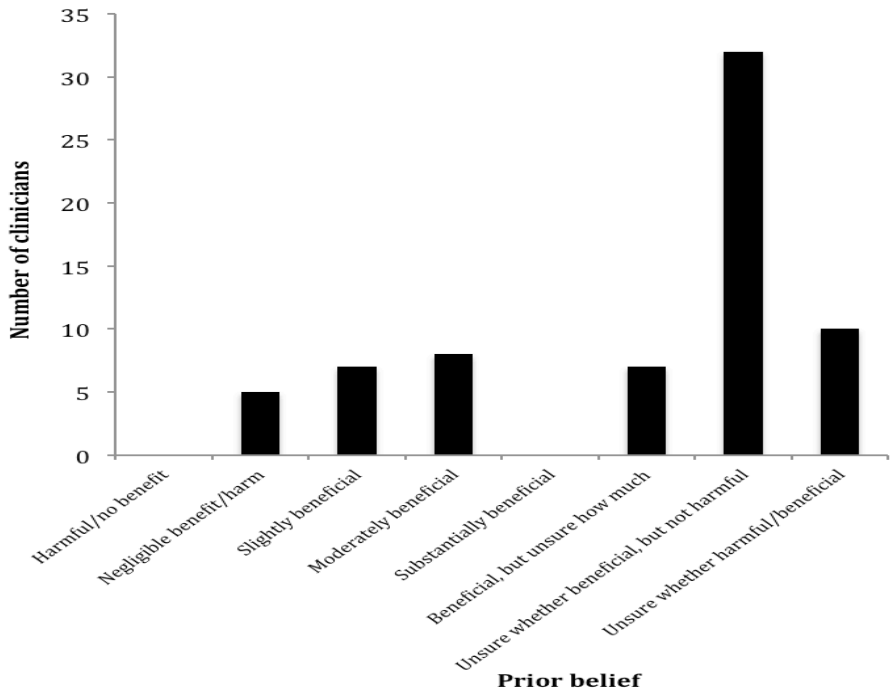
Table 8: Clinician survey results for the management of bladder pain syndrome (BPS)

		Number (n =69)	%
1.	What is your specialty? (please tick as appropriate)		
	o Urogynaecology	52	75 %
	o Urology	1	1.4 %
	o General gynaecology	16	23%
	o Other – eg. Special interest in urogynaecology	3	4.3 %
2.	What is your level of experience?		
	o Consultant	61	88 %
	o Associate specialist	1	1.4 %
	o Staff grade	2	2.9 %
	o Subspecialty trainee	0	0 %
	o Registrar	5	7.2 %
3.	Which of the following investigations do you use to diagnose BPS?		
	o Symptoms alone	8	12 %
	o Symptoms and cystoscopy	64	93 %
4.	If cystoscopy is used, please state how diagnosis is made:		
	o Cystoscopy alone	36	52 %
	o Cystoscopy and bladder biopsy	33	48 %
5.	Do you feel the symptom of ‘bladder filling pain’ is useful in making a diagnosis of BPS?		
	o Yes	56	81 %
	o No	13	19 %
6.	Do you feel the sign of bladder base tenderness on internal examination is useful in making a diagnosis of BPS?		
	o Yes	35	51 %
	o No	33	48 %
7.	In patients with BPS, which of the following treatments do you use?		
	o Behavioural modification eg timed voids, decrease fluid intake	41	59 %
	o Physical therapy eg pelvic floor biofeedback, soft tissue massage	38	55 %
	o Stress reduction	23	33 %
	o Dietary modification	52	75 %
	o Simple analgesia	35	51 %
	o Other analgesia eg. Gabapentin, pregabalin	46	67 %
	o Low dose long-term antibiotics	48	70 %
	o Antidepressants eg. Oral amitriptyline	54	78 %
	o Antihistamines eg. Oral cimetidine	33	48 %
	o Immunosuppressants eg. Oral cyclosporine	1	1.4 %
	o Intravesical glycoaminoglycans eg. Chondroitin sulfate	32	46 %
	o Sodium pentosan polysulphate (Elmiron)	34	49 %
	o Intravesical dimethyl sulfoxide (DMSO)	24	35 %
	o Intravesical hyaluronic acid	29	42 %
	o Anticholinergics eg intravesical oxybutynin	20	29 %

o	Intravesical heparin	9	13 %
o	Intravesical lidocaine	7	10 %
o	Botulinum toxin under cystoscopic guidance	25	36 %
o	Cystoscopic hydrodistension	23	33 %
o	Fulguration or transurethral resection of lesions	7	10 %
o	Neuromodulation	13	19%

On questioning clinicians about the experience with PTNS, 46% (n = 32) reported that they would consider using PTNS. The frequency of treatment ranged from once to twice monthly for up to six months. Figure 7 graphically represents the clinician's prior beliefs on the effectiveness of PTNS to treat refractory BPS with 46% (n = 32) unsure whether the treatment is beneficial, but believed it is not harmful. 80% (n = 55) expressed their interest in participating in a clinical trial to evaluate the effectiveness of PTNS.

Figure 7: Graphical elicitation on the clinicians beliefs of the effectiveness of percutaneous tibial nerve stimulation (PTNS).



4.5 Discussion

This survey highlighted the national variations in the patient's experiences and clinicians management of BPS. Many clinicians are still using cystoscopy as a diagnostic test. Previous surveys of UK clinicians have shown wide variations in the technique for hydrodistension with a non-standardised technique regarding timing and fluid volume used for distension (87). A symptom-based diagnosis is being made by only 12% of clinicians, despite current recommendations advising initiation of treatment using a symptom-based diagnosis. Cystoscopy is a third line treatment, which may be reserved for the diagnosis of complex cases (23).

Patients suffered from a range of symptoms but the most common and problematic one being pelvic or lower abdominal pain, which is often highlighted in the literature as key symptoms in BPS (25). These findings were shared by the clinician survey, which implies there may be some diagnostic value in using bladder filling pain as a screening question for BPS. A variety of treatments are used for BPS. Unfortunately, up to 62% of patients and 70% of clinicians have used low-dose long-term antibiotics to treat BPS, which is not a recommended treatment option (23).

There were variations in beliefs of treatment effectiveness of PTNS varying from unsure whether beneficial but not harmful to unsure whether beneficial or harmful. Both patients and clinicians were willing to participate in clinical trials to test this clinical equipoise.

This survey was UK based inviting all clinicians registered with the British Society of Urogynaecology to participate with good national representation. In order to assess the experiences of patients, the two main UK based patient support groups were invited to

participate. Since patients were self-selected there was no way to directly contact them. This method relied on the pro-activeness of patients to participate in the survey and some responses may be a reflection of the patient's own character, for example, trying several treatments and use of social media. As there are no specific BPS support groups in the UK, patient self-selection had to be used. The two surveys were both electronically conducted and anonymous. The low clinician response was a key weakness of this survey. However, with 88% of respondents being consultant grade their opinions were valuable as they are ultimately responsible for managing these patients. Information about the type of cystoscopy, for example, rigid or flexible, and type of anaesthesia would have been interesting. It would have been useful to establish whether a cystoscopy was performed as a diagnostic test, hence delaying the initiation of treatment, or as a treatment. It was difficult to assess the demography and characteristics of the patients, as this data was not collected. Ideally a larger sample size would have been preferable, but it may have not added any further information to the overall results.

It may have been useful to collect data on lifestyle, for example smoking and caffeine intake of patients, along with possible alternative and conservative therapies such as acupuncture or massage. Pelvic pain is an over-riding symptom in BPS and is known to be multi-factorial in cause, hence more information about patients comorbidities may have been valuable (88). Other useful data may have been quality of life and psychological assessments in order to understand disease impact since patients with BPS and associated comorbidities often have poor quality of life (55, 89, 90). In order to keep the questionnaire short and user friendly limited additional questions were asked as the survey focused on the diagnosis and management of patients.

The complexity of BPS is evident by the range of symptoms associated with the condition. Since pelvic pain is a key symptom, it is important that general gynaecologists are aware of the clinical presentations of BPS as these patients may initially present to their clinics rather than to a urogynaecologist if the patient is referred with pelvic pain.

While many surveys about BPS have focused on patients quality of life and related comorbidities, mine focused on its management (55, 88). It showed that clinicians still appear to be using cystoscopy as a diagnostic tool, implying that the American Urological Association guidance to commence treatments on symptoms alone have not been followed. Clinicians often struggle to diagnose BPS due to the cluster of non-specific symptoms, which may cause difficulty implementing initial community-centred care without referral to secondary care (91). The general lack of consensus about the management of BPS, along with the variety of treatments used implies difficulty achieving symptomatic control (92).

This chapter highlights the variations in clinical practice, suggesting there is a need for national guidance on the management of BPS in order to offer patients consistent care. This has been acknowledged by the RCOG in the UK, who have recently a commissioned such a guideline which aims to help clinicians provide a minimum standard of care.

CHAPTER 5:

EVALUATING THE SENSITIVITY OF BLADDER WALL TENDERNESS AND BLADDER FILLING PAIN IN PATIENTS WITH CHRONIC PELVIC PAIN

(A CASE-CONTROL FEASIBILITY STUDY)

In this chapter I evaluate the usefulness of using two index tests, bladder wall tenderness and bladder filling pain, as diagnostic markers of BPS in women with CPP. I also explore the possibility of using an expert consensus panel to achieve a symptom-based diagnosis for BPS, in the absence of a gold standard test.

5.1 Abstract

Introduction: Patients with BPS often suffer from a cluster of urinary symptoms. This study aimed to validate the use of two simple tests for BPS, bladder wall tenderness and bladder filling pain, in women with CPP.

Methods: In this multi-centre study women with unexplained CPP were recruited from gynaecology clinics across the UK between August 2012 and July 2013. Data on particular signs and symptoms were collected. The diagnosis of BPS was made by expert consensus panel, made up of three urogynaecology consultants, using the complete patient history and examination data, without the index (tests to avoid incorporation bias), as there is no gold standard diagnostic tool. The panel achieved a moderately high level of agreement (intra-class coefficient agreement of 0.46). We computed sensitivity (true positive result) and specificity (true negative result) with 95% confidence intervals.

Results: There were 46 eligible women with a mean age of 30.8 years (n=21, SD 7.20) in the BPS group (cases) and 34.6 years (n=25, SD 9.51) in the control group. The most sensitive symptom was bladder filling pain (sensitivity = 0.57, 95% CI = 0.3-0.8, specificity = 0.84, 95% CI = 0.6-1.0). The most specific test was bladder wall tenderness (sensitivity = 0.10, 95% CI = 0.1-0.3, specificity = 0.96, 95% CI = 0.8-1.0).

Conclusion: In women with unexplained CPP, absence of bladder wall tenderness can be associated with a high specificity and bladder filling pain with a reasonable sensitivity with high specificity. A large multi-centre study is needed to validate these tests in order to aid clinicians diagnose this debilitating condition.

5.2 Introduction

BPS is an often forgotten cause of CPP. Its unknown aetiology, along with the range of symptoms experienced by patients, usually comprising of bladder/pelvic pain, urgency, frequency and nocturia make diagnosis challenging, especially as these symptoms may be present in several other urinary conditions and are not discriminating of BPS (93). There is no gold standard test for BPS, with the recommendation of a symptom-based diagnosis (23), which causes difficulty in the choice of study design for a diagnostic accuracy study.

In practice, the symptom of bladder filling pain and the sign of bladder wall tenderness on vaginal examination have been shown to be present in a high number of patients with BPS, but these have not been incorporated into existing diagnostic tools (46, 94). In a recent survey of clinicians, described in chapter 4, 81% believed the symptom of bladder filling pain was useful in the diagnosis of BPS. In this chapter I assess the usefulness of these tests, while also identifying if other symptoms may be sensitive markers of BPS. I have attempted to show that expert panel diagnosis can be a successful option when no reference standard exists for a given condition.

5.3 Methods

This study evaluated diagnostic accuracy in the absence of a reference standard (95). I assessed the correlation of bladder filling pain, and bladder wall tenderness with the Pelvic Pain Urgency/ Frequency (PUF) questionnaire (and several component questions within it). This should enable an estimation of the accuracy with which a certain combination of signs and symptoms (index tests) can identify the diagnosis of BPS in women with CPP. BPS is often a diagnosis of exclusion, with no validated questionnaires, although several

questionnaires may be used to identify baseline symptoms (23). The PUF questionnaire, rather than the O'Leary Sant Interstitial Cystitis Problem Index/Symptom Index (ICSI/PI), was used because it also captures information about symptoms in relation to sexual intercourse (26, 28). Both the PUF and ICSI/PI questionnaires enquire about pain, which is a key symptom of BPS. Pain was assessed using likert visual analogue scales and pain specific tools like the McGill short form questionnaire. The aim of this questionnaire was to capture pain and urinary symptoms, and not enquire about quality of life, which was not assessed in this study.

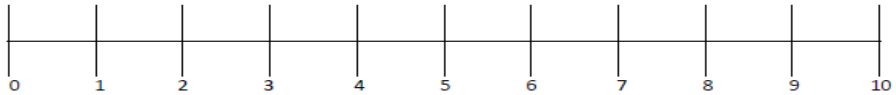
This was a case-control study, which was part of the MEDAL trial (MRI to Establish Diagnosis Against Laparoscopy), which is a multicentre study in the United Kingdom assessing women with unexplained CPP. Patient inclusion criteria were: women presenting to secondary care with unexplained CPP, aged 16 or older with the ability to understand adequate English in order to give informed consent. Exclusion criteria were pregnancy, a previous hysterectomy, a proven urinary tract infection on urine dipstick and a previous diagnosis of BPS. Eligible women were recruited from gynaecology outpatient clinics in the United Kingdom between August 2012 and July 2013 with consecutive recruitment of all eligible patients to minimise selection bias.

Since there is no gold standard test for BPS, an expert consensus panel was used for diagnosis (95). The panel comprised of three consultant specialists in urogynaecology. The diagnosis determined by the panel used patient self-reporting symptoms and signs captured in a range of items from several questionnaires (figure 8) (28).

Figure 8: Consensus panel assessment form for diagnosis of bladder pain syndrome.

1. Negative urine dipstick?	Yes / No
2. Duration of pain	Answer in months
3. Location of pain and severity?	Description of location with pain score 1-10
4. Superficial dyspareunia	Yes / No
5. Deep dyspareunia?	Yes / No
6. Pain on full bladder?	Yes / No
7. Pain on urination?	Yes / No
8. Urinary frequency?	Score 0 (3-6 times) to 4 (over 20 times)
9. Nocturia?	Score 0 (never) to 3 (always)
10. Post void urgency?	Yes / No
11. Degree of urgency?	Mild/ moderate/ severe
12. Pain associated with bladder, urethra, vagina, perineum, pelvis?	Never/occasionally/usually/always
13. PUF score	0 – 35
14. **Do you think this patient has BPS?**	**Yes / No**

15. How certain are you? (0 = uncertain to 10 = very certain)



In order to avoid incorporation bias, we did not include the index tests as part of the symptom based diagnosis made by the expert panel. A diagnosis was made if two out of three consultants felt the patient suffered from BPS. Disease certainty scores from 0-10 were assigned to each case. All recruited patients were allocated into the case or control group depending on the presence or absence of BPS. These scores were used to calculate the intra-class coefficient (ICC), which was moderately high at 0.46.

The two index tests performed were: bladder-filling pain, which was assessed through a clinical history, and bladder wall tenderness on examination, which was assessed by specialists in gynaecology as part of a routine vaginal examination, as the sensation of pain when the bladder wall was palpated. Data were collected on a pre-designed collection form and inputted into a central database as part of the main MEDAL study. Quality assurance included double data entry, visual cross validation, data completeness checks and protocol adherence in accordance with good clinical practice guidance. One of the missing data, limiting recruitment was urine dipstick testing. Manual checking of data collection forms, GP referral letters and patient notes was performed to find missing data.

Data analyses included patient characteristics with descriptive statistics, ranges and standard deviations as appropriate. Statistical analysis of sensitivity, specificity and predictive values was calculated using the StatsDirect software programme version 2.8.0. Data recruitment fell short of an ideal sample size of 100 patients since the main study ended as funding and recruitment deadlines were met and further recruitment was futile as the main study objectives had been met.

5.4 Results

There were 46 eligible patients recruited over an 11-month period. Table 9 shows the 10 centres where patients were recruited from within the United Kingdom.

Table 9: Hospitals within the United Kingdom where individual patients were recruited.

Number of patients	Name of Hospital
2	Cumberland Infirmary, Cumberland
1	Edinburgh Royal Infirmary, Edinburgh
1	Furness General Hospital, Cumbria
5	Homerton University Hospital, London
2	Musgrove Park Hospital, Taunton
5	Royal Hallamshire Hospital, Sheffield
1	Royal Preston Hospital, Preston
24	Royal London Hospital, London
3	Southend University Hospital, Southend
2	University Hospital Of North Staffs

Table 10 shows the study characteristics for the case and control groups of patients.

Table 10: Study characteristics of patients with and without bladder pain syndrome (BPS)

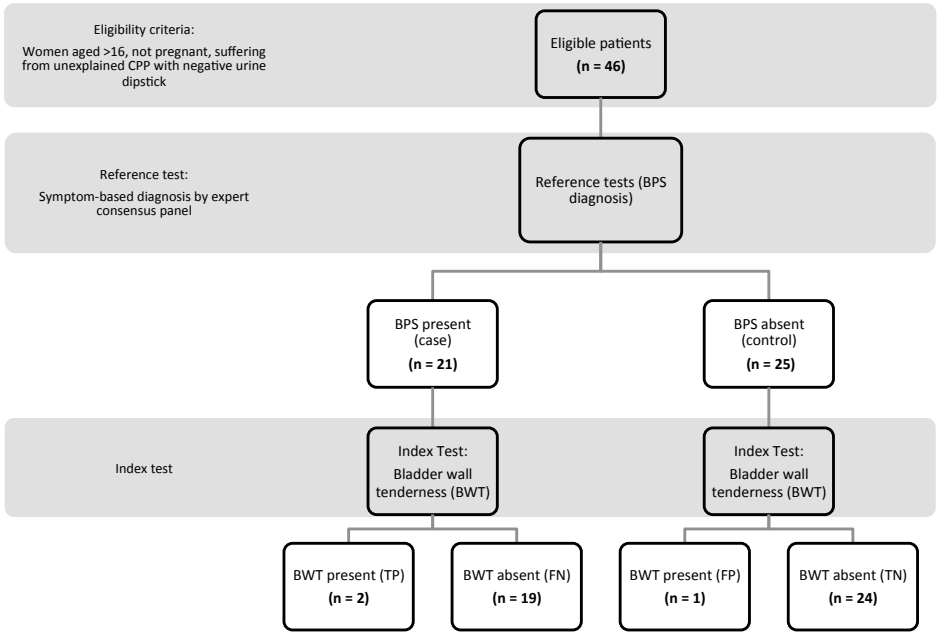
Patient characteristics	Case group (BPS present) (n = 21)	Control group (BPS absent) (n = 25)
Mean age (years)	30.8	34.6
Mean body mass index (kg/m^2)	26.5	25.1
Ethnicity – Caucasian	14 (70%)	13 (54%)
- Asian	4 (20%)	6 (25%)
- Afro-Caribbean	0	2 (8%)
- Mixed race	1 (5%)	1 (4%)
- Other	1 (5%)	2 (8%)
Mean duration of symptoms (months)	59.2	39.2
Mean highest pelvic pain score (0-10)	8.64	9.12
Superficial dyspareunia	18 (86%)	7 (28%)
Deep dyspareunia	19 (90%)	9 (36%)

There were 21 patients who suffered from BPS (case group). Their mean age was 30.8 years (SD 7.20) compared to 34.6 years (SD 9.51) in the control group. The mean body mass index (BMI) was 26.5kg/m^2 in the BPS group and 25.1kg/m^2 in the control group. There was variation in ethnicities; Caucasian 70% in the BPS group and 54% in the control group, Asian 20% in the BPS group and 25% in the control group, Afro-Caribbean 8% in the control group, mixed race Caucasian and Afro-Caribbean 5% in the BPS group and 4% in the control group and other 5% in the BPS group and 8% in the control group.

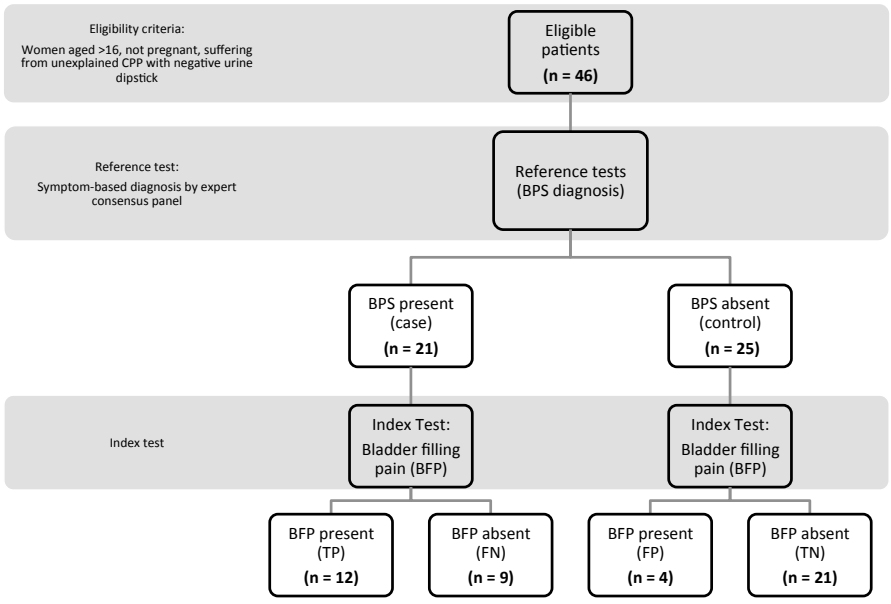
In the disease group, bladder wall tenderness was present in 2/21 (9.5%) and bladder filling pain in 12/21 (57%). In the disease-free group bladder wall tenderness was present in 1/25 (4.0%) and bladder filling pain in 4/25 (16%) (figure 9).

Figure 9: Study flow chart in accordance with the STARD reporting guidelines (96)

a. Bladder wall tenderness



b. Bladder filling pain



In the BPS group, the highest mean pain scores were 8.6/10 with a mean duration of symptoms of 59 months. 18 (86%) patients suffered from superficial dyspareunia and 19 (90%) from deep dyspareunia. In the control group the highest mean pain scores were 9.1/10 with a mean duration of symptoms of 39 months. 2 (28%) patients suffered from superficial dyspareunia and 9 (36%) from deep dyspareunia.

29 patients (63%) had a calculable PUF questionnaire score with a mean score of 15.2 in the BPS group and 9.5 in the control group. Table 11 shows the relationship between the presence of individual urinary symptoms and a diagnosis of BPS. Bladder filling pain had a sensitivity of 0.57 and specificity of 0.84, and bladder wall tenderness had a sensitivity of 0.10 and specificity of 0.96. The most sensitive additional symptoms were urinary frequency, and pain on urination (0.57) and the most specific additional tests were post-void urgency (1.00), pain on urination (0.91) and pain in the urethra, vagina and bladder (0.91).

Table 11: The accuracy of tests for the diagnosis of bladder pain syndrome (BPS)

Test	BPS present (n = 21)	BPS absent (n = 25)	Sensitivity (95% CI)	Specificity (95% CI)	Odds Ratio (95% CI)
Index test					
Bladder wall tenderness	2	1	0.10 (0.1-0.3)	0.96 (0.8–1.0)	2.53 (0.1-155)
Bladder filling pain	12	4	0.57 (0.3-0.8)	0.84 (0.6-1.0)	7.00 (1.5-37)
Additional tests					
Urinary frequency	12	4	0.57 (0.3-0.8)	0.84 (0.6-1.0)	7.00 (1.5-37)
Nocturia	11	3	0.52 (0.3-0.7)	0.88 (0.7-1.0)	8.07 (1.6- 52)
Pain on urination	12	2	0.57 (0.3-0.8)	0.92 (0.7-1.0)	15.3 (2.5-156)
Post-void urgency	5	0	0.24 (0.1-0.5)	1.00 (0.9-1.0)	* (1.2- ∞)
Pain in urethra, bladder, vagina	7	2	0.33 (0.1-0.6)	0.92 (0.7-1.0)	5.75 (0.9-62)
Pain on full bladder	1	5	0.05 (0.0-0.2)	0.80 (0.6-0.9)	0.20 (0.0-2.1)

Urinary frequency = voiding ≥ 7 times per day
Nocturia = ≥ 1 occasion per night
Post-void urgency = present if patient reported presence usually or always
Pain in urethra, bladder or vagina = present if patient reported presence usually or always
Pain on full bladder = patient reported score of ≥ 5

95% CI = 95% confidence interval

A cystoscopy was performed on four patients; three in the BPS group where only one cystoscopy identified pathology showing grade 2 submucosal bleeding and one in the control group which showed grade 2 submucosal bleeding. A laparoscopy was performed on 43 patients with bladder pathology (anterior bladder wall endometriosis or dense adhesions affecting the anterior bladder wall) seen in 2/20 (10%) patients in the BPS group and 3/23 (13%) patients in the control group.

5.5 Discussion

Urinary symptoms may be discriminatory of BPS. The two primary index tests used in this study were bladder wall tenderness and bladder filling pain. Both tests were simple and easy to assess. Bladder wall tenderness had a poor sensitivity but high specificity. Bladder filling pain had a reasonable sensitivity but high specificity. Bladder filling pain is often thought of as a hallmark symptom for BPS (25). The symptoms that had the best sensitivity and specificity were bladder filling pain, urinary frequency, nocturia and pain on urination. There were low levels of PUF questionnaire completion due to missing data. Despite the limitations of the PUF questionnaire, it discriminated between BPS and disease-free patients with higher scores in the BPS group (15.2 versus 9.5).

This study has successfully demonstrated that BPS can be diagnosed by symptoms alone. An expert panel was favourably used to obtain a consensus diagnosis, as no gold standard diagnostic tool exists. Using a case-control study design, we demonstrated that the absence of several urinary symptoms may aid ruling out a diagnosis of BPS.

The patients in the case and control group had similar demographic backgrounds. There was consecutive recruitment using standardised reporting forms and questionnaires to minimise bias. All three members of the expert panel were all urogynaecologists and were not involved in patient recruitment. They were not aware of the index test results when making their diagnosis of BPS, thus avoiding incorporation bias. The major study weakness was the small sample size. During the data collection process it became apparent that some centres did not routinely test patients urine or perform internal vaginal examinations so did not fulfil the inclusion criteria. Despite attempts to remind all recruiting centres of the study inclusion criteria there were high levels of missing data, accounting for the low sample size.

The results of this study have several clinical implications. One recommendation would be that all patients have urine dipstick testing routinely on first presentation to gynaecology clinics, as a urine infection is easy to treat and may explain pelvic pain and urinary symptoms. Clinicians should feel confident making a symptom-based diagnosis of BPS by asking a few salient questions that are part of a routine urogynaecology consultation. Only 14% of patients with BPS had a cystoscopy and only one patient's revealed pathology, showing that symptoms and cystoscopy findings often do not correlate. The duration of symptoms in BPS patients was on average 20 months more than non-BPS patients. There was a higher prevalence of superficial and deep dyspareunia suffered in the BPS group, suggesting sexual dysfunction is associated with the BPS phenotype (97). This highlights the burden of disease and need for prompt initiation of treatment. The symptoms of BPS can be easily elicited as part of a routine history and allow immediate treatment to be commenced. Literature shows that the prevalence of BPS in women with chronic pelvic pain is 61%, hence should be considered as a differential diagnosis of CPP (57).

We successfully undertook a feasibility study to assess if a group of urinary signs and symptoms could be used to diagnose BPS. The impact of BPS on quality of life has been well documented (98). Patients with BPS are known to utilise healthcare resources more than non-sufferers which adds to the burden of the economy so any beneficial treatments would not only benefit sufferers but the healthcare economy (99). A large multi-centre study is needed to validate these tests in order to aid clinicians diagnose this debilitating condition. This has already been described as the Bravado study but in order to validate these tests a large sample size would be needed, requiring funding and adequate time to recruit (100). This may be possible if the study was recruited in primary care where large volumes of symptomatic patients initially present and could be commenced on conservative treatments. In future research, an asymptomatic control group could be recruited, possibly patients that present to gynaecology clinics requesting laparoscopic sterilisation who usually do not have any urinary or pelvic pain symptoms so would make an ideal cohort group.

This work is supported by the National Institute for Health Research Health Technology Assessment (NIHR HTA) (ref: 09/22/50) with ethic approval for the NIHR MEDAL Study from East Midlands Research Ethics Committee - Nottingham 1 (Ref 11/EM/0281), which covers this sub-study.

CHAPTER 6:

THE ROLE OF LAPAROSCOPY AND CYSTOSCOPY IN THE DIAGNOSIS AND MANAGEMENT OF PELVIC AND BLADDER PAIN

In this chapter I explore the role of invasive diagnostic tests to investigate chronic pelvic pain and bladder pain syndrome as most patients with BPS usually present to gynaecology clinics with CPP as their primary complaint.

6.1 Background

We are aware that the prevalence of CPP in women is comparable to that of lower back pain and asthma with a huge negative impact on quality of life and causing a large financial burden on the economy due to days off work and the time spent managing and treating these patients (101). This chapter explores the role of laparoscopy as a diagnostic and therapeutic tool in the management of these patients. Bladder pain syndrome (BPS) may be a manifestation of CPP where cystoscopy can have a diagnostic and therapeutic role. I will also explore other causes of CPP and evaluate the most effective methods of diagnosing these.

6.2 What is chronic pelvic pain (CPP)?

The RCOG definition of CPP is 'an intermittent or constant pain in the lower abdomen for at least 6 months that is not associated with pregnancy and not occurring exclusively with menstruation or sexual intercourse' (102). The International Association for the Study of Pain and the European Association of Urology have revised this definition to include both men and women, including pain perceived in structures related to the pelvis and have acknowledged the negative impact of pain on cognition, behaviour, sexual and emotional well-being, along with its possible association with urinary, bowel, sexual, pelvic floor or gynaecological dysfunction (9, 103).

It is often difficult to diagnose the cause of CPP, as there may be several causes and co-existing pathologies, which makes identification of a single diagnosis sometimes impossible.

The estimated prevalence of CPP ranges between 8-81% worldwide according to a recent systematic review with an extensive range of causes (35). There are a variety of investigations to diagnose each with differing diagnostic accuracy and patient acceptability. Table 12 shows the most common gynaecological causes of CPP, which include endometriosis, adenomyosis, ovarian cysts, uterine fibroids, pelvic congestion syndrome, chronic pelvic inflammatory disease and adhesions. Adhesions may be secondary to endometriosis, pelvic inflammatory disease or previous surgery. There may be non-gynaecological causes of CPP, which include irritable bowel syndrome, BPS, musculo-skeletal, neuropathic and psychological factors, such as a history of sexual abuse and psychosexual difficulties.

6.3 The role of laparoscopy in CPP

Initially management for patients with CPP is a careful clinical assessment consisting of thorough history, physical examination and imaging, usually in the form of a pelvic ultrasound or possibly pelvic magnetic resonance imaging, if needed (102). A diagnostic laparoscopy has traditionally been seen as the 'gold standard' diagnostic test. Unfortunately, as many as 40% of diagnostic laparoscopies fail to detect any pathological cause of the pain (104). It has been well documented that a laparoscopy can successfully diagnose the type and location of adhesions and several types of endometriosis (104, 105). The gynaecological causes of CPP along with the diagnostic accuracy of laparoscopy as a diagnostic tool are shown in table 12.

Table 12: The gynaecological causes of chronic pelvic pain and the accuracy of laparoscopy as a diagnostic tool (106).

Target condition	Diagnostic criteria	Role of laparoscopy
Adenomyosis	Presence of islands of ectopic endometrial tissue within the myometrium confirmed histologically	Uncertain value – appearance bulky 'boggy' uterus
Adhesions	Visual inspection during laparoscopy, or by absence of movement between adjacent organs	Gold standard - visual inspection
Endometriosis	Visual inspection during laparoscopy, noting appearance, size and depth of endometrial	Gold standard – negative laparoscopy can exclude disease but positive findings cannot accurately confirm implants disease (107)
Fibroids	Size and location noted during pelvic ultrasound	Uncertain – visual inspection of size and location of subserosal fibroids
Ovarian cysts	Pelvic magnetic resonance imaging to define size, location and nature of cyst, confirmed histologically	Uncertain value – visual inspection of size and location of cyst
Pelvic congestion syndrome	Definitive diagnosis on catheter-directed venography, showing uterine venous engorgement and ovarian complex congestion (108)	Uncertain value – appearance of pelvic varicosities
Pelvic inflammatory disease	Visual inspection during laparoscopy or histology from fimbrial biopsy (109)	Uncertain value – may identify salpingitis, adhesions and Fitz-Hugh-Curtis syndrome

During laparoscopy, visual inspection of the fallopian tubes and assessment for tubal patency may be performed, along with assessment of disease severity, for example, the presence of severe endometriosis, which may indicate that management in a specialist endometriosis centre may be most appropriate. Regardless of the peritoneal entry technique, up to 57% of surgeons have described major bowel and vascular injures (110). 'See and treat' therapeutic laparoscopies are more preferable in order to avoid multiple operations and the risks associated with repeat surgery (111).

Different imaging modalities, such as pelvic ultrasound scans can be extremely useful in identifying site-specific adnexal pain, decreased ovarian mobility, as well as the presence of endometriomas and hydrosalpinges (112). These findings may be in keeping with the presence of endometriosis and can allow the surgeon to effectively plan surgery with suitably skilled staff, appropriate surgical instruments and possibly transfer to a tertiary centre if severe endometriosis is suspected (111).

Endometriosis

Endometriosis is one of leading causes of CPP, which often affects areas of the pelvis, such as the uterosacral ligaments, pouch of Douglas and rectovaginal septum, which can be difficult to assess by clinical examination (113). Literature shows that while a negative laparoscopy can accurately exclude visually diagnosed endometriosis, a positive laparoscopy needs histological confirmation of disease, with a sensitivity of 94% for laparoscopic diagnosis compared to histological diagnosis (107) . The role of the assisting surgeon is crucial in providing adequate anteversion using the uterine manipulator to allow for anteversion and anteflexion of the uterus in order to thoroughly inspect the pouch of Douglas. Up to 42% of general gynaecologists have reportedly failed to recognise rectovaginal

endometriosis during visual inspection at primary laparoscopy (114). Laparoscopy is still regarded as the 'gold standard' diagnostic investigation for superficial endometriosis. The optimal method of treating superficial endometriosis is debatable as diathermy or excision of disease is usually dependent on surgical preference. Excision of endometriosis allows a biopsy to be obtained for histological disease confirmation but this requires surgical skill to avoid trauma. Ablative therapy with diathermy poses the risk of thermal injury to nearby structures, such as the bowel or ureter. When ablation was compared to excision using monopolar diathermy in patients with mild endometriosis (stage 1 or 2 revised American Fertility Score) in a small RCT, both treatments produced symptomatic relief and there was no difference in six-month symptom questionnaire scores (115). A large-scale randomised trial is needed to obtain more reliable results for these two treatment options. The added advantage of a laparoscopy is the opportunity to visualise and dissect adhesions that may be present and perform a tubal patency test if the woman has fertility desires.

Adhesions

Adhesions may be present as a result of endometriosis, exposure to infection or previous surgery. They can distend or stretch organs causing pain (102). Adhesions may be fine and filmy or dense and vascular. There is uncertainty over the symptomatic benefits of adhesiolysis in CPP with trials showing substantial pain relief reported in groups where adhesions were treated with adhesiolysis compared to no treatment one year post surgery (116). Smaller, observational studies have shown similar results two years after surgery in 45% of patients (117). These results imply there may be a psychologically beneficial effect in performing adhesiolysis with a perceived improvement in pain (118).

Adenomyosis

Adenomyosis is defined by the presence of islands of ectopic endometrial tissue within the myometrium, causing smooth muscle hypertrophy (119). It is a common condition, which is usually reported on ultrasound scans showing a cystic myometrial appearance or seen on laparoscopy with the classical appearance of a bulky 'boggy' uterus. There may be an association with endometriosis and endometrial hyperplasia and patients often present with menorrhagia and dysmenorrhea. The value of laparoscopic or ultrasound diagnosis is questionable since definitive diagnosis is by histology, which is impractical so imaging in the form of an MRI or ultrasound allows initiation of medical treatment and may sometimes avoid the need for surgery.

6.4 Uncertainties of laparoscopy

Diagnostic laparoscopies are useful at evaluating some of the causes of CPP. Unfortunately 40% of laparoscopies show no pathology, which leaves clinicians with the dilemma of weighing up the possible surgical benefits against the risks, as many causes of CPP do not involve gynaecological pathology. Chronic pelvic pain syndrome (CCPS) is the term for the occurrence of chronic pelvic pain where there is no proven infection or other obvious local pathology that may account for the pain, where pain may be focused around a single organ or multiple pelvic organs (9). A 'negative' laparoscopy where no pathology is seen can also have a reassuring effect on the patient (120).

6.5 What is bladder pain syndrome (BPS)?

Patients suffering from BPS can often present with CPP. It has been well documented that due to the wide spectrum of pain and urinary symptoms associated with the condition, diagnosis is challenging leading to inaccurate prevalence rates.

6.6 The role of cystoscopy

The role of cystoscopy has been previously discussed in the introduction, along with the uncertainties of this procedure. Cystoscopy can differentiate between BPS with a normal bladder mucosal appearance from grade 2 and 3 disease with the presence of petechial bleeds, glomerulations and Hunner's lesions/ulcers (121). In the presence of Hunner's ulcers, the clinician may choose to offer alternative treatments such as fulguration at an early stage, rather than persevering with conservative treatments. While hydrodistension during cystoscopy can allow visualisation of petechial haemorrhages, it can also provoke petechial bleeds that are thought to be pathognomonic and prolonged hydrodistension is not recommended due to the rare side effect of bladder rupture (23).

6.7 The uncertainties of cystoscopy

Cystoscopy and histology of bladder biopsies have often been seen as the 'gold standard' diagnosis for BPS as they may confirm disease presence and enable disease classification (7). Cystoscopy has a level A recommendation as a method of diagnosis while bladder biopsies are level B, where guidelines recommend or highly recommend the treatment option based on information from well-conducted studies with or without randomisation (121). Poor correlation has been seen in some studies between cystoscopy findings and diagnosis since glomerulations may be seen in asymptomatic patients and bladder biopsies may not confirm disease in the presence of glomerulations (8, 21). For this reason, the results of cystoscopy or bladder biopsies are unreliable and clinicians are advised to treat symptomatic patients in accordance with the recommendations of AUA guidelines using clinical history and examination to make a symptom- based diagnosis (23).

6.8 Conclusion

CPP may be multi-causal with several identifiable risk factors, such as a history of drug, alcohol and sexual abuse, pelvic inflammatory disease, anxiety and depression (122)**.** Invasive procedures such as a laparoscopy and cystoscopy may be useful diagnostic tools as well as having therapeutic effects. The degree of sensitivity of each test varies with the target condition, but patients must be aware that no obvious cause of pain is always identified (120). For this reason a thorough history, examination and imaging, where appropriate, are essential to correctly plan and offer treatments. Therapeutic 'see and treat' laparoscopies are recommended, rather than purely diagnostic procedures to avoid the need for multiple operations and the risks associated with them.

Worldwide, CPP and BPS affect large numbers of people where the etiology is often unknown and symptoms overlap with possible co-existing disease pathology, which makes the management of such patients difficult (57) (123). These difficulties suggest the need for integrated management between primary and secondary care clinicians (124). Both conditions may have non-specific symptoms but pain is usually the main complaint. It may be prudent for clinicians to consider performing both a laparoscopy and cystoscopy in cases of persistent CPP in order to rule out co-existing gynaecological and bladder pathology.

This chapter is based on the following publication as a book chapter:

The role of laparoscopy and cystoscopy in the diagnosis and management of chronic pelvic and bladder pain.

SA Tirlapur, KS Khan, E Ball

Recent advances in obstetrics and gynaecology 25

(Edited by William Ledger and Justin Clark)

CHAPTER 7:

ASSESSING THE EFFECTIVENESS OF NERVE STIMULATION IN THE TREATMENT OF PELVIC AND BLADDER PAIN: A SYSTEMATIC REVIEW OF THE EVIDENCE

In this chapter I will explore the effectiveness of posterior tibial nerve stimulation (PTNS) and sacral nerve stimulation (SNS) as treatments for CPP and BPS.

7.1 Abstract

Background: Both syndromes of CPP and BPS are associated with poor quality of life. In cases of refractory pain, neuromodulation, or nerve stimulation, has been suggested as a possible treatment option.

Objectives: To assess the effectiveness of posterior tibial nerve and sacral nerve stimulation in the treatment of BPS and CPP.

Data sources: The Cochrane Library, EMBASE (1980-2012), Medline (1950-2012), Web of knowledge (1900-2012), LILACS (1982-2012) and SIGLE (1990-2012) databases were searched until July 2012 with no language restrictions. Manual searches through bibliographies and conference proceedings of the International Continence Society were performed.

Study selection: Included studies were randomised and prospective quasi-randomised versus sham nerve stimulation treatment or usual (standard) care of patients with CPP and BPS who underwent sacral or tibial nerve stimulation. Studies that involved transcutaneous electrical stimulation (TENS) were excluded. The outcome measure was a cure or symptomatic improvement.

Results: There were three eligible studies with 169 patients; two for CPP and one for BPS. Symptomatic improvements were reported for pain, urinary and quality of life questionnaire scores using both tibial and sacral neuromodulation.

Conclusion: There is very limited available literature on neuromodulation, which reports variable success of posterior tibial nerve stimulation (PTNS) in improving pain, urinary symptoms and quality of life in CPP and BPS. There was no available data for the effectiveness of sacral nerve stimulation (SNS). In view of the absence of quality literature, a large multi-centered clinical trial is recommended to investigate the effectiveness of nerve stimulation to treat BPS and CPP. Cost-analysis of these treatments is recommended to assess the feasibility of wide-scale introduction of treatment into hospitals.

7.2 Introduction

BPS and pelvic pain are both chronic pain syndromes known to have a negative impact on quality of life and sexual function (60). As both conditions have an unknown etiology, symptomatic management is the mainstay of treatment. Unfortunately, standard conservative and pharmacological treatments frequently fail (125). Nerve stimulation, or neuromodulation, of the posterior tibial or sacral nerves is minimally invasive and has been described as a treatment for refractory BPS and CPP. Both methods of neuromodulation have been shown to be effective in other bowel and bladder disorders such as overactive bladder and faecal incontinence (126) (127) (128). During posterior tibial nerve stimulation (PTNS) there is insertion of a fine needle 5cm cephalad from the medial malleolus and posterior to the margin of the tibia to the site of the posterior tibial nerve. There is a weekly treatment regime, usually for 10-12 weeks (129). In sacral nerve stimulation (SNS) there is an initial test phase with insertion of a test lead which is tunneled under the skin and transmitted onto the nerve roots exiting the S3 foramen, which causes stimulation of the pelvic and pudendal nerves and this is connected to a stimulator. This is exchanged for a permanent implant if successful (130, 131). Published data about the effectiveness of neuromodulation is contradictory so the aim of this chapter is to assess the effectiveness of PTNS and SNS to treat BPS and CPP by systematically reviewing the available literature.

7.3 Methods

This systematic review was prospectively conducted using a protocol based on contemporary methods, which was registered on the international register of systematic reviews (PROSPERO) registration number CRD42012002465. It was reported in accordance with the PRISMA statement (36).

Data sources

The Cochrane Library, EMBASE (1980-2012), Medline (1950-2012), PSYCHINFO (1806-2012), Web of knowledge (1900-2012), and LILACS (1982-2012) databases were searched from inception to July 2012. Grey literature was searched through SIGLE (1990-2012). No language restrictions were used. The MeSH headings and keywords used were 'chronic pelvic pain' or 'pelvic pain' or 'interstitial cystitis' or 'painful bladder syndrome' or 'bladder pain syndrome' which were combined using the Boolean operator 'and' with the terms 'tibial nerve' or 'sacral nerve' or 'nerve stimulation' or 'neuromodulation'. All bibliographies from relevant articles and conference proceedings of the International Continence Society were hand searched to identify any articles that were not electronically cited.

Study selection

Studies that had a randomised and prospective quasi-randomised trial design and used sham nerve stimulation treatment or usual care of patients as a comparator on patients with CPP and BPS who underwent sacral or tibial nerve stimulation were included. Studies using transcutaneous electrical stimulation (TENS) were excluded, as this was not considered direct nerve stimulation. The patients were men and women suffering from BPS and/or CPP who were not pregnant or suffering from cancer (7, 102). The outcome measured was a cure or symptomatic improvement.

Data extraction and quality assessment

There was independent data extraction by two reviewers (SAT, AV) who used a pre-designed data collection form, which captured study characteristics, information about participants, intervention, comparator and outcomes. Quality assessment of studies was performed using two published indexes (132) (133). These assessed the reporting, external validity, internal

validity (Jadad scale) and power of each study. Each study was assigned a quality score; poor quality (score <14), fair quality (score 15-19) or good quality (score >20) for the Downs and Black quality index. The Jadad scale rated a study as good quality with a score of ≥3 (134). A third assessment of study quality was performed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach in order to assess the quality of evidence for each outcome (135, 136).

Data synthesis

The results were tabulated and graphically represented where possible, although it was not possible to perform statistical analysis on the data due to the variation in outcome scoring systems used.

7.4 Results

There were three included studies in this review with 169 patients (137-139). A summary of the selection of papers is shown in figure 10.

Figure 10: A flow chart for study selection in the systematic review on the effectiveness of neuromodulation in the treatment of chronic pelvic pain (CPP) and bladder pain syndrome (BPS).

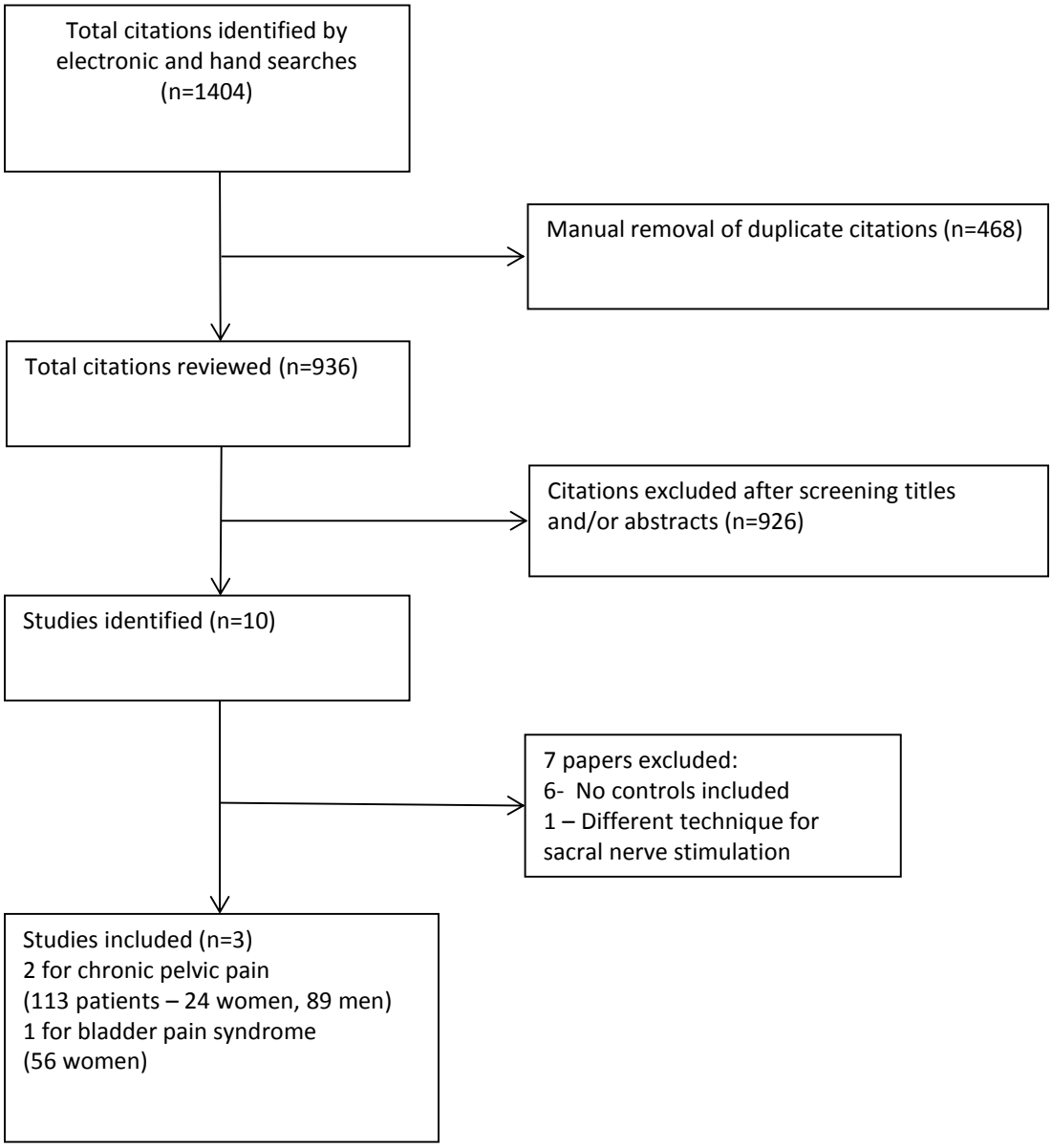


Table 13 shows the characteristics of included studies.

Table 13: Characteristics and summary of results for studies included in a systematic review of the effectiveness of neuromodulation for BPS and CPP.

Primary Author, Date, Locaton	Participants	Methods and duration	Treatment regimen & follow-up	Outcome measures	Effectiveness & complicatons
Gokyildiz 2012 Turkey	24 women CPP Exclusion criteria No reported ages	PTNS versus routine Ethics approval Informed consent No blinding, ITT 2 drop outs	30 mins x 12 weeks	Pain, QoL Sexual function	Improvements Pain & QoL in treatment group 1 haematoma
Kabay 2009 Turkey	89 men CPP Mean age 37.9 Exclusion criteria	PTNS versus sham Ethics approval Informed consent Unknown blinding, Randomisation, ITT	30 mins x 12 weeks Sham had no electrical stimulation	Pain scores QoL score Urinary	Reduction in pain & urgency in treatment
O'Reilly 2004 Australia	56 women IC No reported ages Exclusion criteria	Transdermal PTN laser versus sham Ethics approval Informed consent Unknown blinding, Randomisation, ITT	30 secs x 12 weeks Inactivated sham	Pain scores QoL scores Urinary	Improved QoL Decreased symptoms

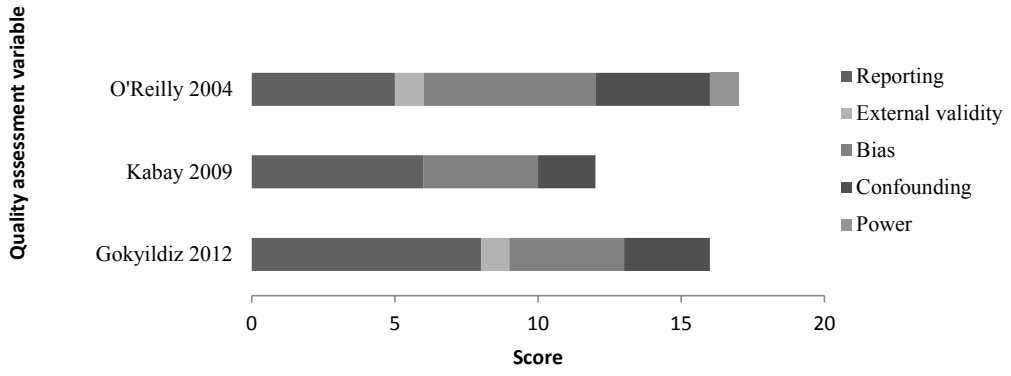
CPP = chronic pelvic pain, UTI = urinary tract infection, PTNS = posterior tibial nerve stimulation, VAS = visual analogue scale, ITT = intention to treat, QoL = quality of life, RCT = randomized controlled trial, FSFI = female sexual function index, NIH CPSI = chronic prostatitis symptom index, BPS = bladder pain syndrome, IC = interstitial cystitis, ICPI/SI = interstitial cystitis problem index/symptom index

One paper was excluded (140), Lee et al, who described an alternative method of sacral neuromodulation which used electroacupuncture, where acupuncture points in the second and third posterior sacral foramen of the sacrum are stimulated with a frequency of 4Hz and an intensity of 5-10mA. Continuous pulse generator stimulation is produced, along with a deeper stimulation that reaches the myofascial trigger point of the piriformis muscle.

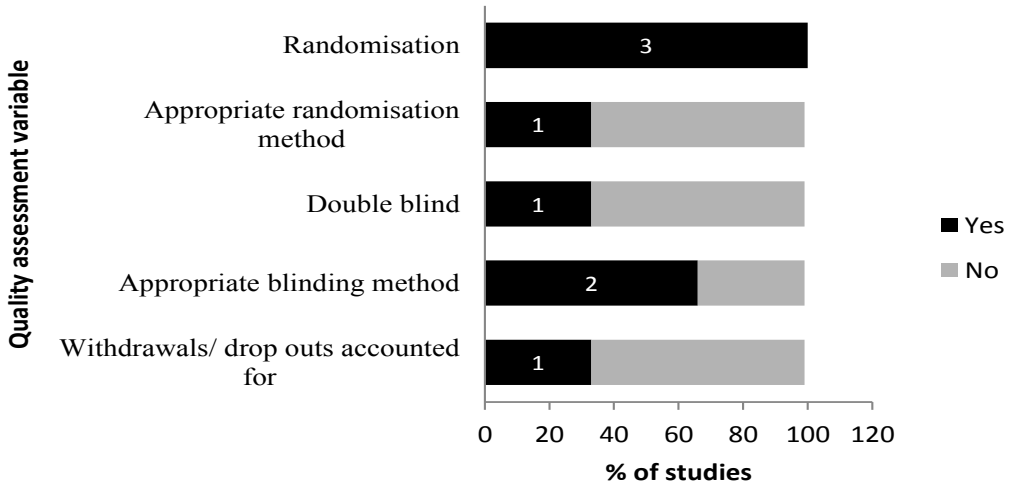
The quality assessment of included studies is graphically represented in figure 11. There were no 'good' quality studies when the Downs and Black quality index was used. One study was found to be 'good quality' when the Jadad criteria was used (137, 140). Non-homogeneous populations were studies. There was variation in the duration of treatment and the number of neuromodulation sessions undertaken per week, as well as the electrical parameters that were used. Hence, a meta-analysis could not be performed.

Figure 11: A quality assessment graph of included studies in a systematic review of the effectiveness of neuromodulation for BPS and CPP.

11a: Downs and Black quality index



11b: Jadad scale



There were two studies where patients had CPP and one with BPS. PTNS was used in three studies and no studies with SNS. In two of the studies a sham treatment was used, while one study had usual care as the comparator. The outcome measure symptoms used were pain, urinary symptoms and quality of life. Each of the studies used different outcome measurements. The McGill questionnaire (137), visual analogue scale (137, 139) and chronic prostatitis symptom index (NIH CPSI) were used to assess pain scores (139, 140). The interstitial cystitis symptom index (ICSI) (138) and NIH CPSI were used to measure urinary symptoms (139, 140). The SF 36 questionnaire (138), female sexual function index (FSFI) (137) and NIH CPSI were used to measure quality of life (139, 140).

The GRADE quality assessment is shown in table 14. Limitations were noted in the study design, directness and precision, with different interventions and questionnaires being used in each study. The emotional component of the quality of life outcome measure performed best as it was reported using the same questionnaire in two papers. This evidence was rated as 'moderate' quality, which indicates that further research may be likely to have an important

impact on the confidence of findings. There was one complication related to nerve stimulation; a needle insertion site hematoma experienced by one patient but there were no reported serious adverse effects.

Table 14: A GRADE assessment table for the evidence presented by outcomes in the included studies in a systematic review of the effectiveness of neuromodulation for BPS and CPP (141, 142).

Quality assessment							No of patients		Importance
Outcome (No of studies)	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Neuromodulation**	**Sham or no treatment**	
Pain (3)	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	86	83	⊕OOO VERY LOW
Urinary symptoms (2)	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	74	71	⊕OOO VERY LOW
Quality of Life (general) (3)	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	86	83	⊕OOO VERY LOW
Quality of Life (emotional) (2)	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[2]	None	41	39	⊕OOO VERY LOW

[1] Study design limitations - lack of blinding, no description of randomization, failure to document intention to treat analysis
[2] Indirectness - indirect comparisons between interventions, comparators, outcome measurement tools
[3] Imprecision - wide confidence intervals, few patients in studies

7.5 Discussion

There is limited available literature on the effectiveness of PTNS in improving pain, urinary symptoms and quality of life in patients with chronic pelvic and bladder pain syndromes, which shows variable success. No studies were found for SNS.

The small number of studies assessing the intervention with a comparator was the main limitation of this systematic review. This limits the inferences that can be drawn. The literature search performed was thorough and imposed no language restrictions. There were at least 30 studies found that did not have a comparator, these were excluded as no meaningful assessment could be performed. There were a variety of different questionnaires that were used to assess outcomes between the included studies. This made it difficult to directly compare scores for each symptom. The treatment follow up period was limited to 12 weeks, which was the duration of treatment, which meant meaningful long-term effectiveness of neuromodulation could not be assessed.

The benefit of posterior tibial nerve stimulation is that it is minimally invasive and can be performed in an outpatient setting (143). The frequency of repeat treatments and the frequency necessary to maintain good symptom control are uncertain. Lead avulsion in sacral nerve stimulation is a recognised complication which can cause sudden loss of function of the neuromodulator after trauma, as has been documented in case reports (144). Both PTNS and SNS are generally well tolerated, although they may cause transient needle site pain, tingling in the legs and local infection as possible side effects. These are usually transient or resolve with removal of the neuromodulator (145).

Neuromodulation is recommended as a fourth-line treatment for BPS, once lifestyle, oral and intravesical treatments as well as cystoscopy with hydrodistension have been tried. The evidence for treatment efficacy of nerve stimulation is level 2, according to both the American and Japanese BPS guidelines. This level of evidence was drawn from well-designed non-randomised or quasi-experimental studies. It was given a recommendation grade of C, which indicates that no clear recommendation for treatment is possible, (8, 23). Recent guidelines are recommending treatment initiation after careful clinical history and physical assessment, which can avoid delays in management and does not rely on diagnosis by cystoscopy, which can be unreliable (23). In order to fully evaluate the effectiveness of treatments, we need to understand the natural course of BPS but this is poorly understood (146).

The Food and Drug Administration (FDA) board approves medical devices in the United States of America. It has not approved the use of nerve stimulation for the treatment of BPS. The American Urological Association guidelines for the management of BPS recommend a trial of nerve stimulation if conservative measures have failed (23, 147). Although the precise mode of action of neuromodulation is unknown, it has the benefits of being minimally invasive and has the possibility to greatly improve the quality of life for patients with refractory pelvic pain (129, 148). This systematic review highlights the lack of good quality evidence for neuromodulation and the recommendation of a thorough investigation of the therapeutic and cost effectiveness needs to be undertaken. Sham treatments have previously been validated in a feasibility study (149). The importance of a prospective, large multi-centered clinical trial to investigate the effectiveness of PTNS and SNS to treat BPS and CPP in order to adequately assess treatment efficacy, long-term effects and produce reliable high quality evidence has been suggested in several studies (128, 150-152).

This chapter is based on the following peer-reviewed paper (81):

Nerve stimulation for chronic pelvic pain and bladder pain syndrome: a systematic review

SA Tirlapur, A Vlismas, E Ball, KS Khan

Acta Obstet Gynecol Scand 2013 Aug;92(8):881-7

CHAPTER 8:

ASSESSING OUTCOME MEASURES FOR TREATMENTS OF BLADDER PAIN SYNDROME: A SYSTEMATIC REVIEW OF THE LITERATURE

In this chapter I will discuss what are the core outcome measures for treatment effectiveness studies in BPS, along with how they are assessed and whether the impact factor of the journal influences the quality of outcome reporting.

8.1 Abstract

Background: The reporting of quality of outcomes in systematic reviews and randomised controlled trials (RCTs) is variable.

Objectives: To evaluate the quality of outcomes reported in systematic reviews and RCTs of BPS, along with the possible relationship with study quality and journal impact factor.

Data sources: The following databases were searched from inception until August 2013: the Cochrane Library, EMBASE, Medline, CINAHL, LILACS and SIGLE, without any language restrictions.

Study selection: A six-point scale was used to assess the quality of outcomes that were reported in systematic reviews and constituent RCTs. AMSTAR and Jadad scoring systems were used to calculate study quality. Each journals impact factor in the year of publication was recorded and Spearman rank correlation was calculated.

Results: A total of 28 RCTS with 1732 patients were reported in eight systematic reviews. Five outcome measures were described, which used 19 different measurement scales. These outcome measures were urinary symptoms (100%), pain (64%), quality of life (39%), general wellbeing (36%) and bladder capacity (36%). The quality of all outcomes was measured, and the mean score was 1.63 (95% CI 0.29 – 2.96) for systematic reviews and 3.25 (95% CI 2.80

– 3.70) for RCTs. There was a correlation between the quality of outcomes and the overall study quality (0.90, 95% CI 0.79 - 0.95, p <0.0001) but no correlation with journal impact factor (0.07, 95% CI -0.31 – 0.43, p = 0.35). Multivariable linear regression was calculated for quality of outcome reporting and study quality, showing a positive relationship ($\beta = 0.05$, $p < 0.0001$), with an adjustment for the effects of study type, impact factor and journal type.

Conclusion: These results highlight the need to generate a consensus to develop a core set of outcomes in bladder pain syndrome, which use standardised reporting tools that can be disseminated through good publication practice.

8.2 Introduction

Outcome measures are examined by effectiveness studies. There are inconsistencies in the reporting of outcomes and the tools that are used to measure these. There can also be missing outcome data along with outcome reporting bias, which is often seen across studies (153). It is essential to have consistency in the reporting of outcomes in order to allow direct comparison of effects. Inconsistency at any stage can delay or hinder evidence syntheses and limit the usefulness of study results and may ultimately have a negative impact on care quality. The development of core study outcomes is needed to improve the translation of evidence into practice (154).

In this chapter, I explored if the quality of reporting outcome measures was linked to other publication features, such as impact factor in the year of publication, study quality etc. There are many studies and reviews evaluating various treatments to achieve symptomatic control in BPS. A range of scores, scales and validated tools were used to measure these outcomes.

There was identification of primary and secondary study outcome measures used to assess BPS treatments in published systematic reviews and their constituent trials along with assessment of the variation and quality of these outcome measures. The relationship between the quality of outcomes that were reported and overall study quality and journal impact factor was performed in a controlled analysis with adjustment for the year of publication and factors like the presence of commercial funding, study design and the journal type.

8.3 Methods

There was prospective adherence of a protocol based on contemporary methods and reported in accordance with the PRISMA guidelines for this systematic review (62).

Search strategy

The Cochrane Library, EMBASE (1980-2013), Medline (1950-2013), CINAHL (1981-2013) and LILACS (1982-2013) were searched for relevant citations from the date of inception to August 2013, along with searches in the grey literature in SIGLE (1990-2013), with no language restrictions. The following MeSH headings were used 'interstitial cystitis' or 'painful bladder syndrome' or 'bladder pain syndrome', along with their keywords and variants, which were combined using the Boolean operator 'and' with the term 'systematic review' within the title or abstract. There was hand searching of the bibliographies from relevant articles and conference proceedings of the International Continence Society in order to capture any references not found through electronic database searches.

Study selection and data extraction

I used the definition of a systematic review to be one in which at least two databases were used to perform literature searches, along with the PRISMA guidance for reporting and evaluating treatments for BPS. I noted whether primary and secondary outcomes had been described and recorded, as well as the measurement tools or questionnaires, which had been used to collect this information. This usually took the form of patient-rated improvement scores (23). In order to evaluate a possible relationship between quality of outcome reporting and journal type, I recorded the type of journal (general or specialist) that studies were published in, the journal impact factor in the year of publication, along with any recorded sources of pharmaceutical funding and whether any sample size calculations had been

performed for randomised controlled trials (RCTs). As for other systematic reviews, all data were extracted in duplicate by two independent researchers (SAT, RNR) using an electronic pre-designed data extraction form and any disagreements in results were resolved through consensus after discussion.

Quality assessments

All outcomes reported in systematic reviews and RCTs were assessed for quality. A six-point scoring system was used with the following questions (155): if a primary outcome was stated (1-point), if a clear definition was provided for reproducible measurement (1-point), if a secondary outcome was stated (1-point), if a clear definition was provided for reproducible measurement (1-point), if the authors explained the use of the outcomes (1-point) and if methods were used to enhance quality of measures, for example repeating measures or training in use of measurement tools (1-point). As measuring the quality of core outcomes is a relatively new concept, there is no rating system for these questions. Therefore, an arbitrary level of ≥ 4 was used to represent 'good' quality. The six questions have been used in published literature on core outcome development and hence were used to assess quality, as there does not appear to be any alternative tool (155).

The 11-point AMSTAR (assessment of multiple systematic reviews) measurement tool was used to assess study quality for systematic reviews. This served as a standardised checklist, which evaluated study methodology, study characteristics, quality assessment, publication bias assessment and any conflict of interest declaration. All of the 11 questions were answered with yes, no, cannot be answered or not applicable. Scores of eight to 11 were designated as 'high' quality, scores of four to seven were 'medium' quality and 0 to three were 'low' quality (156). Quality assessment of RCTS was performed using the Jadad

criteria, which evaluates the methodology used, while taking into account patients who drop out of the study, scoring all five questions with an answer of yes or no. The scores can range from 0-5, where 'good' quality is assigned to scores ≥ 3 (134). Both the AMSTAR and Jadad quality assessment scores were transformed into a 0-100 scale in order to graphical display results and perform analysis.

Data synthesis

Study characteristic were represented in tabular form and Spearman's rank correlation was calculated with 95% confidence intervals (CI) for the quality of reporting outcomes versus overall study quality assessment, and for the quality of reporting outcomes versus journal impact factor in the year of publication. A multiple regression analysis was performed to assess a possible relationship between quality of reported outcomes and study quality, using StatsDirect version 2.7.9. It was adjusted for the following factors: impact factor, year of publication, commercial funding and study and journal type.

8.4 Results

The selected articles are summarised in figure 12. There were eight systematic reviews with a total of 1732 patients (157-164). I excluded four articles as three of them did not adhere to the definition of a systematic review and one did not affect patients with the target condition of BPS (127, 165-167).

Figure 12: Flow chart of systematic review selection

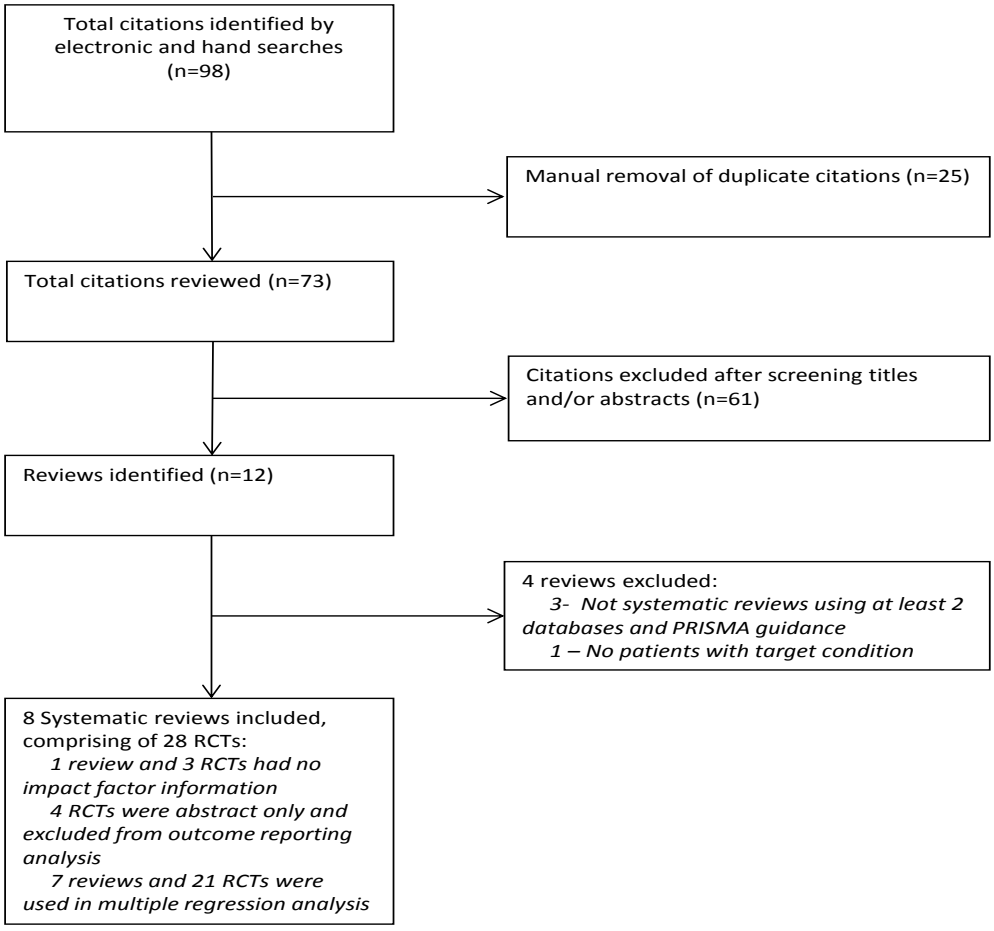


Table 15 identifies all the different outcomes reported and the types of measurement tools used in each RCT and systematic review.

Table 15: Characteristics of systematic reviews for treatments of bladder pain syndrome.

Author (Year)	Impact factor (AMSTAR)	Treatment	No. of RCTs (no. patients)	No. of studies (total patients)	Outcome	Tool	No RCTs per outcome
Srivastava (2012)	Not documented (3)	SNS	1 (22)	11 (480)	Pain	VAS	1
					QoL	GRA, SF 36, BDI	0
					Urinary	ICPI, PUF	0
					Bladder capacity	ND	0
Dawson (2009)	4.65 (11)	Intravesical treatments	8 (586)	9 (616)	Pain	VAS, NRS	3
					QoL	ICSI, Rand 36	5
					Urinary	ICSI, GRA, PUF	4
					Bladder	Diaries, UDS	4
					Economic	ND	0
Dimitrakov (2007)	8.39 (6)	Pharmacological	21 (1470)	21 (1470)	Urinary	ICSI/PI, diary	21
					Global status	ND	0
Mangera (2011)	8.49 (4)	Botulinum toxin A	1 (20)	9 (231)	Pain	VAS	1
					Urianry freq	ND	1
					Nocturia	ND	1
					Bladder	UDS	0
					Global QoL	CPSI, PSS, GICS, AUA SI	1
Matsuoka (2012)	2.17 (5)	Intravesical treatments	5 (596)	5 (596)	Pain	VAS, PUF	3
					QoL	SF 36, Rand 36	0
					Bladder	UDS	3
Mourtzoukou (2008)	2.38 (2)	Intravesical resiniferatoxin	3 (203)	6 (225)	Pain	VAS, PUF	3
					QoL	ND	0
					Urinary	GRA, ICSI, voiding	3
Tirlapur (2013)	1.85 (7)	Neuromodulation	1 (56)	1 (56)	Pain	ICSI/PI	1
					QoL	ICSI/PI	1
					Urinary	SF 36	1
Tirumuru (2012)	1.73 (7)	Intravesical Botulinum toxin	3 (155)	10 (260)	Pain	VAS	2
					Urinary	BFLUTS, GRA, IIQ, ICSI, KHQ	2
					Bladder	UDS	2
					QoL	IPPS, UDI	2

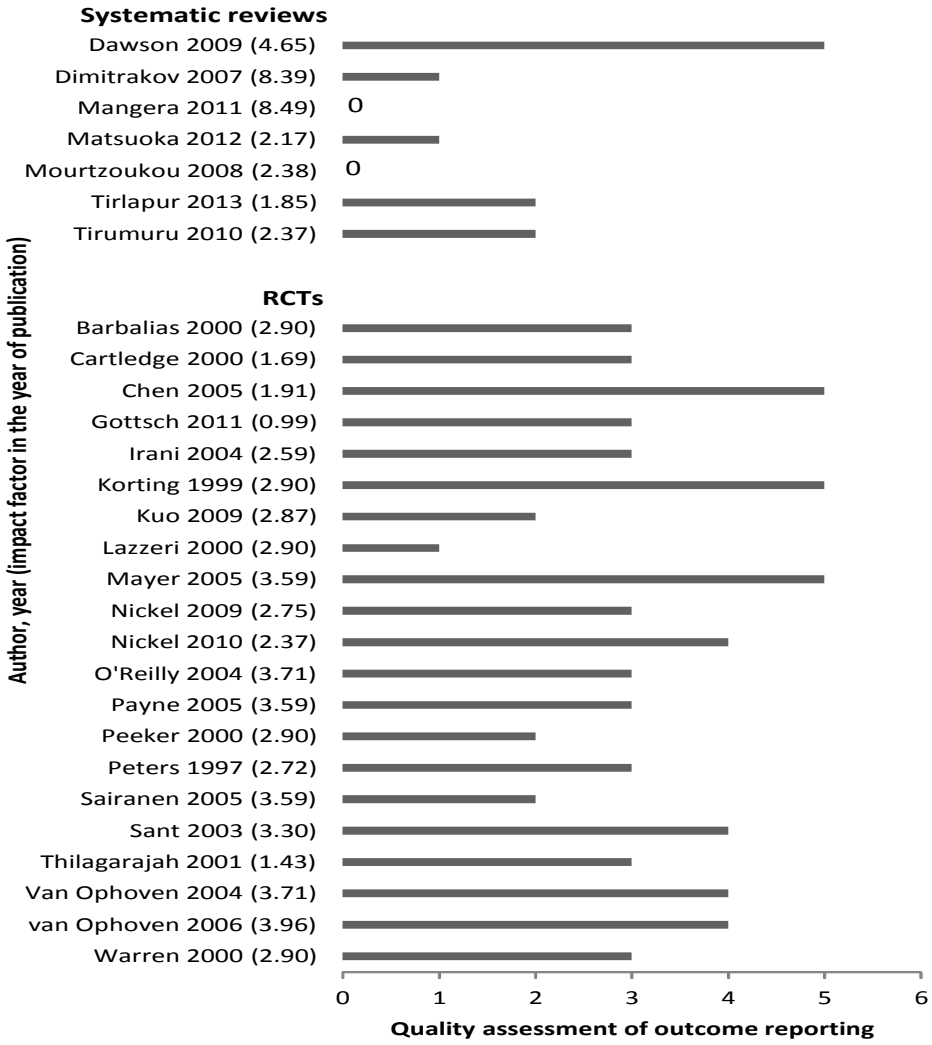
SNS: sacral neuromodulation; **QoL:** quality of life; **ND:** not documented; **UDS:** urodyanmics
AMSTAR: Assessment of multiple systematic reviews; **VAS**: visual analogue scale; **GRA**: global response assessment; **SF 36**: short-form 36 quality of life survey; **BDI**: Beck's depression inventory; **ICPI**: interstitial cystitis problem index; **PUF**: pelvic pain urgency/frequency; **NRS**: numeric rating scale; **ICSI**: interstitial cystitis symptom index; **RAND 36**: Research and development health survey; **CPSI:** chronic prostatitis symptom index; **PSS**: perceived stress scale; **GICS**: global interstitial cystitis score; **AUA SI**: American Urological Association symptom index; **BFLUTS**: Bristol female lower urinary tact symptoms; **IIQ**: incontinence impact questionnaire; **KHQ**: King's health questionnaire; **IPPS**: International prostate symptom score; **UDI**: urogenital distress inventory

In the 28 unique RCTs that were identified (138, 168-192), there were five outcomes, which were; urinary symptoms, pain, quality of life, general wellbeing and bladder capacity. Every RCT (100%) had the outcome of urinary symptoms, which were measured with seven different tools. In 18 RCTs (64%) five different tools were used to measure pain. In 11 RCTs (39%) six different tools were used to measure quality of life. In 10 RCTS (36%) only one tool was used to measure general wellbeing and in 12 RCTs (43%) one tool was used to measure bladder capacity. For the outcome of quality of life, the general or 'physical' component of the measurement tool was used, rather than the emotional or 'mental' component, which is referred to in the SF 36 questionnaire. The mean AMSTAR score of 5.63 (95% CI 3.26 – 7.99) was calculated for quality of systematic reviews. The mean Jadad score of 3.13 (95% CI 2.58 – 3.67) was calculated for quality of RCTS.

On analysing the type of journal, I found that half of the systematic reviews were published in specialists' urology or urogynaecology journals (n= 4), 13% (n = 1) were published in a general obstetrics and gynaecology journal and 38% (n = 3) in non-women's health journals. It was noted that 100% of RCTs were published in specialty urology or urogynaecology journals (n = 28). The sample size was only calculated in 46% (n = 15) of RCTS. There was no pharmaceutical company funding in any of the of systematic reviews but was present in 33% (n = 8) of RCTs.

In 21 RCTs and seven systematic reviews the quality of outcomes was assessed (figure 13). Despite several attempts to contact the authors, the full text for four RCTs could not be obtained so these were excluded from this analysis, since it was not possible to accurately assess quality from the limited information provided in the study abstract (174, 181, 193, 194).

Figure 13: Quality of outcomes reported for systematic reviews and randomised controlled trials (RCTs)

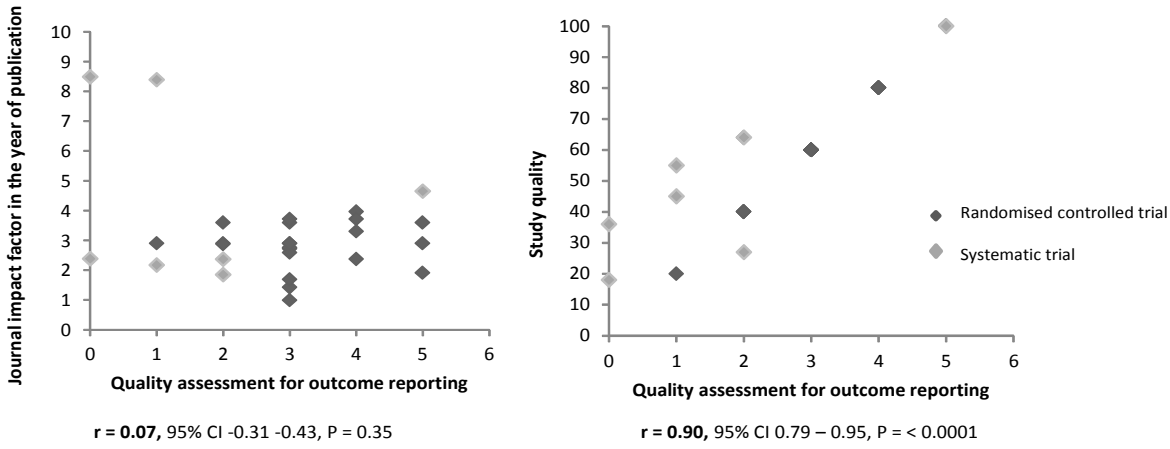


Systematic reviews had a mean score of 1.63 (95% CI 0.29 – 2.96) for quality of outcomes and RCTs had a mean score of 3.25 (95% CI 2.80 – 3.70). There was good quality of reported outcomes in 13% (n = 1) of systematic reviews and in 33% (n = 8) of RCTS, which is represented in figure 13. There was no difference in the reporting of primary outcomes (4 versus 21, 50% versus 88%, p = 0.51), however, I did find that secondary outcomes were

reported more frequently in RCTs compared to systematic reviews (1 versus 11, 13% versus 46%, p = 0.003).

The relationship between the quality of reported outcomes with impact factor in the year of publication and study quality in all the included systematic reviews and RCTs is represented in figure 14. There was an exclusion of one systematic review and three RCTs because the information about the journal impact factor in the year of publication could not be obtained (162, 168, 180, 190). There was a positive correlation between the quality of outcomes reported and the study quality (0.90, 95% CI 0.79 - 0.95, p = <0.0001) but there was no correlation with journal impact factor (0.07, 95% CI -0.31 – 0.43, p = 0.35) when the Spearman's rank coefficient was calculated.

Figure 14: Relationship of quality of outcomes reporting with journal impact factors at publication and overall study quality.



The positive correlation between quality of outcome reporting and study quality was confirmed using multivariable linear regression analysis (β= 0.05, p < 0.0001) with adjustment for effects of study type, impact factor and journal type (table 16). There was an

association between the quality of reporting outcomes and systematic reviews versus RCTs (β = -1.24, p < 0.0001), specialist versus general journals (β = -0.41, p = 0.03), and lower versus higher impact factor (β = -0.07, p = 0.02).

Table 16: Multiple linear regression analysis to determine factors associated with quality of outcome reporting.

Factor	Univariable		Multivariable*	
	β	p	β	p
Study quality+	0.05	<0.0001	0.05	<0.0001
Impact factor at publication	-0.08	0.02	-0.07	0.02
Type of study (systematic review/RCT)	-1.20	<0.0001	-1.24	<0.0001
Journal type (specialist/general)	-0.40	0.05	-0.41	0.03
Year of publication	-0.01	0.70	-	-
Commercial funding	-0.01	0.93	-	-

+ measurement details in methodology section
* Based on best sub-set regression

8.5 Discussion

In this chapter I have shown that studies use several outcomes as reporting endpoints, and these are measured using various tools to assess treatment effectiveness in BPS. Most studies on treatment effectiveness are observational with a lack of RCTs, possibly due to the difficulty using placebo or sham procedures for surgical interventions. The quality of reporting outcomes was poor. I found that the reporting of secondary outcomes was better in individual RCTs compared to systematic reviews. Generally, the quality of individual systematic reviews and RCTs was variable. Dawson et al had the best quality systematic review, assessing intravesical treatments for BPS. This paper clearly described the primary and secondary outcomes and performed well using the quality assessment tools. However, this study was a Cochrane collaboration publication which needs to adhere to the Cochrane

guidance and hence incorporates all expected elements of reporting a systematic review, which may explain its high quality (157). Surprisingly, Mangera et al had the publication with the highest impact factor but this had the lowest quality assessment score because it did not describe the primary or secondary outcomes (159). A positive relationship was noted between the quality of outcomes reported and the quality of a study. Contrary to belief, there was no relationship between quality of outcomes and journal impact factor, which may suggest the authors with good quality studies do not aim to publish in high impact journals, resorting to speciality specific journals, which are often lower ranking.

The five outcomes of urinary symptoms, pain, quality of life, bladder capacity and general wellbeing were assessed using a variety of patient-reported questionnaires. These questionnaires were composed of a composite symptom and sign scores and visual analogue scales. There was a lot of heterogeneity, which made it impossible to compare the effects on treatment as I was unable to evaluate their impact on disease (195). The problem with many patient-reported questionnaires is that they lack the ability to be truthful. They are often difficult or unfeasible to replicate and do not have discriminative power to gauge the reliability and sensitivity of the measurement tool (196). The patient populations varied as RCTs were international with so no meaningful comparisons could be made relating to ethnicity, disease effects on different patient groups and treatment effectiveness.

The five outcome measures identified in this chapter may serve as a starting point for the development of a core outcome set. In order to develop and prioritise a finalised set of outcomes, a Delphi consensus panel survey of stakeholders, including patient representatives would need to be undertaken (197). The Grading, Recommendations, Assessment, Development and Evaluation (GRADE) working group recommendation scale allows

outcome measures to be prioritized, in order to improve standardisation and transparency of results by rating outcomes from ‘critically important’ to ‘not important’ (141, 198).

In the field of urogynaecology, there are attempts to standardise terminology (199, 200). In order for this to happen, we need standardised, validated tools, which give clear reporting on time of testing to allow repeatable results. This will allow the development of an inventory of core outcomes (155). Many common gynaecological conditions need core outcomes to be developed, with intended primary and secondary outcomes explicitly described, to facilitate and improve the transparency of results in trials, reviews and guidelines. Symptom severity and general physical and mental quality of life are the ‘soft markers’ often forgotten but so important to patients as a means of evaluating treatment effectiveness. Although there are many validated disease-specific questionnaires that can be used for BPS, there is no single internationally adopted one. Delphi panels of specialists may be used to develop a single symptom-based questionnaire, which incorporates the five core outcomes identified in this paper. This is especially important in diagnosing a condition, which has no gold standard diagnostic criteria and often depends on recognition of patient symptoms.

In order to minimise reporting bias, it is necessary to have methods of measuring outcomes, and the reporting of frequency of incomplete outcomes in results to improve the reliability of outputs from evidence syntheses (201-203). The CROWN (CoRe Outcomes in WomeN’s health) initiative is a working group, which has been recently set up, led by journal editors in obstetrics and gynaecology to minimise inconsistencies in the reporting of outcomes and avoid reporting bias in women’s health (204).

This chapter is based on the following peer-reviewed publication (205):

Variations in the reporting of outcomes used in systematic reviews of treatment effectiveness research in bladder pain syndrome

SA Tirlapur, R Ni Riordain, KS Khan in collaboration with EBM-CONNECT

Eur J Obstet Gynecol Reprod Biol. 2014 Jun 13;180C:61-67

CHAPTER 9:

ASSESSING THE DISCREPANCIES IN GRADING OF EVIDENCE FOR THE MANAGEMENT OF BLADDER PAIN SYNDROME

In this chapter I explore the different rating systems to evaluate the quality of evidence available on the management of BPS.

9.1 Abstract

Background: There are a variety of international clinical guidelines on bladder pain syndrome (BPS). These rate quality of evidence, which is based on the study design. Along with the quality of evidence described in current BPS guidelines, we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, which accounts for several domains to assign quality ratings apart from the limitations of study design.

Methods: We reviewed clinical guidelines and all existing systematic reviews on the management of BPS along with the evidence included, which was rated according to GRADE on a four-point scale (1- 4, from very low to high). The GRADE ratings were compared to the other two reported quality assessments; level of evidence 1- 4, from meta-analysis of randomised studies to expert opinion; strength of evidence 1- 4, from very low to high.

Results: 19 treatments were identified for BPS where GRADE ratings were assigned. In comparison with level of evidence ratings, the latter overestimated quality by 1.8 points (1.1 v 2.9; 95% CI of mean difference 1.2 to 2.3; p= <0.0001). In comparison with strength of evidence ratings, the latter overestimated quality by 1.7 points (1.1 v 2.8; 95% CI of mean difference 1.3 to 2.1; p= <0.0001).

Conclusion: The GRADE quality scoring system is a refined method of assigning quality to evidence, which provides a more conservative measurement of quality of evidence that can give a realistic assessment of the value of recommendations, which can be considered in practice.

9.2 Introduction

There have been numerous treatments suggested for BPS with varying evidence about their effectiveness.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system assesses the quality of evidence using several domains which include: study design, indirectness, imprecision, inconsistency and risk of bias (206, 207). This system was developed allowing clinicians to evaluate the evidence and strength of recommendations in systematic reviews and guidelines by creating transparency over the reporting of evidence. The quality of evidence is usually summarised focusing on the study design in existing guidelines (8, 23). Hence, traditionally high quality was assigned to randomised controlled trials (RCTs) without a distinction to whether the RCT was high and low quality. In these situations the GRADE evaluation can be helpful (208).

The different methods of evaluating evidence and recommendations for BPS in current guidelines are assessed and I explore how recommendations may be affected if the GRADE approach were to be adopted.

9.3 Methodology

Medline and EMBASE databases were searched from inception to May 2013 using the following search terms and word variants: ‘chronic pelvic pain’ OR ‘interstitial cystitis’ OR ‘painful bladder syndrome’ OR ‘bladder pain syndrome’ combined with the Boolean operator AND with ‘guideline’ OR ‘systematic review’. Hand searching for additional articles not identified through electronic database was performed. Quality of evidence in recent

guidelines was compared using the GRADE approach versus standard quality measures. The 2009 Japanese guidelines for IC used level of evidence scores ranging from 1-4 where 1 was assigned to an RCT and 4 was assigned to expert opinion, along with strength of evidence scores A, B, C or D where A represented highly recommended treatments with evidence from good quality studies and D represented treatments that were not recommended (8). In 2011 the AUA produced their guidelines on the management of BPS which used strength of evidence assessments (23). In addition to these two guidelines, information from 2012 European Association of Urology guidelines on the management of chronic pelvic pain, which used both level and strength of evidence scores, a 2008 review and 2012 systematic review on the management of the painful bladder were obtained in order to incorporate all available sources of information (127) (24, 103).

GRADE methodology

The evidence was assessed for each treatment option according to GRADE, incorporating five domains, which were study design, inconsistency, indirectness, imprecision and risk of bias. Historically, randomised trials have been considered as 'high' quality studies and observational studies are 'low' quality. Downgrading of evidence occurs when assigning a score for study design (207). Inconsistency is associated with relative treatment effects, where scores may be downgraded if there are different point estimates, overlapping confidence intervals and lack of heterogeneity (209). The domain of directness compares important interventions in applicable populations with patient-related primary outcomes. There is indirectness when a study does not correctly address these (210). There may be imprecision within a study when large confidence intervals, small sample sizes or numbers of events are observed (211). The limitations in study design can lead to a high risk of bias, which includes failure of adequate concealment, blinding, adherence to intention to treat

analysis and accountability of losses to follow up in RCTs, as well as selective reporting and inappropriate use of controls in observational studies (142).

Downgrading of evidence occurs every time there is a deficiency; by one level, ranging from no deficiency to serious to very serious deficiencies. These assessments are dependent upon the reviewer's subjectivity. The quality of evidence may also be subject to downgrading from high quality where further research is unlikely to change our confidence in the effect, moderate, low and very low evidence where any estimate of effect is very uncertain (208).

Comparison of GRADE with level of evidence in guidelines

I compared the recommendations and levels of evidence in guidelines on the diagnosis and management of BPS from the United States of America (23), Japan (8), Europe (24) and a recent systematic review (127) to GRADE assessment. Quality ratings in the guidelines used four-point ordinal scale for level of evidence; level 1a was meta-analysis of a randomised control trial and level 4 was expert opinion and in strength of evidence ratings, A represented a highly recommended treatment to D for a treatment that was not recommended. Definitions of GRADE, level and strength of evidence scores are summarised in table 17. If any discrepancies arose regarding the rating scores between guidelines, there was a review of the evidence and the most accurate score was awarded.

Table 17: Quality assessment methods used in different guidelines for the management of bladder pain syndrome (23, 103).

Quality assessment method		Numerical scale assigned for analysis
Level of evidence*		
1a	Meta-analysis of randomised control trials (RCT)	4
1b	Evidence obtained from a single RCT	4
2a	Evidence obtained from one well-designed, controlled study without randomization	3
2b	Evidence obtained from one other type of well- designed quasi-experimental study	3
3	Evidence obtained from non-experimental studies (comparative, correlation or case-reports)	2
4	Evidence obtained from expert committees, expert opinions or clinical practice	1
Strength of evidence**		
A	Highly recommended – Clinical studies of good quality and consistency including at one RCT	4
B	Recommended – Well-conducted clinical studies without randomised trials	3
C	No clear recommendation possible – Absence of directly applicable clinical studies of good quality	2
D	Not recommended	1
Grading, Recommendations, Assessment, Development and Evaluation (GRADE) ***		
4	High	4
3	Moderate	3
2	Low	2
1	Very low	1

* e.g. Japanese guidelines for interstitial cystitis, European Urology Association guidelines for chronic pelvic pain

** e.g. American Urology Association guidelines for bladder pain syndrome

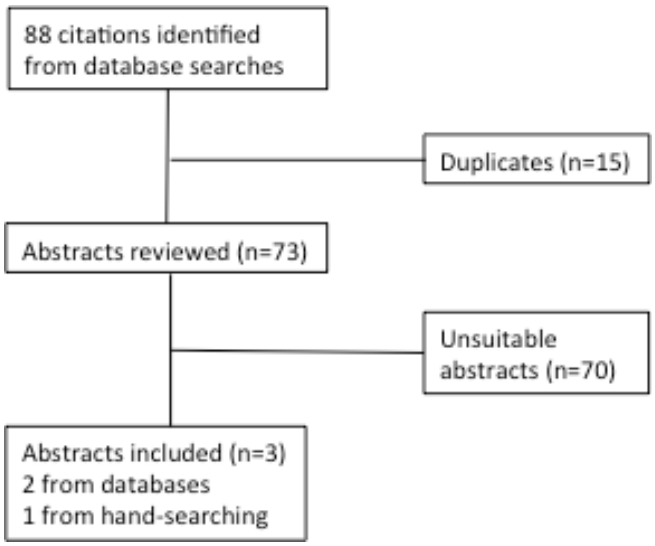
*** See methodology for details and table 2 for a worked example of a GRADE table

Stats direct software programme were used for statistical analysis in order to calculate the mean and median differences and 95% confidence interval for strength of evidence versus GRADE and level of evidence versus GRADE.

9.4 Results

Three suitable guidelines were identified from 88 citations. These were: The 2009 Japanese Urology Association clinical guidelines for interstitial cystitis, the AUA guidelines for the diagnosis and management of IC/BPS in 2011 and the 2012 European Urology Association guidelines on chronic pelvic pain (8, 23, 103) (figure 15).

Figure 15: A flow chart identifying suitable guidelines for bladder pain syndrome.



First line treatments (conservative management):

Self-care and behavioural modifications: In a 2012 published survey involving 1,982 patients, it was revealed that 87.6% reported a symptomatic improvement with an elimination diet and 86.1% by completely avoiding certain items. Treatment durations were not indicated.

65.2% of patients reported a symptomatic improvement by participating in regular exercise (212).

Stress management: In the same 2012 survey, there was symptomatic improvement in 76.4% of patients using relaxation techniques, 66.8% reported improvement using meditation, 64.5% when listening to music and 80.5% reported improvement while employing stress reduction to their lifestyle (212).

Second line treatments:

Manual physical (massage) therapy: The effectiveness of massage therapy was assessed in an electronic questionnaire which revealed that 74.2% of patients experienced symptomatic improvement with this treatment, 61.5% with physical therapy and 66.1% through a combination of physical therapy with internal treatment (212).

Analgesia: There is no available data about the efficiency of different forms of analgesia in the treatment of BPS.

Oral Amitriptyline: This H1 receptor antagonist can modify pain transmission in the central nervous system to relieve symptoms in BPS. In one prospective randomised control double-blind study, which was undertaken on 50 patients, they were treated with a self-titrating dose of amitriptyline over 4 months, to a maximum dose of 100mg. There was a reported decrease in the mean scores for the O'Leary-Sant symptom questionnaire of 8.5 points in the treatment group and 3.5 in the control group. There was a demonstratable improvement in pain and urgency symptoms that was statistically significant (182). The commonly noted side effects

of amitriptyline are dry mouth and weight gain. In long-term follow up studies of 19 months, 46% patient satisfaction was observed with treatment (213).

Oral Cimetidine: A placebo-controlled randomised double blind study, which compared 36 patients treated with a three-month course of 400mg oral cimetidine versus placebo twice daily, showed a marked improvement in the treatment group in pain and urinary symptoms, especially in nocturia. More than ten years ago, it was reported that post treatment cystoscopy and bladder biopsies showed no histological changes, which would not be a surprising finding in this day (185).

Oral Hydroxyzine: There is one reported randomised study comparing a treatment group of 31 patients who were treated with a three week course of 10-50 mg hydroxyzine daily then were on he highest dose for 21 weeks compared to a placebo group. In 31% of treated patients a response rate was found compared to 20% of the control group (187).

Oral Pentosan polysulfate sodium (PPS): PPS is thought to repair the damaged glycosaminoglycan (GAG) layer of the bladder mucosa, which acts as a protective mechanism (8). There are two prospective double-blind studies evaluating the effectiveness of PPS. In the first one 115 patients were treated with a four month course of 200mg PPS twice daily but showed no difference in scores for pain or urinary symptoms in the treatment and placebo arms. The second study had 148 patients who were treated with 100mg PPS three times daily. There was a 32% improvement in symptoms in the treatment group compared to a 16% improvement in the placebo group (193, 214).

Intra-vesical dimethyl sulfoxide (DMSO): DMSO has a combination of effects. It acts as an analgesic, anti-inflammatory and muscle relaxant (8). In one prospective cross-over study it was reported that 33 patients who were randomised into treatment with 50% DMSO or placebo (normal saline) for a two week period with two treatment sessions each week had a 93% objective improvement in the treatment group and 35% in the placebo group (174). The main side effects of DMSO are a garlic-like odour and bladder spasm.

Intra-vesical Heparin: 48 patients were treated with 10,000 units of heparin in 10mls sterile water in one observational study. This was instilled three times a week for three months. Over a three month period, 56% of patients achieved clinical remission and after one year 50% of patients had symptomatic control (215).

Intra-vesical Lidocaine: Lidocaine is a local anaesthetic which blocks sensory nerve fibres in the bladder. 102 patients were treated in one randomised double-blind study with 200mg intravesical lidocaine with alkalinised instillation of 8.4% sodium bicarbonate to a final volume of 10mls versus a placebo treatment over a five-day course. In the treatment group 30% of patients reported a moderate or marked symptom improvement, whereas only 9.6% of the placebo group reported improvement over a 29 day follow up period (160).

Third line:

Cystoscopy with short-duration low-pressure hydrodistension: Cystoscopy used to be used solely as a diagnostic tool but is nowadays also used as a treatment if conservative treatment measures have failed. There are effectiveness data from three observational studies, which describe variable symptomatic improvement after treatment in a total of 265 patients but the effects are short-lived and within six months symptoms had recurred in the majority of

patients (216-218). A recognised but rare complication of prolonged bladder distension is rupture, therefore low-pressure distension is advised (219).

Fulguration +/- triamcinolone for Hunner's lesions: There are two observational studies which report successful outcomes when using Nd:YAG laser under cystoscopic control in BPS with Hunner's ulcers. In 51 patients who were treated in this way, 88% expressed symptomatic relief within 2-3 days of treatment. However, 45% needed additional treatment within 23 months of initial treatment (220, 221).

Fourth line:

Neurostimulation: There is limited data on the effectiveness of sacral and posterior tibial nerve stimulation (neuromodulation) for the treatment of BPS. There are no randomised trials that compare these treatments with a placebo. There is one observational study that reported efficacy of posterior tibial nerve stimulation in 18 patients. There are six studies that have reported effectiveness of sacral nerve stimulation in a total of 150 patients, both showing improvements in symptoms and quality of life scores (222-227). While both forms of nerve stimulation are effective, they are minimally invasive procedures that need frequent repeat treatment to sustain the treatment effect, which may deter patients.

Fifth line:

Cyclosporin A: There have been two RCTs evaluating the effectiveness of cyclosporine A. Both of them compared a six-month course of oral cyclosporin A versus oral pentosan polysulfate sodium (228-230). In the treatment group, 75% of patients had a symptomatic improvement, compared to 19% of the PPS group but it is difficult to directly compare results as the intervention was not compared to a placebo. The urinary marker, epidermal growth

factor (EGF), has been shown to be higher in BPS patients, and EGF levels were found to be significantly reduced in the treatment group.

Botulinum toxin A: This is a treatment, which is administered when other treatments have failed to control symptoms. There is one systematic review that evaluated botulinum toxin A in the treatment of BPS, which included data from three RCTs and seven prospective cohort studies with a total of 260 patients. In eight studies there was a symptomatic improvement, even though although 7% of patients needed post-treatment self-catheterisation (231).

Sixth line:

Major surgery: This is often considered the last resort for refractory BPS. Surgical management takes the form of a total cystectomy and urinary diversion will lead to self-catheterisation. Patients also need to be aware of the complications of persistent pelvic pain and pouch pain post-surgery (8). 47 patients who had reconstructive surgery for BPS were reviewed in a retrospective observational study, which found that 82% of patients with Hunner's ulcerations had symptomatic relief after surgery. This compared with 23% of patients with non-ulcer disease after an average of 89 months follow up period (232).

Treatments that should not be offered (not recommended):

Long-term oral antibiotics: The practice of using long-term rotating antibiotics to treat BPS is not recommended. There was one RCT, which compared sequential antibiotics versus placebo but showed no significant benefit, with a high proportion of adverse effects reported. (184). In the study 50 patients were randomised to receive an 18-week course of antibiotics. These were rifampicin plus a sequence of doxycycline, erythromycin, metronidazole, clindamycin, amoxicillin and ciprofloxacin for three weeks each, or a placebo. In the

treatment group, 48% reported overall improvement compared to 24% in the placebo group (p = 0.14), but 10 (20%) patients in the treatment group and five (10%) in the placebo group noticed improvement in pain and urgency (p = 0.22). 80% of patients in the antibiotic treatment group suffered from had adverse effects, in comparison to 40% in the placebo group (p = 0.009).

Intravesical instillation of Bacillus Calmette-Guerin (BCG): No clinical benefit has been reported using BCG instillation treatment, although serious adverse effects are anticipated and have been reported in studies. There are two RCTs, which compared intravesical BCG with placebo in 282 patients over a six-week period (171, 175). There was no reported statistical difference for symptomatic outcomes for patients in the BCG treatment arm but there were a large number of adverse outcomes, which included arthralgia, headaches and infection. A 68 week extended follow up period was undertaken for 86% of the treatment group and 75% of the placebo group who felt there was a marked or moderate symptomatic improvement (233). The second smaller RCT of 30 patients observed a 60% improvement in symptoms within the treatment group compared to 27% in the placebo group (P = 0.065).

High-pressure, long-duration hydrodistension: Hydrodistension is performed at the time of cystoscopy where high-pressure water of greater than 80-100cm, stretches the bladder for a prolonged duration of greater than 10 minutes. This may cause adverse effects, with the most serious being bladder rupture or sepsis. Three observational studies have reported outcomes for this intervention. They showed variable efficacy rates, ranging from 22-67% with at least one case of bladder rupture in each study (23, 234, 235). Guidelines have recommended avoiding this treatment option as the risks far outweigh the benefits.

Oral long-term glucocorticoid: The side effects associated with use of long-term steroids, such as prednisolone, have led to this treatment not being recommended as a therapy for BPS. Limited data exists on the therapeutic effectiveness with only one observational study, which treated patients with prednisolone and hydrodistension simultaneously so meaningful comparisons of efficacy could not be evaluated (236).

Rating of evidence with GRADE versus strength of evidence in guidelines

An example of a GRADE table is seen in table 18, which uses second-line treatments for BPS as an exemplar, created using GRADE software.

Table 18: A sample GRADE table: Second-line treatments for bladder pain syndrome.

Quality assessment								Quality
Treatment	**No of studies**	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	
Oral analgesia	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Oral hydroxyzyine	1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	⊕OOO VERY LOW
Manual physical therapy	1	observational studies	very serious[1]	very serious	no serious indirectness	no serious imprecision	reporting bias[2]	⊕OOO VERY LOW
Oral amitriptyline	1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	⊕⊕OO LOW
Oral cimetidine	1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	⊕⊕OO LOW
Oral pentosan polysulfate sodium (PPS)	2	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	reporting bias[2]	⊕OOO VERY LOW
Intravesical dimethyl sulfoxide (DMSO)	1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	⊕OOO VERY LOW
Intravesical heparin	1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	⊕OOO VERY LOW
Intravesical lidocaine	1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	⊕⊕OO LOW

[1] Lack of blinding, failure to report intention to treat, method of randomisation, lack of allocation or concealment
[2] Evidence based on less than 10 trials
[3] Variations in outcome assessment tools, populations compared

In figure 16, the scores for the level of evidence score were compared to GRADE, to show any overestimations in the scores. There were 19 comparable treatment options, which were all downgraded with six of these options being downgraded by three points, from 'high' to 'very low', four options were downgraded by two points and nine of them by one point. There was a mean over estimation score of 1.8 (1. v 2.9, with a 95% CI of mean difference of 2.3 to 1.2; p = <0.0001 using an unpaired t test. Using the Wilcoxon's signed rank test the median difference was 2 (95% CI of 2.0 to 1.0).

Figure 16: Graphical representation of the level of evidence score versus GRADE for the management of bladder pain syndrome

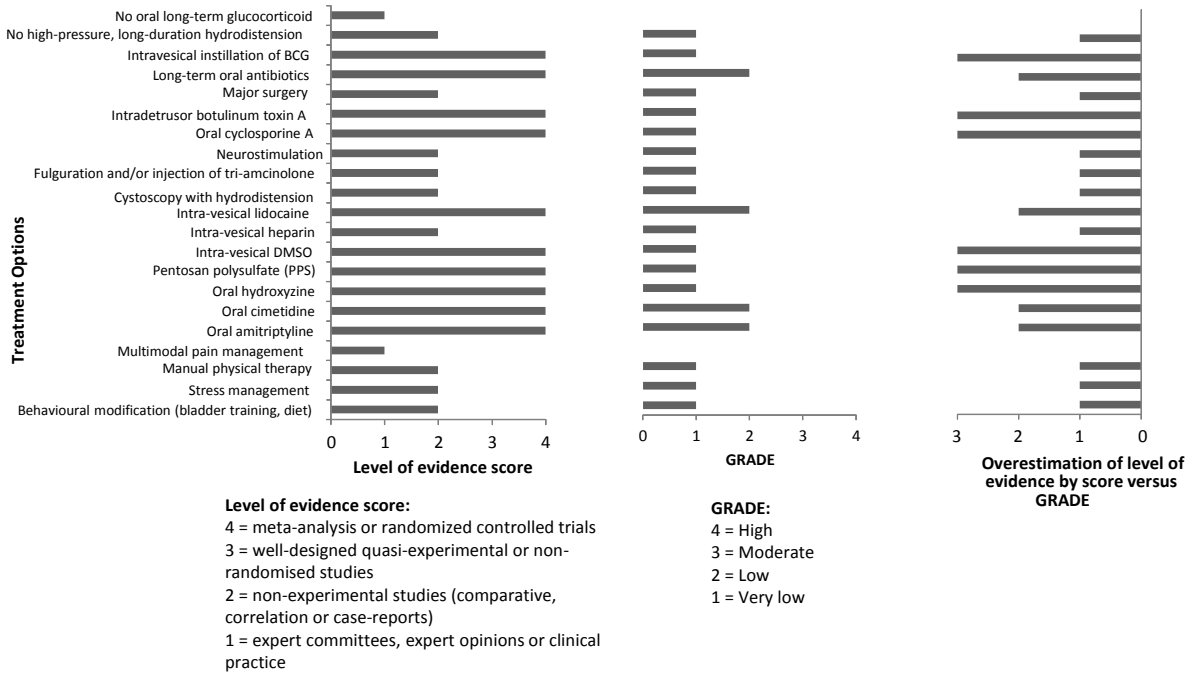
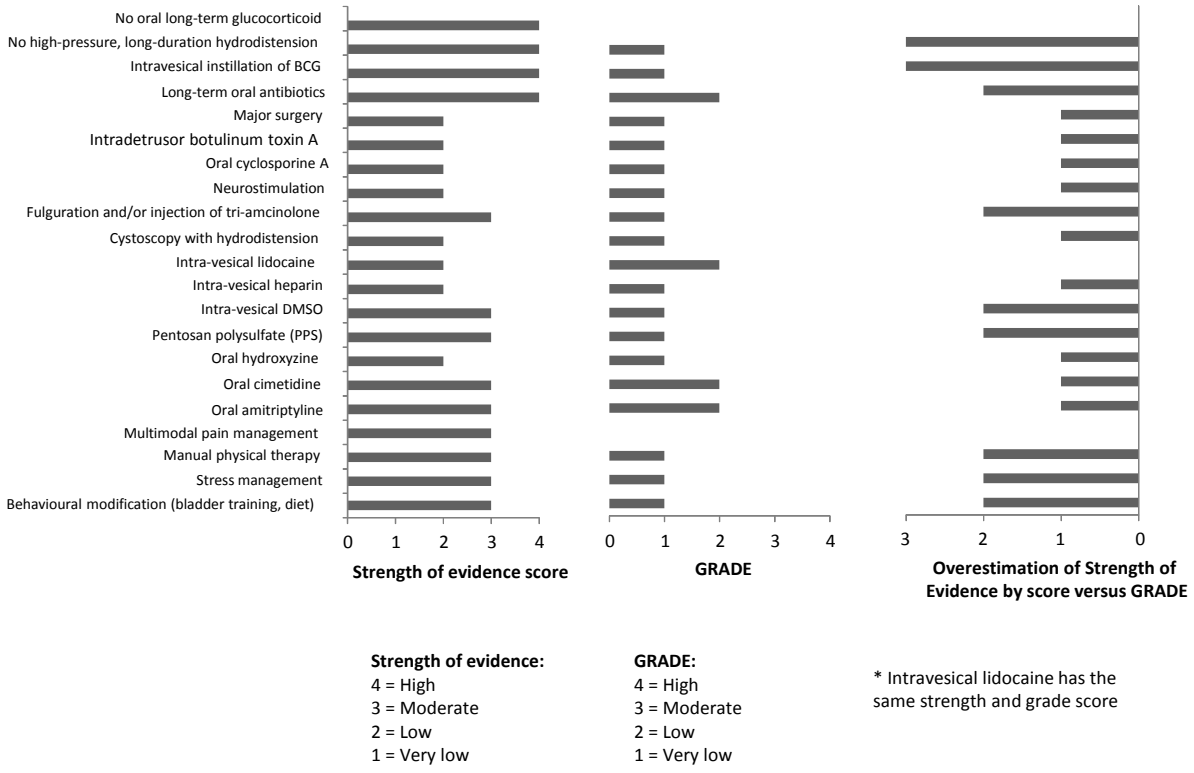


Figure 17 shows the overestimation in GRADE versus strength of evidence. Out of the 21 treatment options, 19 were assigned GRADE scores. In all 19, the GRADE and strength of evidence scores could be compared. 18 treatment options were downgraded using GRADE with a mean over estimation score of 1.7 (1.1 v 2.8), with a 95% CI mean difference of 2.2 to 1.3; p = <0.0001 using unpaired t test and the median difference was 1.5 (95% CI of 2.0 to 1.0) using Wilcoxon's signed rank test. There was downgrading of nine treatment options by one mark, for example this changed the evidence quality from low to very low, downgrading by two marks occurred for seven treatment options and by three marks for two treatment options. Intravesical lidocaine was the only treatment that had the same strength and GRADE scores.

Figure 17: Graphical representation of the strength of evidence score versus GRADE for the management of bladder pain syndrome



9.5 Conclusion

Main findings

The literature for treatment effectiveness of BPS is variable in its quality of evidence ratings depending on which guideline you consult. This can cause much confusion for clinicians who may not know the difference between the rating scales that have been used or how they were derived. In this chapter I have reviewed all the available evidence for BPS treatment options and evaluated the discrepancies between strength and level of evidence and GRADE ratings. The majority of treatment options were downgraded when compared to GRADE, giving them lower overall quality scores.

Strengths and weaknesses

This was a thorough literature review of all the available data, which incorporated several international guidelines and clinical reviews. I believe the GRADE approach provides an opportunity to combine information across five domains in order to create the most comprehensive scoring system to assess evidence quality. A notable limitation of GRADE scoring system is the computer software programme, which automatically assigns randomised studies a GRADE quality of evidence rating, which is not done for observational studies. The formation of GRADE tables is subjective with assignment of bias for study design, inconsistency, indirectness, imprecision and publication bias being assessor dependent (136). The use of GRADE tables allows assessment of several randomised studies across all five domains. However, the overall quality of the information obtained is dependent on the combined data from all studies, which means a very good quality study may be downgraded by combining its data with a poor quality study. This chapter shows that clinicians and readers of guidelines need to understand how data and study quality is derived and exercise caution when reading guideline recommendations.

Recommendations

I would propose that a single method of reporting quality ratings is used to allow for transparency of results. The GRADE reporting system would be an ideal option, as it does not limit its assessment of a study solely on the study design, as is common to most other quality evidence scores. Clinicians could be helped to understand guidelines if a single standardised reporting methodology was employed, which would enable them to communicate best treatment options to their patients.

This chapter is based on the following peer-reviewed paper (237):

Discrepancies in the grading of evidence for bladder pain syndrome: A comparative review of quality assessment methods

SA Tirlapur, KS Khan

Int Urogynecol J. 2014 Aug;25(8):1005-13

CHAPTER 10:

DISCUSSION AND PERSPECTIVES

10.1 Summary of findings

10.11 Prevalence of BPS in women with chronic pelvic pain

Nine studies (1016 patients) were identified with varying quality of data. The mean prevalence of BPS was 61% and co-existing BPS and endometriosis was 48%. With almost 2/3 of patients presenting with CPP suffering from BPS, basic urinary symptoms need to be assessed in these patients. Almost 50% of patients have co-existing pathology so multi-disciplinary care should be considered.

10.12 Assessing the information on the internet related to BPS

Eighteen websites were identified; seven (39%) were specific to BPS. There was a wide variation in combined mean scores for the four quality parameters of accuracy, quality, credibility and readability. There was good inter-observer agreement with an ICC ranging from the highest score of 0.80 for DISCERN to the lowest of 0.53 for readability. Four websites were selected that fulfilled the criteria for good quality information related to BPS. This showed that good sources of information are available on the internet but caution is needed when recommending websites to patients.

10.13 Assessing patients and clinicians experiences managing bladder pain syndrome and their prior beliefs on posterior tibial nerve stimulation

The survey questionnaire was completed by 133 patients and 69 clinicians. The main patient-reported symptom was pain when the bladder was full in 80% with the most bothersome symptom of pelvic pain in 22% of women. 93% of clinicians relied on making their diagnosis

by history and cystoscopy. 77% of patients reported using simple analgesia as a treatment, 74% dietary modification and 62% low-dose long-term antibiotics. This variation highlights the need for national guidance in order to standardise care.

10.14 Assessing the sensitivity of bladder pain syndrome and bladder wall tenderness for BPS in women with chronic pelvic pain

46 eligible women were recruited, with a mean age of 30.8 years (n=21, SD 7.20) in the BPS group (cases) and 34.6 years (n=25, SD 9.51) in the control group. An expert panel was successfully used to obtain a consensus diagnosis, as no gold standard diagnostic tool exists. The most sensitive symptom was bladder filling pain (sensitivity = 0.57, 95% CI = 0.3-0.8, specificity = 0.84, 95% CI = 0.6-1.0). Other sensitive symptoms were urinary frequency, nocturia and pain on urination. The most specific test was bladder wall tenderness (sensitivity = 0.10, 95% CI = 0.1-0.3, specificity = 0.96, 95% CI = 0.8-1.0). A large multi-centre study is needed to validate these tests in order to aid clinicians diagnose this debilitating condition.

10.15 The role of cystoscopy and laparoscopy in pelvic and bladder pain

BPS may be a manifestation of CPP where cystoscopy can have a diagnostic and therapeutic role. CPP may be multi-causal with several identifiable risk factors**.** Invasive procedures such as a laparoscopy and cystoscopy may be useful diagnostic tools as well as having therapeutic effects, where the degree of sensitivity of each test varies with the target condition. Therapeutic ‘see and treat’ laparoscopies, rather than purely diagnostic procedures may help avoid the need for multiple operations and the risks associated with them.

10.16 Assessing the effectiveness of nerve stimulation in the treatment of pelvic and bladder pain

Three eligible studies were identified with 169 patients; two for CPP and one for BPS. Symptomatic improvements were reported for pain, urinary and quality of life symptoms using posterior tibial nerve stimulation (PTNS). There was very limited available literature on neuromodulation, as most studies were observational, rather than randomised against a sham treatment, so they did not allow meaningful comparison. There was no available data for the effectiveness of sacral nerve stimulation (SNS). A large multi-centered clinical trial is recommended to investigate the effectiveness of nerve stimulation to treat BPS and CPP, along with cost-effectiveness analysis to assess the feasibility of wide-scale introduction of this treatment.

10.17 Assessing outcome measures of treatments for BPS

A total of 28 RCTS with 1732 patients were reported in eight systematic reviews. Five outcome measures were described, using 19 different measurement scales. These were urinary symptoms (100%), pain (64%), quality of life (39%), general wellbeing (36%) and bladder capacity (36%). The quality of all outcomes were measured with scores ranging from 0-6 and a mean score of 1.63 (95% CI 0.29 – 2.96) for systematic reviews and 3.25 (95% CI 2.80 – 3.70) for RCTs. These results highlight the need to generate a consensus to develop a core set of outcomes in BPS.

10.18 Assessing the evidence of GRADE ratings for BPS

From all the international guidelines, 19 treatments were identified for BPS where GRADE ratings were assigned. Comparing GRADE and level of evidence ratings (1-4), the latter overestimated quality by 1.8 points (1.1 v 2.9; 95% CI of mean difference 1.2 to 2.3; p= <0.0001). Comparing GRADE and strength of evidence ratings (A-D), the latter overestimated quality by 1.7 points (1.1 v 2.8; 95% CI of mean difference 1.3 to 2.1; p= <0.0001). The GRADE quality scoring system is a refined method of assigning quality to evidence, which provides a more conservative measurement of quality of evidence that can give a realistic assessment of the value of recommendations for practice.

10.2 Strengths and limitations

In attempting to understand how BPS is managed, a series of systematic reviews was undertaken. All the included systematic reviews (chapters 2, 3, 7 and 8) had robust methodology with prospective protocols adhering to the PRISMA guidance (appendix 6). The limitation is the sparse literature available on treatment effectiveness for BPS with a sham or standard/no treatment comparator.

The survey of clinicians and patients was an anonymous questionnaire (chapter 4). Although there was a low response rate of clinicians, it did sample urogynaecologists practicing in the UK who are on the British Society of Urogynaecology (BSUG) database in order to gain an idea of current opinions and practice. Patients were invited to participate but this may have only been the proactive ones and those who are computer literate. The survey gave insight into their experiences, without knowledge of who treated them.

In the feasibility study (chapter 5) there was prospective recruitment to minimise missing data and selective recall. Despite the weakness of a small sample size, a case-control feasibility study successfully proved that expert panel consensus diagnosis could be used to make a symptom-based diagnosis of BPS. It also showed that bladder filling pain was a useful symptom to aid diagnosing BPS.

10.3 Implications on clinical practice

- The realisation that the prevalence of BPS in women with CPP was high, along with my experiences of clinical practice and the results from the clinician survey on the management of BPS, as well as the lack of UK based guidelines for BPS inspired my work with members of BSUG, patient support groups and the RCOG to develop national RCOG green-top guidelines on the management of BPS (appendix 7). I hope these will aid general practitioners and clinicians to diagnose and initiate conservative treatments and avoid long delays trying to find a definitive diagnosis.

- Given the prevalence of CPP and BPS, policy makers need to consider the disease burden when designing referral pathways and improving pelvic pain and gynaecology services.
- The benefit of conservative treatments, patient awareness and self-management should be highlighted when counselling patients in order to empower them about the disease.

10.4 Implications for future research

When planning research projects, clear definitions of BPS and methods of diagnosis need to be used. It is important to identify study outcomes and use validated assessment tools. Since so many questionnaires for pain and urinary symptoms are used and these are usually patient reported, standardisation and comparability between studies is difficult.

My review of RCTs and systematic reviews identified key outcomes for studies in BPS. The development of a validated questionnaire to aid in the analysis of a symptom-based diagnosis would be beneficial in both the clinical and research settings.

Given the disease burden of CPP and BPS with a significant number of patients suffering from refractory pain, neuromodulation, in the form of PTNS may be a possible treatment modality. As part of the clinician and patient survey, we asked specifically about PTNS. Clinicians expressed an interest in a clinical trial and affected patients expressed an interest in participating in such a study. An RCT to assess the effectiveness of PTNS in the treatment of CPP and BPS in a large multi-centre study will help reduce uncertainty about its effectiveness.

Appendix 1: Contribution to each chapter

- **Chapter 1 –** I wrote this chapter in its entirety.
- **Chapter 2 –** I conceived the idea for the study, performed searches, selected studies, designed the data extraction form, extracted and synthesised data, performed quality assessment of studies, created figures and drafted the manuscript.
- **Chapter 3 –** I devised the protocol, performed searches, selected studies, designed the data extraction form, extracted and synthesised data, performed quality assessment of studies, created figures and drafted the manuscript.
- **Chapter 4 –** I drafted, piloted and distributed surveys, analysed data and prepared the manuscript.
- **Chapter 5 –** I refined the study design, drafted and revised the protocol, recruited patients, collected, collated and analysed data and prepared the manuscript.
- **Chapter 6 –** I researched and prepared the manuscript and created the tables of information.
- **Chapter 7 -** I conceived the idea for the study, performed searches, selected studies, designed the data extraction form, extracted and synthesised data, performed quality assessment of studies, created figures and drafted the manuscript.
- **Chapter 8 –** I devised the review protocol, performed searches, data extraction, quality assessment, data analysis, created figures and tables and drafted the manuscript.
- **Chapter 9** – I reviewed the evidence, prepared figures and tables, researched and wrote the manuscript.
- **Chapter 10 –** I wrote this chapter in its entirety.

Appendix 2: National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) diagnostic criteria for Interstitial Cystitis (4)

Diagnostic criteria:

- Glomerulations on cystoscopy or classic Hunner's ulcer AND pain associated with bladder or urinary frequency
- Examination for glomerulations should be undertaken after hydrodistension under anaesthesia to 80-100cm water pressure for 1-2 minutes
- Glomerulations must be diffuse, present in at least 3 quadrants of the bladder, and there must be at least 10 glomerulations per quadrant and not along the path of the cystoscope as they may be an artifact

Exclusion criteria:

1. Bladder capacity ≥ 350cc on awake cystometry using either a gas or liquid filling medium
2. Absence of an intense urge to void with the bladder filled to 100cc gas or 150cc water during cystometry, using a fill rate of 30 to 100cc per minute
3. The demonstration of phasic involuntary bladder contractions on cystometry using the fill rate above
4. Duration of symptoms < 9 months
5. Absence of nocturia
6. Symptoms relieved by antimicrobials, urinary antiseptics, anticholinergics or antispasmodics
7. A frequency of urination, while awake, of less than 8 times a day
8. A diagnosis of bacterial cystitis or prostatitis within a 3 month period
9. Bladder or urethral calculi
10. Active genital herpes
11. Uterine, cervical, vaginal or urethral cancer
12. Urethral diverticulum
13. Cyclophosphamide or any type of chemical cystitis
14. Tuberculosis cystitis
15. Radiation cystitis
16. Benign or malignant bladder tumours
17. Vaginitis
18. Age less than 18 years

Appendix 3: O'Leary Sant (OLS) Symptom and Problem Index Questionnaire (26)

Symptom Index	Problem Index
1. During the past month, how often have you felt the strong need to urinate with little or no warning? 0____not at all 1____less than 1 time in 5 2____less than half the time 3____about half the time 4____more than half the time 5____almost always	During the past month, how much has each of the following been a problem for you? 1. Frequent urination during the day? 0____no problem 1____very small problem 2____small problem 3____medium problem 4____big problem
2. During the past month, have you had to urinate less than 2 hours after you finished urinating? 0____not at all 1____less than 1 time in 5 2____less than half the time 3____about half the time 4____more than half the time 5____almost always	2. Getting up at night to urinate? 0____no problem 1____very small problem 2____small problem 3____medium problem 4____big problem
3. During the past month, how often did you most typically get up at night to urinate? 0____none 1____once 2____2 times 3____3 times 4____4times 5____5 or more times	3. Need to urinate with little warning? 0____no problem 1____very small problem 2____small problem 3____medium problem 4____big problem
4. During the past month, have you experienced pain or burning in your bladder? 0____not at all 1____a few times 2____almost always 3____fairly often 4____usually	4. Burning, pain, discomfort, or pressure in your bladder? 0____no problem 1____very small problem 2____small problem 3____medium problem 4____big problem
Total score:_____ (add all questions in column) IC >,=6, controls <6	Total score:_____ (add all questions in column) IC >,=6, controls <6

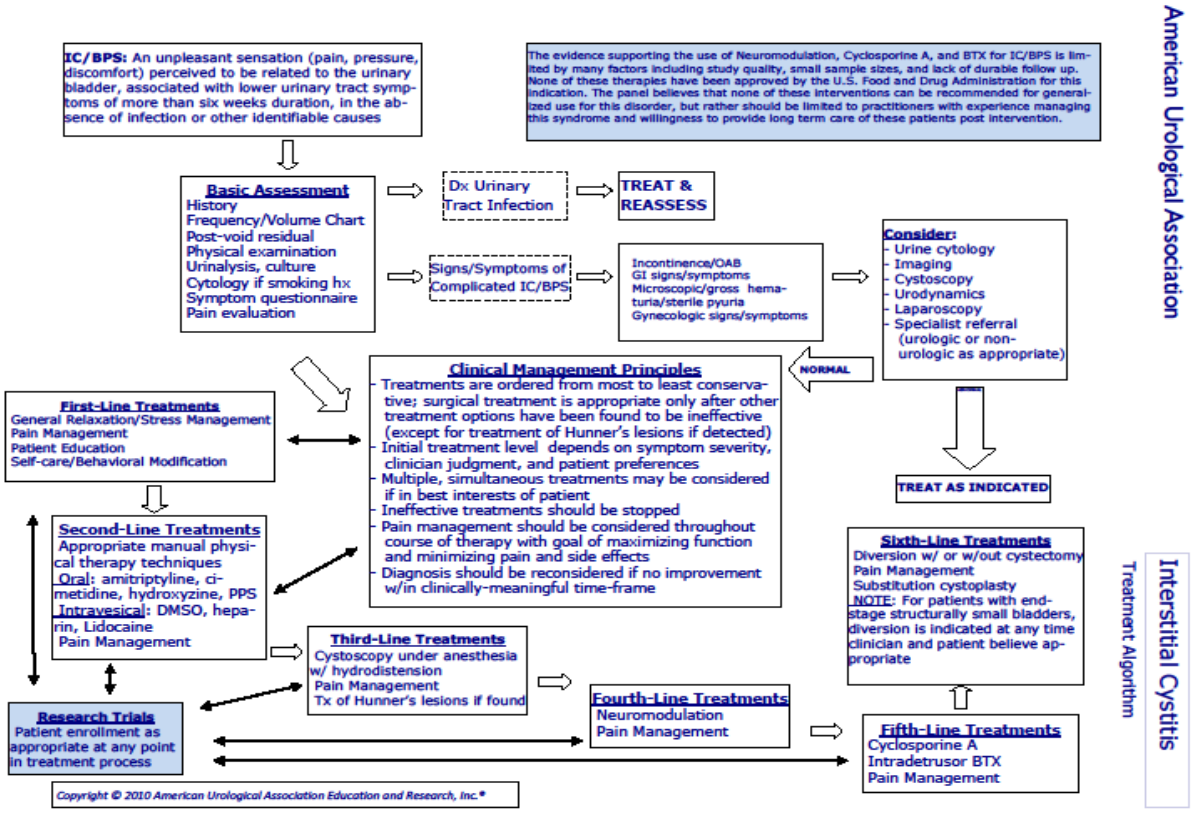
Appendix 4: Pelvic Pain and Urgency/Frequency (PUF) Questionnaire (28)

Instructions

For each question below, please circle the answer that best describes how you feel. Then, mark your score (0 to 4) for each answer in the column on the right. When you are finished add up the numbers in the column for your total score.

		0	1	2	3	4	Month 1 Score	Month 3 score
1	How many times do you go to the bathroom during the day?	3-6	7-10	11-14	15-19	20+		
2	a. How many times do you go to the bathroom at night?	0	1	2	3	4+		
	b. If you get up at night to go to the bathroom, does it bother you?	Never	Mildly	Moderate	Severe			
3	Are you currently sexually active **YES** _____ **NO** _____							
4	a. **IF YOU ARE SEXUALLY ACTIVE,** do you now or have you ever had pain or symptoms during or after sexual intercourse?	Never	Mildly	Moderate	Severe			
	b. If you have pain, does it make you avoid sexual intercourse?	Never	Mildly	Moderate	Severe			
5	Do you have pain associated with your bladder or in your pelvis (vagina, lower abdomen, urethra, perineum, testes or sacrum)? **If you do not have pain, please skip question 6.**	Never	Mildly	Moderate	Severe			
6	a. If you have pain, is it usually...	No pain	Mild	Moderate	Severe			
	b. Does your pain bother you?	Never	Occasionally	Usually				
7	Do you have urgency after going to the bathroom? **If you do not have urgency, please skip final question.**	Never	Occasionally	Usually	Always			
8	**a.** If you have urgency, is it usually...	No Urgency	Mild	Moderate	Severe			
	b. Does your urgency bother you?	Never	Occasionally	Usually	Always			
					Total Score			

Appendix 5: The management summary for bps according to the American Urological Association guidelines (23)



Appendix 6: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist (238)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Page 2 of 2

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Page 1 of 2

Appendix 7: Draft RCOG Green-top guideline on the management of bladder pain syndrome (included with permission from the RCOG).

Green-top Guideline No. XX

First Draft – Summer 2014

The Management of Bladder Pain Syndrome (BPS)

	[Edition statement]	
	This is the first edition of this guideline.	
1	**Purpose and scope**	
	This guideline aims to provide information, based on clinical evidence, to clinicians in primary and secondary care settings in order to recognise the symptoms of bladder pain syndrome (BPS) and the possible treatments for this condition, along with appreciating the current uncertainties that exist around the condition.	
2.	**Introduction and background epidemiology**	
	Bladder pain syndrome (BPS) has been defined in 2008 by the European Society for the Study of Interstitial Cystitis/Painful Bladder Syndrome as 'pelvic pain, pressure or discomfort perceived to be related to the bladder, lasting at least 6 months, and accompanied by at least one other urinary symptom, for example persistent urge to void or frequency, in the absence of other identifiable causes.' (1) The term BPS has been recommended rather than previous names for this condition: interstitial cystitis (IC) was first described in 1915 and criteria were defined in 1987 by the National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), with the following inclusion criteria: pain associated with bladder or urinary frequency and glomerulations on cystoscopy or classic Hunner's ulcer seen after hydrodistension under anaesthesia to 80-100cm water pressure for 1-2 minutes, where the glomerulations must be diffuse, present in at least 3 quadrants of the bladder, and there must be at least 10 glomerulations per quadrant and not along the path of the cystoscope as there may be an artefact (2). This strict criteria meant many patients were under-diagnosed so a new term, painful bladder syndrome was proposed in 2002 by the International Continence Society as 'suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency in the absence of any identifiable pathology or infection with typical cystoscopic and histological features' (2-4). BPS is a chronic condition with unknown aetiology. As the definition of BPS has constantly evolved, it has been seen as a diagnosis of exclusion with no definitive diagnostic test, hence it is difficult to estimate prevalence, which can be dependent on whether symptoms are clinician-assigned or patient reported. A large American study found prevalence rates of 2.3% to 6.5% of women (5). BPS is between 2-5 times more common in women than men (6-8).	

	There is very limited data on BPS in the United Kingdom but a recent survey of urogynaecologists has showed variable practice regarding the diagnosis and management of BPS (9).	
3.	**Identification and assessment of evidence**	
	[RCOG staff to complete]	
4.	**What is the effect of BPS on quality of life?**	
	Recommendation: **Patients with BPS can have low self-esteem, sexual dysfunction and reduced quality of life. It is important to enquire about the effects on quality of life and refer as appropriate.**	**Grade:** **C**
	Supporting Text: Patients will often be highly anxious about their symptoms and possible diagnosis with low self esteem and poor quality of life (QoL) (10). Women with BPS can have high levels of sexual dysfunction (11). Spousal and family support are important and referral to a clinical psychologist should be considered if symptoms are persistent or for refractory BPS.	Evidence Level: 2+
	Recommendation: **Patients with BPS may have other co-existent conditions impacting on their quality of life.**	**Grade:** **C**
	Supporting Text: One of the key symptoms of BPS is chronic pelvic pain, which may be associated with other organic and non-organic causes, for example endometriosis, fibromyalgia, depression and irritable bowel syndrome (12, 13). This co-existence can make diagnosis and management of BPS particularly challenging.	Evidence Level: 2+
5.	**Diagnosis of BPS**	
5.1	*How is BPS diagnosed?*	
	Recommendation: **Diagnose bladder pain syndrome on the basis of symptoms of pain, pressure or discomfort perceived to be related to the bladder accompanied by at least one other lower urinary tract symptom such as urgency, frequency or nocturia, for at least 6 months in the absence of other identifiable causes.**	**Grade:** **B**
	Supporting Text: A systematic literature review found the most commonly reported symptoms of BPS to be bladder/pelvic pain, urgency, frequency and nocturia (14). A number of expert panels including ESSIC (European Society for the study of IC/PBS), AUA (American Urological Association), EAU (European Urological Association) and ICI (International Consultation on Incontinence) have published symptom based diagnostic criteria for BPS. All include the symptoms of pain related to the bladder, at least one other urinary symptom, absence of identifiable causes and minimum duration of symptoms of 6 weeks (AUA) or 6 months (15-17).	Evidence Level: 2++
	Recommendation: **Cystoscopy, bladder biopsies and hydrodistension are not recommended for the diagnosis of BPS. Clinicians should consider cystoscopy to diagnose/exclude other conditions, which may mimic BPS.**	**Grade:** **C**
	Supporting Text: Cystoscopy without hydrodistension is expected to be normal (except for discomfort and reduced bladder capacity) in most patients with BPS. Characteristic cystoscopic findings have been ascribed to BPS, including post	Evidence Level: 2+

	distension glomerulations (pinpoint petechial haemorrhages), reduced bladder capacity and bleeding. Cystoscopy findings correlate poorly with symptoms. 150 women in the Interstitial Cystitis Database Study underwent cystoscopy and hydrodistension. There was no correlation between severity of symptoms and the finding of glomerulations or bleeding following hydrodistension. Pain, urgency and reduced bladder capacity were associated with the presence of Hunner's lesions in 11.7% (18). Similar findings have been seen in other studies, along with glomerulations in asymptomatic women (19, 20). Pathological features have been described in patients with BPS including inflammatory infiltrates, detrusor mastocytosis, granulation tissue and fibrosis but these are non-specific. The diagnosis of BPS cannot be made or excluded on the basis of any specific finding on bladder biopsy and these are not required for the diagnosis. In a study of 108 people with BPS, no correlation was found between histological and cystoscopic findings (21). In an earlier study of 50 patients, there was a correlation with reduced bladder capacity, inflammation and mast cell count however, both cystoscopic and histological findings showed large variation (22). Bladder biopsy may be indicated to exclude other pathologies such as carcinoma in situ, if suspected by a focal lesion or abnormal cytology.	
	Recommendation: **Potassium sensitivity test, urodynamic assessment and urinary biomarkers should not be used in the diagnosis of BPS.**	**Grade:** **C**
	Supporting Text: The potassium chloride bladder permeability test is not recommended in the diagnosis of BPS as specificity and sensitivity are poor, adding no information over standard diagnostic techniques (23). Pain on bladder filling, a reduced first sensation to void and reduced bladder capacity are consistent with BPS, however, there are no urodynamic criteria that are diagnostic for BPS. The presence of detrusor overactivity, which is seen in approximately 15% of patients with BPS, should not preclude a diagnosis of BPS. Pressure flow studies may be considered in patients where there are coexistent voiding symptoms but are not recommended in the diagnosis of BPS (23).	Evidence Level: 2+
5.2	*How can we classify the severity of BPS?*	
	Recommendation: **Clinicians should use a validated symptom score to assess baseline severity of BPS and assess response to treatment.**	**Grade:** **B**
	Supporting Text: Symptoms scores for BPS should be used to grade the severity of symptoms and assess response to treatment. There are 3 published BPS symptom questionnaires: the University of Wisconsin IC Scale (UW-IC), the O'Leary-Sant IC Symptom Index and IC Problem Index (ICSI/PI), and the Pelvic Pain and Urgency/Frequency (PUF) Scale (24-26). All have been validated in patients with BPS and the UW-IC and ICSI/ICPI have shown responsiveness to change over time (23). In a comparison of questionnaires used for the evaluation of chronic pelvic pain, there was moderate to good correlation between the ICSI and PUF symptoms scores for bladder complaints and the ICPI and PUF bother	Evidence Level: 2++

	scores for quality of life.	
	Recommendation: **The use of visual analogue scales for pain should be considered to assess severity of pain in BPS.**	**Grade:** **D**
	Supporting Text: A number of different rating scales have been devised to measure pain. They rely on a subjective assessment of the pain and therefore make inter-individual comparisons difficult. A 1 to 10 Likert style visual analogue scale (VAS) is an easily administered instrument to capture pain intensity and should be considered to measure baseline pain and response to treatment.	Evidence Level: 4
	Recommendation: **The use of bladder diaries are recommended to assess severity of BPS.**	**Grade:** **D**
	Supporting Text: A bladder diary is recommended to document voiding frequency and functional capacity. It aids assessment of severity of storage symptoms and can be used to measure progress with treatment.	Evidence Level: 4
	Recommendation: **Consider cystoscopy and bladder biopsy to identify the presence of Hunner's ulcer (and assess bladder capacity).**	**Grade:** **C**
	Supporting Text: Whilst cystoscopy is not recommended for the diagnosis of BPS it may be used to identify and treat patients with more severe disease by the presence of Hunner's lesions and reduced bladder capacity (18).	Evidence Level: 2+
5.3	*What are the differential diagnoses?*	
	Recommendation: **Exclude or diagnose other disorders that could be the cause of the symptoms.**	**Grade:** **D**
	Supporting Text: ESSIC has published a list of confusable diseases, by expert consensus (17) These include: • Malignancy e.g. bladder carcinoma / carcinoma in situ, cervical, urterine or ovarian cancer • Infection of urinary or genital tract • Overactive bladder • Radiation cystitis or drug mediated cystitis e.g. cyclophosphamide, ketamine • Bladder outlet obstruction or incomplete bladder emptying • Calculus of bladder or lower ureter • Urethral diverticulum • Prolapse • Endometriosis • Pudendal nerve entrapment, pelvic floor muscle related pain	Evidence Level: 4
6.	**Initial assessment**	
6.1	*What initial clinical assessment should be performed?*	
	Recommendation: **BPS is a chronic pain syndrome and the principles of management of chronic pelvic pain apply to the initial assessment of this condition too.** **Adequate time should be allocated to allow women to feel they are being listened to and believed. Some women will have preconceived theories**	**Grade:** **B**

	regarding the origins of the pain and the initial consultation should address these.	
	Supporting Text: The initial consultation is aimed at generating trust between the patient and the caregiver. In chronic pain syndromes it is well recognised that a favourable patient rating of the initial consultation was associated with greater likelihood of complete recovery at follow-up (27). Patients should be encouraged to talk about their symptoms and any theories they have about the origins of the pain. This allows engagement in further investigations and management of their condition (28, 29).	Evidence Level: 2+
	Recommendation: **The symptoms should be assessed systematically and where possible a validated questionnaire should be used (see section 5.2).**	**Grade:** **B**
	Supporting Text: Symptom assessment forms the basis of the initial assessment. The location of the pain has been described in several studies and the commonest reported sites are the bladder, urethra and vagina. The description of the pain ranged from pressure, aching to a burning. A study of 565 patients with the condition was used to identify factors, which can aggravate and alleviate the condition. Voiding was found to relieve the pain in 57-73%. Pain was aggravated by stress (61%), sexual intercourse (50%), constrictive clothing (49%), acidic beverages (54%) coffee (51%) and spicy foods (46%). In the EPIC study (Events preceding interstitial cystitis) of 158 women with BPS, found that pain worsened with certain food or drink and/or worsened with bladder filling and/or improved with urination in 97% of patients (24, 30, 31).	Evidence Level: 2++
	Recommendation: **A thorough medical history should be taken and physical examination including pain mapping performed.**	**Grade:** **GPP**
	Supporting Text: As the diagnosis of BPS is a diagnosis of exclusion it is important to rule out other possible causes of bladder pain in that area. The history should include details of previous pelvic surgery, UTIs, STDs, bladder disease and autoimmune disease. The location of the pain and relationship to bladder filling and emptying should be established. The characteristics of the pain including trigger factors and onset, correlation with other events and description of the pain should be recorded. A history of physical and sexual abuse should be elicited, as it is a recognised cause of pelvic pain (32). Enquire about prior or current use of oral contraception, which a recent systematic review has found to be associated with BPS symptoms (33). The physical examination should be aimed at ruling out bladder distension due to retention, hernias and trigger points abdominally. A genital examination should be performed to rule out atrophic changes, prolapse, vaginitis, vulvodynia and trigger point tenderness over the urethra, vestibular glands, vulvar skin or bladder. Features of dermatosis including vulvar or vestibular disease should be looked for. An evaluation of the introitus and tenderness during insertion or opening of the speculum should be made. Superficial/deep vaginal tenderness and tenderness of the levator muscles should be assessed during the course of the examination. Cervical pathology should be excluded. A	Evidence Level: 4

	bimanual pelvic examination is helpful to rule out abdominal, cervical or adnexal pathology.	
6.2	*What baseline investigations should be performed before deciding on treatment?*	
	Recommendation: **A bladder diary (frequency volume chart) should be completed.**	**Grade:** **B**
	Supporting Text: A 3 day diary with input and output is useful for initial assessment. Patients with BPS classically void small volumes so this is useful to identify the severity of the storage symptoms. The first morning void is a useful guide to the functional capacity of the bladder. The bladder diary can also be used to reinforce behavioural therapy and where necessary pharmacological treatment.	Evidence Level: 2+
	Recommendation: **A food diary may be used to identify if specific foods cause a flare up of symptoms.**	**Grade:** **GPP**
	Supporting Text: Maintaining a food diary and its association with pain can be useful to identify if certain types of food cause symptoms to flare up.	Evidence Level: 4
	Recommendation: **Urine should be tested to rule out a UTI as this is a prerequisite for a diagnosis of BPS.** **Investigations for ureaplasma and chlamydia should be considered**	**Grade:** **C**
	Supporting Text: A dipstick should be performed and where there is a suggestion of a UTI a culture and sensitivity should be obtained with consideration given to testing for acid-fast bacilli where there is sterile pyuria. Ureaplasma is not isolated in routine culture tests, so needs to be specifically looked for. A study of 92 patients diagnosed with BPS demonstrated that the condition itself was not associated with persistence of bacterial or viral DNA on bladder biopsy and all biopsies were negative for adenovirus, cytomegalovirus, herpes simplex virus types I and II, human papillomavirus (all subtypes) and Chlamydia trachomatis in all samples (34). These findings exclude a chronic infective etiology for the condition. A separate study looking at clinical characteristics of 87 women with the condition, found that 12% had a past history of chlamydia, which is higher than the national average. It is therefore important to rule this out with appropriate cultures (35).	Evidence Level: 2–
	Recommendation: **In high-risk groups, urine cytology should be tested.**	**Grade:** **C**
	Supporting Text: In the presence of persistent microscopic haematuria urine cytology is usually indicated. In a study of 148 patients with BPS, at least one episode of haematuria was reported in 41% of BPS over the preceding 18 months (36). In this group, of those who agreed to a full evaluation, no cases of malignancy were identified. No statistically significant differences were found in age, bladder capacity, and the presence of Hunner's ulcers or glomerulations between patients with hematuria and those without. Cytology is also indicated	Evidence Level: 2+

	when there are other risk factors for urothelial carcinoma, for example those who smoke, have a family history or have received radiotherapy or chemotherapy.	
	Recommendation: **Laboratory investigation for urinary markers of inflammation is of no proven value.**	**Grade:** **C**
	Supporting Text: Urine IL-6 levels (37), anti-proliferative factor (APF) (38), inter-α-trypsin inhibitory heavy chain H4 (39) were found to be elevated in some women with interstitial cystitis/BPS and uromodulin and kininogen were found to be reduced. These were tested in relatively small cohorts of populations and corresponded to different stages of disease progression. There is however no evidence that laboratory testing of these urinary markers is of any proven value in the initial assessment or diagnosis of BPS.	Evidence Level: 2+
7.	**What is the initial management?**	
7.1	*Conservative treatments (efficacy and safety)*	
	Recommendation: **Dietary modification can be beneficial and avoidance of caffeine, alcohol and acidic foods should be suggested to patients.**	**Grade:** **D**
	Supporting Text: A survey of 1,982 participants revealed 87.6% of patients had a symptomatic improvement with an elimination diet and 86.1% by complete avoidance of these items, although treatment duration was not indicated (40). Certain foods that worsen pain are alcohol, citrus fruits, coffee, carbonated drinks, tea, chocolate, and tomatoes (30).	Evidence Level: 3
	Recommendation: **Regular exercise can be beneficial.**	**Grade:** **D**
	Supporting Text: 65.2% of patients gained symptomatic improvement with regular exercise (40).	Evidence Level: 3
	Recommendation: **Stress management should be recommended.**	**Grade:** **D**
	Supporting Text: 76.4% of patients reported symptomatic improvement, through a patient survey, using relaxation techniques, 66.8% using meditation, 64.5% listening to music and 80.5% with stress reduction (40).	Evidence Level: 3
	Recommendation: **Physical therapy and massage can help relieve symptoms.**	**Grade:** **C**
	Supporting Text: An electronic questionnaire revealed that 74.2% of patients experienced symptomatic improvement with massage therapy, 61.5% with physical therapy and 66.1% through physical therapy with internal treatment (40). A randomised study of 10 scheduled treatments of myofascial physical therapy versus global therapeutic massage on 81 women showed a reduction in pain, frequency and urgency in both groups with no significant difference in therapies (41).	Evidence Level: 2–
	Recommendation: **Analgesia is recommended for the key symptom of pelvic or bladder pain, suffered by most patients.**	**Grade:** **GPP**
	Supporting Text:	Evidence

	Between 30-61% of patients presenting with chronic pelvic pain have BPS so although there is no data available about the efficiency of different forms of analgesia in the treatment of BPS, analgesia is useful at treating the key symptom of pain in this condition (12, 42).	Level: 4
	Recommendation: **There is limited data on the benefit of acupuncture.**	**Grade:** **C**
	Supporting Text: A systematic review of 3 small observational studies with a total of 22 patients showed that acupuncture provided moderate symptomatic improvement, however, a large randomised trial is needed to properly evaluate treatment effectiveness (43).	Evidence Level: 2–
7.2	*Pharmacological treatments (efficacy and safety)*	
	Recommendation: **Oral Amitriptyline should be considered when first-line conservative treatments have failed.**	**Grade:** **A**
	Supporting Text: A meta-analysis of 2 RCTs showed improvements in urinary urgency, frequency and pain scores (44). A total of 281 patients were treated with increasing titrated doses of amitriptyline between 10-100mg over a 4-month period (45, 46). Compliance is often affected by the side effects, which include dry mouth, constipation, sedation, weight gain and blurred vision.	Evidence Level: 1+
	Recommendation: **Oral cimetidine should be considered when first-line conservative treatments have failed.**	**Grade:** **A**
	Supporting Text: A meta-analysis of 1 RCT compared 36 patients treated with a 3-month course of 400mg of cimetidine orally versus placebo twice daily (44). All treated patients had symptomatic improvements, especially in pain and nocturia, however, no histological changes in post-treatment cystoscopy or bladder biopsies were noted (47).	Evidence Level: 1–
	Recommendation: **Oral hydroxyzine does not appear to be an effective second-line treatment for BPS.**	**Grade:** **A**
	Supporting Text: A meta-analysis of 1 RCT of 31 patients treated with oral hydroxyzine 10-50mg daily in titrated doses for 3 weeks, then treated on the highest effective dose for 21 weeks was compared to a placebo group (44). There was no significant response rate in the treatment group (31%) versus the control group (20%) (48).	Evidence Level: 1+
	Recommendation: **Oral Pentosan Polysulfate Sodium (PPS) (Trade name Elmiron®) may be considered when first-line conservative treatments have failed.**	**Grade:** **A**
	Supporting Text: Pentosan polysulfate sodium (PPS) is thought to repair the damaged glycosaminoglycan layer, which acts as a protective mechanism for the bladder mucosa (49). A meta-analysis of 3 RCTs with a total of 379 patients compared 100mg oral PPS three times daily to placebo (44). All 3 studies showed variable effectiveness with a mean symptom improvement of 31% versus 15% in the placebo group (48, 50, 51). Recognised side effects include gastrointestinal upset, headaches and mood swings. This treatment may not be offered in all hospitals in the UK.	Evidence Level: 1+

	Recommendation: **Long-term antibiotics, intravesical Resiniferatoxin, intravesical Bacillus Calmette-Guerin (BCG), high-pressure long-duration hydrodistension and long-term oral glucocorticoids are treatments that should not be recommended for BPS.**	**Grade:** **GPP**
	Supporting Text: Long-term antibiotics should not be used as a treatment option. 1 RCT reports on 50 patients randomised to receive an 18-week course of antibiotics (rifampicin plus a sequence of doxycycline, erythromycin, metronidazole, clindamycin, amoxicillin and ciprofloxacin for 3 weeks each) or placebo, where there was 48% symptomatic improvement in the treatment group and 24% in the placebo group but in the treatment group 80% reported adverse effects (52). Intravesical Resiniferatoxin was evaluated in a systematic review of 8 RCTS but failed to show symptomatic improvement and caused pain, which reduced treatment compliance (53). Intravesical Bacillus Calmette-Guerin (BCG) has been studied in 2 RCTS on 282 patients compared to a placebo (54, 55). While it has variable effectiveness there are a large number of adverse effects including arthralgia, headaches and infection. High-pressure long duration hydrodistension with pressures over 80-100cm of water over more than 10 minutes may cause sepsis or bladder rupture. Three observational studies showed a wide range of efficacy rates between 22–67% with at least one case of bladder rupture in each study (56, 57). The risks of this treatment far outweigh the benefits. Long-term oral glucorticoid administration is not recommended due to its long-term side effect profile.	Evidence Level: 2+
8.	**Further management**	
8.1	*Who should manage bladder pain syndrome?*	
	Recommendation: **A history, urinalysis and possible physical examination should be carried out in primary care.**	**Grade:** **GPP**
	Supporting Text: Patients should be commenced on first-line conservative treatments and if these fail to resolve or improve symptoms, a referral to secondary care should be considered. If the patient's symptoms are prevalently urinary, referral to a urogynaecologist would be preferable.	Evidence Level: 4
	Recommendation: **Treatments for Hunner's lesions**	**Grade:** **GPP**
	Supporting Text: Hunner's lesions, or ulcers, do not respond to oral treatments and need surgical management. They are usually diagnosed by cystoscopy with the appearance of a well-demarcated reddish mucosal lesion lacking in the normal capillary structure, which usually bleeds (49). Two observational studies reported success when using Nd:YAG laser under cystoscopic control in patients with BPS with Hunner's ulcers. Fifty-one patients were treated,	Evidence Level: 2–

	resulting in 88 % symptomatic relief within 2–3 days of treatment; however, 45 % needed additional treatment within 23 months (58, 59).	
	Recommendation: **Referral to a physiotherapist should be considered as BPS symptoms may be improved with physical therapy.**	**Grade:** **GPP**
	Supporting Text: An RCT comparing global massage and myofascial physical therapy showed that both forms of treatment were beneficial at improving pain, urinary frequency and urgency (41).	Evidence Level: 2+
	Recommendation: **Oral cyclosporin A may be considered after conservative, oral, intravesical and neuromodulation treatments have failed.**	**Grade:** **GPP**
	Supporting Text: One observational study of 23 patients treated with low dose oral cyclosporine showed improvements in bladder capacity, voiding volumes, pain and decreased urinary frequency, however, symptoms recurred with treatment cessation (60). Side effects include hypertension, gingival hyperplasia, and facial hair growth.	Evidence Level: 2–
8.2	*Who should be referred to secondary care?*	
	Recommendation: **Patients who fail to respond to conservative treatment should be referred to secondary care.**	**Grade:** **GPP**
	Supporting Text: The pain and urinary symptoms of BPS can be debilitating and primary care physicians or general practitioners should not wait for definite diagnosis or treatments to be commenced in secondary care. However, after commencing conservative treatments if symptoms are unchanged or having a negative impact on the patient's quality of life, they should be referred to secondary care.	Evidence Level: 4
8.3	*Surgical treatments (efficacy and safety)*	
	Recommendation: **Intravesical Dimethyl sulfoxide (DMSO) should be considered if conservative and oral treatments have failed.**	**Grade:** **B**
	Supporting Text: A systematic review of 1 randomised cross-over study evaluated 33 patients given placebo (saline) or 50% DMSO for 2 sessions each week for 2 weeks (61). 53% of the treatment group had marked symptomatic improvement compared to 18% of the placebo group (62). Side effects include a garlic-like odour and bladder spasm.	Evidence Level: 2++
	Recommendation: **Intravesical heparin may be considered if conservative and oral treatments have failed.**	**Grade:** **D**
	Supporting Text: One observational study evaluated 48 patients treated with 10,000 Units of heparin in 10 ml sterile water instilled three times a week for 3 months and reported that 56% of patients achieved clinical remission over 3 months and 50 % of patients had symptomatic control after 1 year (63).	Evidence Level: 2–
	Recommendation: **Intravesical lidocaine may be considered if conservative and oral treatments have failed.**	**Grade:** **C**
	Supporting Text:	Evidence

	Lidocaine is a local anaesthetic that acts by blocking sensory nerve fibres in the bladder. 1 RCT reported on 102 patients treated with a 5-day course of 200 mg intravesically administered lidocaine with alkalinised instillation of 8.4% sodium bicarbonate to a final volume of 10ml versus placebo (64). 30% of treated patients compared to 9.6% of the control group reported symptomatic improvement over a 29-day follow up period (65).	Level: 2+
	Recommendation: **Botulinum toxin A may be considered when conservative and oral treatments have failed.**	**Grade: B**
	Supporting Text: A systematic review evaluating botulinum toxin A in BPS patients found three RCTs and seven prospective cohort studies with a total of 260 patients. Eight studies reported symptomatic improvement, although 7% of patients needed post-treatment self-catheterisation (66).	Evidence Level: 2++
	Recommendation: **Intravesical chondroitin sulphate may be considered if conservative and oral treatments have failed.**	**Grade: A**
	Supporting Text: An individual participant meta-analysis of 213 patients showed some benefit using 2% intravesical chondroitin sulphate (67). Small studies have shown symptomatic improvement using a combination of intravesical hyaluronic acid and chondroitin sulphate (68-70).	Evidence Level: 1–
	Recommendation: **Neuromodulation (nerve stimulation), in the form of posterior tibial or sacral neuromodultaion may be considered after conservative, oral and/or intravesical treatments have failed.**	**Grade: GPP**
	Supporting Text: Posterior tibial nerve stimulation (PTNS) involves insertion of a fine needle 5 cm cephalad from the medial malleolus and posterior to the margin of the tibia at the site of the posterior tibial nerve. The treatment regimen is usually weekly for 10–12 weeks (71). Sacral nerve stimulation involves an initial test phase with insertion of a test lead tunneled under the skin transmitted onto the nerve roots exiting the S3 foramen, so stimulating the pelvic and pudendal nerves, and connected to a stimulator which is exchanged for a permanent implant if successful (72). There are no RCTs evaluating either form of neuromodulation. Effectiveness data comes from observational studies. One study reported efficacy of posterior tibial nerve stimulation in 18 patients, and six studies reported on sacral nerve stimulation in 150 patients, all studies showing improvements in symptoms and quality of life (73-78). Whereas both forms of neuromodulation are effective, they are invasive procedures, which may deter patients.	Evidence Level: 2–
	Recommendation: **Cystoscopy+/- hydrodistension may be considered if conservative and oral treatments have failed or if there is suspicion of Hunner's ulcers.**	**Grade: D**
	Supporting Text: Cystoscopy is recommended as a treatment rather than solely as a diagnostic tool. Three observational studies with a total of 265 patients have described variable symptomatic improvement. However, within 6 months, symptoms had recurred in the majority of patients (19, 79, 80). Rupture is a possible complication of prolonged distension of a diseased bladder; hence, low-pressure distension is advised (81).	Evidence Level: 2–

	Recommendation: **Major surgery may be considered as last-line treatment in refractory BPS.**	**Grade:** **D**
	Supporting Text: Total cystectomy and urinary diversion will lead to the need for self-catheterisation, and patients must be aware of persistent pelvic and pouch pain post surgery (49). A retrospective observational study of 47 patients who had reconstructive surgery, including cystectomy, ileocystoplasty and urinary diversion, for BPS found that 82% of patients with Hunner's ulcerations had symptomatic relief after surgery compared with 23% with non-ulcer disease after an average 89-month follow-up period (82, 83).	Evidence Level: 3
8.4	*What is the role of the multidisciplinary team – physiotherapist, pain team, clinical psychologist?*	
	Recommendation: **Consider referring patients with refractory BPS for psychological support or counselling if it is impacting on their quality of life or the patient's requests a referral.**	**Grade:** **GPP**
	Supporting Text: It is a well-known fact that some patients benefit from speaking to a counsellor or clinical psychologist and engaging in behavioural therapy to modify their lifestyle and improve their quality of life.	Evidence Level: 4
	Recommendation: **Patients with refractory BPS should be referred to a multidisciplinary team (MDT) in order to explore alternative treatment options. Those patients who may benefit for neuromodulation should be referred to an MDT before treatment is commenced.**	**Grade:** **GPP**
	Supporting Text: Referrals to pain clinics or clinical psychologists may need to be considered if conservative and oral treatments have failed.	Evidence Level: 4
8.5	*What is the role of support groups?*	
	Recommendation: **Support groups can provide invaluable information, support and advocate patient-centred care.**	**Grade:** **GPP**
	Supporting Text: These groups provide a platform to share experiences, exchange information, raise awareness and promote patient self-help management (84).	Evidence Level: 4
	Recommendation: **Patients should be given written information about patient organisations that provide evidence-based information.**	**Grade:** **GPP**
	Supporting Text: There are many patient organisations with variable quality information and resources, which help patients find information that is relevant to them personally using existing guidelines as well as patient experience as a basis (85, 86).	Evidence Level: 4
9.	**Long-term management and prognosis**	
9.1	*Which patients need follow-up?*	
	Recommendation: **Patients whose symptoms are not adequately controlled need to be followed up after each new treatment has been tried for 6-12 weeks.**	**Grade:** **D**
	Supporting Text:	Evidence

	Long-term follow up is needed in poorly controlled BPS. Clemens et al. reported that the mean yearly costs were 2.4-fold greater for treating these patients than for controls in a managed care population with 130% higher direct costs (87).	Level: 2+
	Recommendation: **Comorbidities should be addressed in order to provide holistic management.**	**Grade:** **C**
	Supporting Text: Due to the multifactorial nature of pelvic pain, these patients often suffer from multiple co-morbidities that need to be addressed. Multiple-regression-analyses of a National Health Insurance Database study from Taiwan showed that the patients with BPS had significantly higher total costs for all healthcare services than the controls, which could partly be due to higher medical co-morbidities (88).	Evidence Level: 2+
9.2	*What should be the duration of follow-up?*	
	Recommendation: **Patients should be followed up periodically until their symptoms become controlled to the extent that they are happy to be discharged.**	**Grade:** **GPP**
	Supporting Text: It is difficult to estimate a finite time for follow up as it is often difficult to achieve symptomatic control to an extent where the patient may be happy so individualised management plans need to take into consideration response to treatment, effects on quality of life and other existing comorbidities. Patients may benefit from regular appointments as most may find it takes time to find a suitable treatment and for them to respond to these.	Evidence Level: 2–
	Recommendation: **The effect of pregnancy on the severity of symptoms can be variable**	**Grade:** **D**
	Supporting Text: There is little published information about the changes in symptoms that may occur during pregnancy (89). The Interstitial Cystitis Association conducted a patient survey about symptoms and pregnancy in 1989, where patients who described their symptoms as ‘‘mild’’ experienced worsening symptoms during pregnancy, which persisted up to 6 months after delivery. In contrast, patients who described their symptoms as ‘‘severe’’ had a significant improvement in symptoms during the second trimester, which lasted up to 6 months after delivery or for the duration of breastfeeding. BPS was not affected by the mode of delivery. Another study found that only 7% of patients stated that their BPS symptoms had improved during pregnancy (90).	Evidence Level: 3
	Recommendation: **Pregnancy outcomes appear to be good following 1 course of DMSO.**	**Grade:** **D**
	Supporting Text: A prospective study included 12 patients who had a course of dimethylsulfoxide (DMSO) (every two weeks for 12 weeks) and all had symptom remission. Pregnancy occurred 6 months to 5 years after the DMSO treatment. Nine patients continued to have good symptom remission throughout pregnancy. The other 3 had worsening symptoms, and 2 patients terminated the pregnancy because of severe symptoms. Because this small group of patients was more homogeneous than the general IC population, with all patients having chronic inflammation on bladder biopsy and good remission after DMSO, it is unclear how the results of this study apply to the general BPS population (91).	Evidence Level: 2–
	Recommendation:	**Grade:**

	A patient who is experiencing significant symptom relief with PPS might choose to continue it during pregnancy.	**GPP**
	Supporting Text: Of the commonly used oral treatments, pentosan polysulfate and amitriptyline have the lowest risks, and hydroxyzine has more risks (89). Of the usual intravesical treatments, heparin is the safest because it is unlikely to be absorbed from the bladder or to cross the placenta. Lidocaine does cross the placenta and there is no information about the safety of chronic exposure to the fetus. DMSO and systemic corticosteroids have known teratogenic effects, but the absorption of intravesical corticosteroids is unknown. Sacral nerve stimulators should not be placed during pregnancy and, if present already, should be turned off for the duration of pregnancy as the effect on fetus is unknown (92)	Evidence Level: 4
	Recommendation: **The pregnant patient can be reassured that the risk of passing the condition to her child is very low.**	**Grade:** **D**
	Supporting Text: In a few cases, multiple members of the same family have BPS. This suggests that some patients may have a genetic predisposition. Unless she belongs to a family that has multiple members with the condition, the pregnant patient can be reassured that the risk for passing it on to her child is low (89).	Evidence Level: 4
10.	**Recommendations for future research**	
	• Create a single standardised validated assessment questionnaire and patient related outcome measures for BPS • Assess the role of conservative treatment versus placebo for BPS • Assess the role of the clinical psychologist • Assess the number of patients with co-existing conditions	
11.	**Auditable topics**	
	• What proportion of patients presenting with BPS have a positive urine dipstick or cytology? • What proportion of patients with BPS symptoms are commenced on conservative treatments in primary care? • What proportion of patients with BPS are referred to a general gynaecologist versus a urogynaecologist? • What proportion of patients have a symptomatic improvement with conservative treatment options? • What proportion of patients have a cystoscopy to either diagnose symptoms or as a treatment option?	
12.	**Useful links and support groups**	
	The following organisations provide support for BPS: Cystitis and overactive bladder foundation: www.cobfoundation.org Pelvic pain support network: www.pelvicpain.org.uk International painful bladder foundation: http://www.painful-bladder.org	
13.	**References**	
	1. 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. Eur Urol 2008;53(1):60-67.	

2. Gillenwater JY, Wein AJ. Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis, National Institutes of Health, Bethesda, Maryland, August 28-29, 1987. J Urol 1988;140(1):203-206.
3. Hanno PM, Landis JR, Matthews-Cook Y, Kusek J, Nyberg L. The diagnosis of interstitial cystitis revisited: lessons learned from the National Institutes of Health Interstitial Cystitis Database study. J Urol 1999;161(2):553-557.
4. Butrick CW. Interstitial cystitis and chronic pelvic pain: new insights in neuropathology, diagnosis, and treatment. Clin Obstet Gynecol 2003;46(4):811-823.
5. Konkle KS, Berry SH, Elliott MN, Hilton L, Suttorp MJ, Clauw DJ et al. Comparison of an Interstitial Cystitis/Bladder Pain Syndrome Clinical Cohort With Symptomatic Community Women From the RAND Interstitial Cystitis Epidemiology Study. J Urol 2012;187(2):508-512.
6. Clemens JQ, Link CL, Eggers PW, Kusek JW, Nyberg LM, McKinlay JB et al. Prevalence of painful bladder symptoms and effect on quality of life in black, Hispanic and white men and women. J Urol 2007;177(4):1390-1394.
7. Clemens JQ, Stoto MA, Elliott M, Suttorp M, Bogart L, Berry SH. Prevalence of interstitial cystitis/painful bladder syndrome in the United States. Neurourology and Urodynamics 2009;28(7):907-907.
8. Clemens JQ, Meenan RT, O'Keeffe Rosetti MC, Brown SO, Gao SY, Calhoun EA. Prevalence of interstitial cystitis symptoms in a managed care population. J Urol 2005;174(2):576-580.
9. Tirlapur SA, Khan KS. An assessment of clinicians and patients experiences in the management of bladder pain syndrome . 2014. Personal communication.
10. Rapariz-González M, Castro-Díaz D, Mejía-Rendón D, EURCIS. Evaluation of the impact of the urinary symptoms on quality of life of patients with painful bladder syndrome/chronic pelvic pain and radiation cystitis: EURCIS study. Actas Urol Esp 2014;38(4):224-231.
11. Bogart LM, Suttorp MJ, Elliott MN, Clemens JQ, Berry SH. Prevalence and correlates of sexual dysfunction among women with bladder pain syndrome/interstitial cystitis. Urology 2011;77(3):576-580.
12. Tirlapur SA, Kuhrt K, Chaliha C, Ball E, Meads C, Khan KS. The 'evil twin syndrome' in chronic pelvic pain: a systematic review of prevalence studies of bladder pain syndrome and endometriosis. Int J Surg 2013; 11(3):233-7
13. Suskind AM, Berry SH, Suttorp MJ, Elliott MN, Hays RD, Ewing BA et al. Health-related quality of life in patients with interstitial cystitis/bladder pain syndrome and frequently associated comorbidities. Qual Life Res 2013;22(7):1537-1541.
14. Bogart LM, Berry SH, Clemens JQ. Symptoms of interstitial cystitis, painful bladder syndrome and similar diseases in women: a systematic review. The Journal of urology 2007;177(2):450-456.
15. 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):191-198.
16. Hanno PM, Burks DA, Clemens JQ, Dmochowski RR, Erickson D, Fitzgerald MP et al. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. The Journal of urology 2011;185(6):2162-2170.

17. 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):60-67.
18. Messing E, Pauk D, Schaeffer A, Nieweglowski M, Nyberg LM, Jr., Landis JR et al. Associations among cystoscopic findings and symptoms and physical examination findings in women enrolled in the Interstitial Cystitis Data Base (ICDB) Study. Urology 1997;49(5A Suppl):81-85.
19. Cole EE, Scarpero HM, Dmochowski RR. Are patient symptoms predictive of the diagnostic and/or therapeutic value of hydrodistention? Neurourology and urodynamics 2005;24(7):638-642.
20. Waxman JA, Sulak PJ, Kuehl TJ. Cystoscopic findings consistent with interstitial cystitis in normal women undergoing tubal ligation. The Journal of urology 1998;160(5):1663-1667.
21. Geurts N, Van Dyck J, Wyndaele JJ. Bladder pain syndrome: do the different morphological and cystoscopic features correlate? Scandinavian journal of urology and nephrology 2011;45(1):20-23.
22. Wyndaele JJ, Van Dyck J, Toussaint N. Cystoscopy and bladder biopsies in patients with bladder pain syndrome carried out following ESSIC guidelines. Scandinavian journal of urology and nephrology 2009;43(6):471-475.
23. Carr LK, Corcos J, Nickel JC, Teichman J. Diagnosis of interstitial cystitis June 2007. Canadian Urological Association journal = Journal de l'Association des urologues du Canada 2009;3(1):81-86.
24. 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):573-578.
25. O'Leary MP, Sant GR, Fowler FJ, Whitmore KE, Spolarich-Kroll J. The interstitial cystitis symptom index and problem index. Urology 1997;49(5A Suppl):58-63.
26. 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. J Urol 1998;159(3):1085-1090.
27. Selfe SA, Matthews Z, Stones RW. Factors influencing outcome in consultations for chronic pelvic pain. J Womens Health 1998;7(8):1041-1048.
28. McGowan L, Luker K, Creed F, Chew-Graham CA. How do you explain a pain that can't be seen?: the narratives of women with chronic pelvic pain and their disengagement with the diagnostic cycle. Br J Health Psychol 2007;12(Pt 2):261-274.
29. Price J, Farmer G, Harris J, Hope T, Kennedy S, Mayou R. Attitudes of women with chronic pelvic pain to the gynaecological consultation: a qualitative study. BJOG 2006;113(4):446-452.
30. Warren JW, Brown J, Tracy JK, Langenberg P, Wesselmann U, Greenberg P. Evidence-based criteria for pain of interstitial cystitis/painful bladder syndrome in women. Urology 2008;71(3):444-448.
31. Tincello DG, Walker AC. Interstitial cystitis in the UK: results of a questionnaire survey of members of the Interstitial Cystitis Support Group. Eur J Obstet Gynecol Reprod Biol 2005;118(1):91-95.
32. Latthe P, Mignini L, Gray R, Hills R, Khan K. Factors predisposing women to chronic pelvic pain: systematic review. BMJ 2006;332(7544):749-755.

33. D'Andrea RM, Champaneria R, Latthe P. Hormone contraception and pelvic floor function: a systematic review. 2014. Personal communication.
34. Al-Hadithi HN, Williams H, Hart CA, Frazer M, Adams EJ, Richmond DH et al. Absence of bacterial and viral DNA in bladder biopsies from patients with interstitial cystitis/chronic pelvic pain syndrome. J Urol 2005;174(1):151-154.
35. Peters KM, Carrico DJ, Diokno AC. Characterization of a clinical cohort of 87 women with interstitial cystitis/painful bladder syndrome. Urology 2008;71(4):634-640.
36. Gomes CM, Sánchez-Ortiz RF, Harris C, Wein AJ, Rovner ES. Significance of hematuria in patients with interstitial cystitis: review of radiographic and endoscopic findings. Urology 2001;57(2):262-265.
37. Daha LK, Lazar D, Simak R, Pflüger H. Is there a relation between urinary interleukin-6 levels and symptoms before and after intra-vesical glycosaminoglycan substitution therapy in patients with bladder pain syndrome/interstitial cystitis? Int Urogynecol J Pelvic Floor Dysfunct 2007;18(12):1449-1452.
38. Keay S, Zhang CO, Chai T, Warren J, Koch K, Grkovic D, Colville H, Alexander R. Antiproliferative factor, heparin-binding epidermal growth factor-like growth factor, and epidermal growth factor in men with interstitial cystitis versus chronic pelvic pain syndrome. Urology. 2004 Jan;63(1):22-6.
39. Canter MP, Graham CA, Heit MH, Blackwell LS, Wilkey DW, Klein JB et al. Proteomic techniques identify urine proteins that differentiate patients with interstitial cystitis from asymptomatic control subjects. Am J Obstet Gynecol 2008;198(5):553.e551-556.
40. O'Hare PG, Hoffmann AR, Allen P, Gordon B, Salin L, Whitmore K. Interstitial cystitis patients' use and rating of complementary and alternative medicine therapies. Int Urogynecol J 2012. Jun;24(6):977-82
41. FitzGerald MP, Payne CK, Lukacz ES, Yang CC, Peters KM, Chai TC et al. Randomized multicenter clinical trial of myofascial physical therapy in women with interstitial cystitis/painful bladder syndrome and pelvic floor tenderness. J Urol 2012;187(6):2113-2118.
42. Cervigni M, Natale F. Gynecological disorders in bladder pain syndrome/interstitial cystitis patients. Int J Urol 2014;21 Suppl 1:85-88.
43. Verghese TS, Ni Riordain R, Latthe P. A systematic review of complementary therapies for bladder pain syndrome. 2014. Personal communication.
44. Giannantoni A, Bini V, Dmochowski R, Hanno P, Nickel JC, Proietti S et al. Contemporary management of the painful bladder: a systematic review. Eur Urol 2012;61(1):29-53.
45. Foster HE, Hanno PM, Nickel JC, Payne CK, Mayer RD, Burks DA et al. Effect of amitriptyline on symptoms in treatment naïve patients with interstitial cystitis/painful bladder syndrome. J Urol 2010;183(5):1853-1858.
46. van Ophoven A, Pokupic S, Heinecke A, Hertle L. A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. J Urol 2004;172(2):533-536.
47. Thilagarajah R, Witherow RO, Walker MM. Oral cimetidine gives effective symptom relief in painful bladder disease: a prospective, randomized, double-blind placebo-controlled trial. BJU Int 2001;87(3):207-212.
48. Sant GR, Propert KJ, Hanno PM, Burks D, Culkin D, Diokno AC et al. A pilot clinical trial of oral pentosan polysulfate and oral hydroxyzine in patients with interstitial cystitis. J Urol 2003;170(3):810-815.

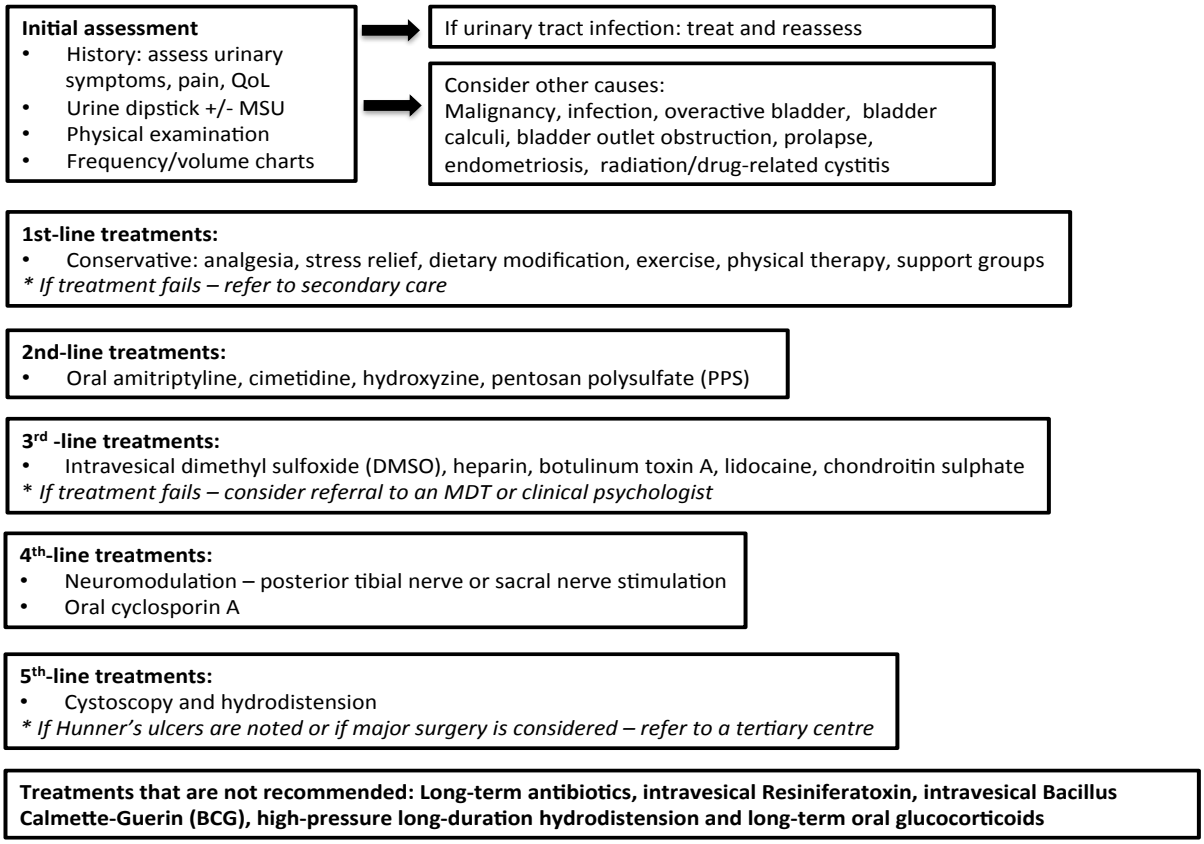
49. Homma Y, Ueda T, Ito T, Takei M, Tomoe H. Japanese guideline for diagnosis and treatment of interstitial cystitis. International Journal of Urology 2009;16(1):4-16.
50. Parsons CL, Benson G, Childs SJ, Hanno P, Sant GR, Webster G. A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosanpolysulfate. J Urol 1993;150(3):845-848.
51. Mulholland SG, Hanno P, Parsons CL, Sant GR, Staskin DR. Pentosan polysulfate sodium for therapy of interstitial cystitis. A double-blind placebo-controlled clinical study. Urology 1990;35(6):552-558.
52. Warren JW, Horne LM, Hebel JR, Marvel RP, Keay SK, Chai TC. Pilot study of sequential oral antibiotics for the treatment of interstitial cystitis. J Urol 2000;163(6):1685-1688.
53. Dawson TE, Jamison J. Intravesical treatments for painful bladder syndrome/ interstitial cystitis. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD006113
54. Peters K, Diokno A, Steinert B, Yuhico M, Mitchell B, Krohta S et al. The efficacy of intravesical Tice strain bacillus Calmette-Guerin in the treatment of interstitial cystitis: a double-blind, prospective, placebo controlled trial. J Urol 1997;157(6):2090-2094.
55. Mayer R, Propert KJ, Peters KM, Payne CK, Zhang Y, Burks D et al. A randomized controlled trial of intravesical bacillus calmette-guerin for treatment refractory interstitial cystitis. J Urol 2005;173(4):1186-1191.
56. McCahy PJ, Styles RA. Prolonged bladder distension: experience in the treatment of detrusor overactivity and interstitial cystitis. Eur Urol 1995;28(4):325-327.
57. Glemain P, Rivière C, Lenormand L, Karam G, Bouchot O, Buzelin JM. Prolonged hydrodistention of the bladder for symptomatic treatment of interstitial cystitis: efficacy at 6 months and 1 year. Eur Urol 2002;41(1):79-84.
58. Malloy TR, Shanberg AM. Laser therapy for interstitial cystitis. Urol Clin North Am 1994;21(1):141-144.
59. Rofeim O, Hom D, Freid RM, Moldwin RM. Use of the neodymium: YAG laser for interstitial cystitis: a prospective study. J Urol 2001;166(1):134-136.
60. Sairanen J, Forsell T, Ruutu M. Long-term outcome of patients with interstitial cystitis treated with low dose cyclosporine A. J Urol 2004;171(6 Pt 1):2138-2141.
61. Dimitrakov J, Kroenke K, Steers WD, Berde C, Zurakowski D, Freeman MR et al. Pharmacologic management of painful bladder syndrome/interstitial cystitis: a systematic review. Arch Intern Med 2007;167(18):1922-1929.
62. Perez-Marrero R, Emerson LE, Feltis JT. A controlled study of dimethyl sulfoxide in interstitial cystitis. J Urol 1988;140(1):36-39.
63. Parsons CL, Housley T, Schmidt JD, Lebow D. Treatment of interstitial cystitis with intravesical heparin. Br J Urol 1994;73(5):504-507.
64. Matsuoka PK, Haddad JM, Pacetta AM, Baracat EC. Intravesical treatment of painful bladder syndrome: a systematic review and meta-analysis. Int Urogynecol J 2012;23(9):1147-1153.
65. Nickel JC, Moldwin R, Lee S, Davis EL, Henry RA, Wyllie MG. Intravesical alkalinized lidocaine (PSD597) offers sustained relief from symptoms of interstitial cystitis and painful bladder syndrome. BJU Int 2009;103(7):910-918.
66. Tirumuru S, Al-Kurdi D, Latthe P. Intravesical botulinum toxin A injections in the treatment of painful bladder syndrome/interstitial cystitis: a systematic review. Int Urogynecol J 2010;21(10):1285-1300.

67. Thakkinstian A, Nickel JC. Efficacy of intravesical chondroitin sulphate in treatment of interstitial cystitis/bladder pain syndrome (IC/BPS): Individual patient data (IPD) meta-analytical approach. Can Urol Assoc J 2013;7(5-6):195-200.
68. Cervigni M, Natale F, Nasta L, Mako A. Intravesical hyaluronic acid and chondroitin sulphate for bladder pain syndrome/interstitial cystitis: long-term treatment results. Int Urogynecol J 2012;23(9):1187-1192.
69. Porru D, Cervigni M, Nasta L, Natale F, Gardella B, Lo Voi R et al. Effects of endovesical hyaluronic acid/chondroitin sulfate in the treatment of interstitial cystitis/painful bladder syndrome. European Urology Supplements 2008;7(3):286-286.
70. Giberti C, Gallo F, Cortese P, Schenone M. Combined intravesical sodium hyaluronate/chondroitin sulfate therapy for interstitial cystitis/bladder pain syndrome: a prospective study. Ther Adv Urol 2013;5(4):175-179.
71. Bosch J. Electrical neuromodulatory therapy in female voiding dysfunction. Bju International 2006;98:43-48.
72. Hassouna MM, Siegel SW, Nyeholt A, Elhilali MM, van Kerrebroeck PEV, Das AK et al. Sacral neuromodulation in the treatment of urgency-frequency symptoms: A multicenter study on efficacy and safety. Journal of Urology 2000;163(6):1849-1854.
73. Zhao J, Bai J, Zhou Y, Qi G, Du L. Posterior tibial nerve stimulation twice a week in patients with interstitial cystitis. Urology 2008;71(6):1080-1084.
74. Whitmore KE, Payne CK, Diokno AC, Lukban JC. Sacral neuromodulation in patients with interstitial cystitis: a multicenter clinical trial. Int Urogynecol J Pelvic Floor Dysfunct 2003;14(5):305-308; discussion 308-309.
75. Maher CF, Carey MP, Dwyer PL, Schluter PL. Percutaneous sacral nerve root neuromodulation for intractable interstitial cystitis. J Urol 2001;165(3):884-886.
76. Comiter CV. Sacral neuromodulation for the symptomatic treatment of refractory interstitial cystitis: A prospective study. Journal of Urology 2003;169(4):1369-1373.
77. Steinberg AC, Oyama IA, Whitmore KE. Bilateral S3 Stimulator in Patients with Interstitial Cystitis. Urology. 2007 Mar;69(3):441-3.
78. Powell CR, Kreder KJ. Long-Term Outcomes of Urgency-Frequency Syndrome Due to Painful Bladder Syndrome Treated With Sacral Neuromodulation and Analysis of Failures. Journal of Urology 2010;183(1):173-176.
79. Erickson DR, Kunselman AR, Bentley CM, Peters KM, Rovner ES, Demers LM et al. Changes in urine markers and symptoms after bladder distention for interstitial cystitis. J Urol 2007;177(2):556-560.
80. Ottem DP, Teichman JM. What is the value of cystoscopy with hydrodistension for interstitial cystitis? Urology 2005;66(3):494-499.
81. Higson RH, Smith JC, Whelan P. Bladder rupture: an acceptable complication of distension therapy? Br J Urol 1978;50(7):529-534.
82. Rössberger J, Fall M, Jonsson O, Peeker R. Long-term results of reconstructive surgery in patients with bladder pain syndrome/interstitial cystitis: subtyping is imperative. Urology 2007;70(4):638-642.
83. Tirlapur SA, Khan KS. Grading of evidence for bladder pain syndrome: a comparative review of study quality assessment methods. Int Urogynecol J 2014;25(8):1005-1013.
84. Birch J, Watel F, Meijlink J, Kruse L, Crowe S, Birch J. The role of the

patient organisation. International Association for the Study of Pain; 2014.
85. Tirlapur SA, Leiu C, Khan KS. Quality of information on the internet related to bladder pain syndrome: a systematic review of the evidence. Int Urogynecol J 2013;24(8):1257-1262.
86. McMullan M. Patients using the Internet to obtain health information: how this affects the patient-health professional relationship. Patient Educ Couns 2006;63(1-2):24-28.
87. Anger JT, Zabihi N, Clemens JQ, Payne CK, Saigal CS, Rodriguez LV. Treatment choice, duration, and cost in patients with interstitial cystitis and painful bladder syndrome. International Urogynecology Journal 2011;22(4):395-400.
88. Chung SD, Liu SP, Li HC, Lin HC. Health care service utilization among patients with bladder pain syndrome/interstitial cystitis in a single payer healthcare system. PLoS One 2014;9(1):e87522.
89. Erickson DR, Propert KJ. Pregnancy and interstitial cystitis/painful bladder syndrome. Urol Clin North Am 2007;34(1):61-69.
90. Simon LJ, Landis JR, Erickson DR, Nyberg LM. The Interstitial Cystitis Data Base Study: concepts and preliminary baseline descriptive statistics. Urology 1997;49(5A Suppl):64-75.
91. Onwude JL, Selo-Ojeme DO. Pregnancy outcomes following the diagnosis of interstitial cystitis. Gynecol Obstet Invest 2003;56(3):160-162.
92. El-Khawand D, Montgomery OC, Wehbe SA, Whitmore KE. Sacral nerve stimulation during pregnancy: case report and review of the literature. Female Pelvic Med Reconstr Surg 2012;18(2):127-129.

Appendix I. Proposed treatment algorithm for BPS

Bladder pain syndrome (BPS)*: Pain/pressure/discomfort in the pelvis/bladder, associated with urinary symptoms (frequency, urgency, nocturia, bladder filling pain) lasting at least 6 months, with no identifiable cause.*



Appendix II. Explanation of guidelines and evidence levels

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No.1 *Development of RCOG Green-top Guidelines* (available on the RCOG website at http://www.rcog.org.uk/green-top-development). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1 –	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of Recommendation

A — At least one meta-analysis, systematic reviews or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results

B — A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1++ or 1+

C — A body of evidence including studies rated as 2+ directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2++

D — Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2+

Good Practice Points

✓ Recommended best practice based on the clinical experience of the guideline development group

This guideline was produced on behalf of the Royal College of Obstetricians and Gynaecologists by: **Dr SA Tirlapur, London; Ms J Birch, Pelvic Pain Support Network; Dr CL Carberry MD, Rhode Island, USA; Professor KS Khan MRCOG, London; Dr P Latthe MRCOG, Birmingham; Dr S Jha FRCOG, Sheffield, British Society of Urogynaecology; Dr KL Ward MRCOG, Manchester, British Society of Urogynaecology; Ms A Irving, Cystitis and Overactive Bladder Foundation, UK**

and peer-reviewed by: XXX

Committee lead reviewers were: XXX

Conflicts of interest: XXX

The final version is the responsibility of the Guidelines Committee of the RCOG.

The review process will commence in XXX, unless otherwise indicated.

Appendix 7: All published manuscripts. Licensing copyrights have been obtained from all publishing companies.

REVIEW

International Journal of Surgery 11 (2013) 233–237

Contents lists available at SciVerse ScienceDirect

International Journal of Surgery

journal homepage: www.theijs.com

Review

The 'evil twin syndrome' in chronic pelvic pain: A systematic review of prevalence studies of bladder pain syndrome and endometriosis

S.A. Tirlapur [a,c,*], K. Kuhrt [b], C. Chaliha [c], E. Ball [c], C. Meads [a,d], K.S. Khan [a,c]

[a] Women's Health Research Unit, Queen Mary, University of London, Turner Street, London E1 2AB, United Kingdom
[b] Barts and The London School of Medicine and Dentistry, London E1 2AB, United Kingdom
[c] Barts Health NHS Trust, The Royal London Hospital, Whitechapel Road, London E1 1BB, United Kingdom
[d] Health Economics Research Group, Brunel University, Uxbridge, Middlesex UB8 3PH, United Kingdom

ARTICLE INFO

Article history:
Received 6 October 2012
Received in revised form
11 January 2013
Accepted 6 February 2013
Available online 15 February 2013

Keywords:
Chronic pelvic pain
Bladder pain syndrome
Painful bladder syndrome
Interstitial cystitis
Endometriosis
Prevalence

ABSTRACT

Background: Chronic pelvic pain (CPP), a common gynaecological presentation, may be due to bladder pain syndrome (BPS) or the co-existence of BPS and endometriosis, known as the 'evil twins syndrome'.
Objectives: To estimate the prevalence of BPS and the co-existence of BPS and endometriosis in women with CPP.
Data sources: We searched until March 2012: The Cochrane Library, DARE (1997–2012), EMBASE (1980–2012), Medline (1950–2012), PSYCHINFO (1806–2012), Web of knowledge (1900–2012), LILACS (1982–2012) and SIGLE (1990–2012) with no language restrictions. We manually searched through bibliographies and conference proceedings of the International Continence Society.
Study selection: Observational studies of women suffering from CPP, who were not pregnant or suffering from cancer, who underwent a laparoscopy and cystoscopy to investigate their symptoms. Study selection, data extraction and quality assessment was performed independently by two reviewers. Statistical analysis was performed to estimate prevalence and confidence intervals (CI).
Results: Nine studies were included with 1016 patients with CPP. Study quality and diagnostic assessment varied. The mean prevalence of BPS was 61% (range 11–97%, CI 58–64%, $I^2 = 98\%$). The mean prevalence of endometriosis was 70% (range 28–93%, CI 67–73%, $I^2 = 93\%$) and co-existing BPS and endometriosis was 48% (range 16–78%, CI 44–51%, $I^2 = 96\%$).
Conclusion: Almost two thirds of women presenting with CPP have BPS. Large variations in prevalence may be due to variable study selection and quality. Clinicians need to actively investigate patients for BPS, a condition that appears to co-exist with endometriosis.

1. Background

The diagnosis and treatment of chronic pelvic pain (CPP) has a large financial burden on health care economies. Bladder pain syndrome (BPS) is a recognised cause of CPP. It can have a huge impact on quality of life and sexual function.[1]

BPS is defined as the symptoms of CPP, bladder pressure or discomfort along with at least one other urinary symptom in the absence of any identifiable pathology or infection.[2,3] This definition was proposed by the European Society for the Study of Interstitial Cystitis/Painful Bladder Syndrome (ESSIC) in 2008. The condition can be further classified by cystoscopy grading and biopsy results. BPS was formerly known as interstitial cystitis (IC) and painful bladder syndrome (PBS). It has an unknown aetiology with a reported prevalence between 5 and 16 per 100,000 of the population.[4,5] The prevalence of BPS amongst women with CPP is unknown. The co-existence of diseases in CPP, such as BPS and endometriosis, described by Chung et al. as the 'evil twins syndrome'[6,7] can make management very difficult.[8] While the term 'the evil twin syndrome' is not a medical definition, it conveys the misery of the co-existence of these two chronic pain conditions.

The purpose of this systematic review was to estimate the prevalence of BPS in women suffering from CPP. Secondarily we

Abbreviations: BPS, bladder pain syndrome; CI, confidence interval; CPP, chronic pelvic pain; ESSIC, European Society for the Study of Interstitial Cystitis/Painful Bladder Syndrome; IC, interstitial cystitis; NIDDK, National Institute of diabetes and digestive and kidney diseases; OLS, O'Leary-Sant; PBS, painful bladder syndrome; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PUF, pelvic pain urgency/frequency; SD, standard deviation.

* Corresponding author. Women's Health Research Unit, Queen Mary, University of London, 58 Turner Street, London E1 2AB, United Kingdom. Tel.: +44 207 882 5883; fax: +44 207 882 2552.
E-mail address: s.a.tirlapur@qmul.ac.uk (S.A. Tirlapur).

1743-9191/$ – see front matter © 2013 Surgical Associates Ltd. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ijsu.2013.02.003

estimated the prevalence of endometriosis and the co-existence of BPS and endometriosis within this group of women.

2. Methods

Our systematic review was conducted and reported in accordance with the PRISMA statement.[9]

3. Data sources

A search through the following databases was performed until March 2012: The Cochrane Library, DARE (1997–2012), EMBASE (1980–2012), Medline (1950–2012), PSYCHINFO (1806–2012), Web of knowledge (1900–2012) and IJLACS (1982–2012). Grey literature was searched through SIGLE (1990–2012). There were no language restrictions.

3.1. Search strategy

We used MeSH headings and keywords for 'chronic pelvic pain' and 'chronic pain' combined using the Boolean operator 'and' with the terms 'interstitial cystitis' or 'painful bladder syndrome' or 'bladder pain syndrome' or 'urinary frequency' or 'urinary urgency'. The search was restricted to those studies involving female patients. A hand search of bibliographies from relevant articles and conference proceedings of the International Continence Society was performed to identify articles not electronically cited, as prevalence studies are not well indexed in database searches.

3.2. Study selection

Relevant studies on CPP were identified which met the following criteria:

3.3. Participants

Women suffering from chronic pelvic pain with, or without, urinary symptoms suggestive of IC, PBS or BPS, who were not pregnant or suffering from cancer, who underwent a laparoscopy and cystoscopy to investigate their symptoms. Patients diagnosed solely on intravesical potassium sensitivity test (PST) were excluded. CPP was defined as intermittent or constant pain in the lower abdomen or pelvis of at least 6 months duration, not occurring exclusively with menstruation or intercourse and not associated with pregnancy.[10]

3.4. Outcome

Most of the studies were performed prior to introduction of the BPS disease nomenclature, but for the purpose of this review all those with IC were considered to have a symptom based diagnosis of BPS, as this would logically happen under the new disease classification. BPS was defined according to the 1987 National Institute of diabetes and digestive and kidney diseases (NIDDK) criteria. The patient needed to have glomerulations on cystoscopy or a classic Hunner's ulcer, and either pain associated with the bladder or urinary urgency. Glomerulations are punctuate petechial hemorrhages on the bladder wall.[11] These were diagnosed after two minutes of bladder distension under anaesthesia. At least ten glomerulations were needed in at least three quadrants of the bladder.[12]

3.5. Study selection

A systematic review was performed on the prevalence of BPS in women with chronic pelvic pain. This included cross-sectional studies, which are neither prospective nor retrospective but measure the given condition at one point in time. Cohort studies were also included as it is possible to get prevalence figures from the baseline data collection phase.

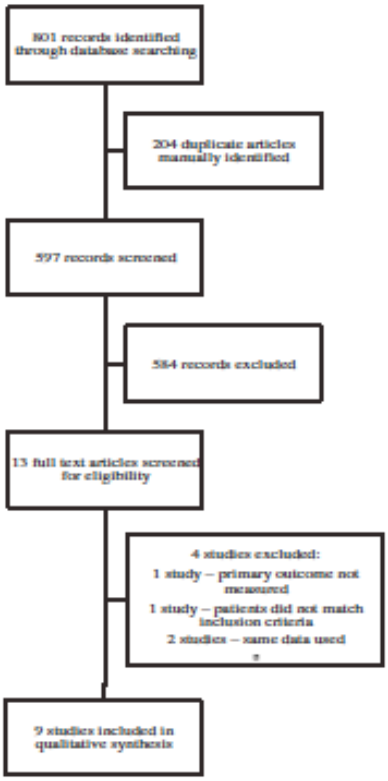


Fig. 1. Study selection for a systematic review on prevalence of bladder pain syndrome amongst women with chronic pelvic pain.

3.6. Data extraction and quality assessment

The data were independently extracted by two reviewers (SAT, KK) using a pre-designed data collection form. Data were collected for patient characteristics (number of participants, age and ethnicity), study details (study design, location, setting, and participant recruitment as part of the study quality assessment to assess possible selection bias) and outcomes assessed (diagnostic tools and rates of BPS, endometriosis and co-existing pathology).

Quality assessment was performed to assess the overall quality of the studies used in this systematic review. It was carried out by one reviewer and checked by a second reviewer. Studies not published in English were translated by individuals with command of the relevant language.[13] Data from one study was extracted from a conference abstract[14] where the full article could not be obtained. A quality assessment checklist was developed to evaluate internal validity using the following characteristics[15,16]: (a) Study design to determine if BPS assessment had been performed prospectively to

Table 1
Study characteristics for papers included in the systematic review of bladder pain syndrome and endometriosis.

Study	Country	Mean age in years (age range)	Ethnicity	Number of patient	Duration of study (months)	Source of recruitment
Cheng 2012	Australia	30	Not documented	150	29	Specialist clinic
Chung 2002	USA	19–62	Not documented	60	12	Specialist clinic
Chung 2005	USA	18–60	Not documented	178	24	Specialist clinic
Clemens 2002	USA	35.2 (20–53)	73% Caucasian, 16% Hispanic, 2% African American, 9% other	45	7	Operating list
Paulson 2011	USA	Not documented	Not documented	284	72	Operating list
Radcow 2009	USA	13–25	96% Caucasian, 4% African-American	28	168	Operating list
Shahmohammady 2005	USA	36 (20–60)	Not documented	92	Not documented	Specialist clinic
Stanford 2005	USA	32.7	Not documented	64	12	Community gynaecology clinic
Villegas 2011	Columbia	32.6 (17–53)	Not documented	115	26	Specialist clinic

minimise recall bias; (b) Adequacy of sampling by assessing whether participant recruitment was random or consecutive; (c) Sufficiently high response rate (>80%); (d) Use of diagnostic criteria to diagnose BPS to ensure participants response rates are a true representation of the underlying condition; (e) Sample size calculation so as to ascertain prevalence reliably. A study was considered 'high quality' if it complied with 3/5 quality criteria.[17] External validity was considered separately as the representativeness of the sample for the general population (source of sample).[8]

3.7. Data synthesis

The prevalence and 95% confidence interval (CI) was computed for each study. Heterogeneity was assessed using I^2 using the Metadisc statistical software package.[18] Pooled results were given for information only as the results of individual studies were too heterogenous to be used as combined results. Results with $I^2 > 50\%$ are considered highly heterogenous.

4. Results

The search identified 801 citations (Fig. 1). After removal of duplicates there were 597 citations, of which 13 were deemed relevant and their full papers were retrieved. Four studies were excluded; in one only the secondary outcome of co-existing BPS and endometriosis was measured, in another the presenting condition was BPS rather than CPP and two studies reported the same patient population, as confirmed by the corresponding author. Nine studies were included in the systematic review.

4.1. Study characteristics

The nine included observational studies were performed between 1990 and 2011 and included 1016 patients in total. The study characteristics are summarised in Table 1.

In all the studies, even though the disease nomenclature may have varied, the diagnosis was defined using the NIDDK criteria. The diagnosis of BPS ranged from 11%[19]–97%,[7] with a mean prevalence of 61% (58–64%). Five of the studies were prospective in design. Only one study performed sample size calculations using Piface software.[17] There was a lack of reporting about whether participants were randomly or purposefully recruited, making it difficult to assess external validity, although, in three studies participants were recruited retrospectively from theatre operating lists. Seven studies were considered 'high quality' (Fig. 2). In one study routine bladder biopsies were performed when glomerulations were seen on cystoscopy.[20] In 44% of these patients, normal histopathology was noted. In two studies bladder biopsies were performed; one to rule out carcinoma and in the other where no cause was identified on cystoscopy.

The prevalence of endometriosis was given in all nine studies. It ranged from 28%[19]–93%,[7] with a mean prevalence of 70% (CI 67–73%) (Fig. 3). It was diagnosed by visual inspection on laparoscopy with biopsy confirmation of disease performed in 3 studies.[6,7,19] In 2 other studies[20,21] biopsies were obtained to confirm the diagnosis of endometriosis where possible. The co-existence of endometriosis and BPS was given in seven studies. The prevalence ranged from 16%[22]–78%,[7] with a mean prevalence of 48% (CI 44–51%) (Fig. 3).

In five (45%) studies the affected patient group was identified through their symptoms and clinical examination. In the other four studies (44%) validated questionnaires were used; one used the IC symptom index problem index (O'Leary Sant questionnaire, OLS) which correlated with the diagnosis of BPS in 94% of patients, two used the pelvic pain urgency/frequency (PUF) questionnaire, showing higher PUF scores in the BPS patients, and one used both questionnaires to assess the degree of BPS, showing higher scores in the BPS patients (mean PUF score of 8.6 and OLS score of 7.5).[20] Three studies (33%) used the visual analogue scale questionnaire to assess pain. The mean pain score for CPP ranged from 5.3–8, and 5.4–7 for BPS.[20–22]

5. Discussion

A range of prevalence rates for BPS were reported in the literature. The large variation in rates observed in this paper may be explained by the variable study quality and sample selection. The highest prevalences were noted in patients recruited from specialist clinics and operating lists. From the nine studies, in 4 studies patients suffered from CPP and urinary symptoms and notably, some of the highest prevalences of BPS were seen in these

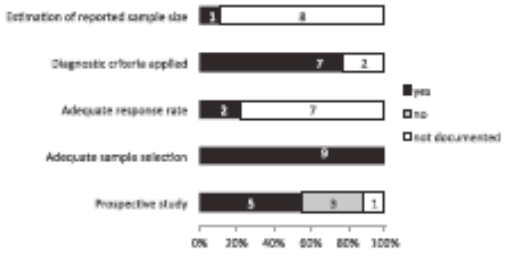
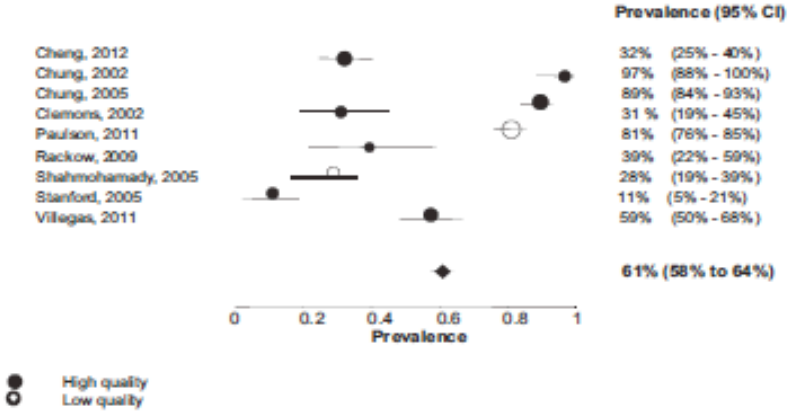
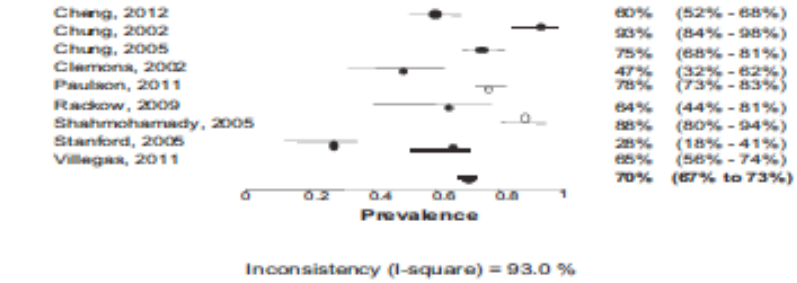


Fig. 2. Quality of studies included in the systematic review of the prevalence of bladder pain syndrome and endometriosis.

3a: Prevalence of BPS amongst women with CPP



3b: Prevalence of endometriosis amongst women with CPP



3c: Prevalence of BPS and endometriosis amongst women with CPP

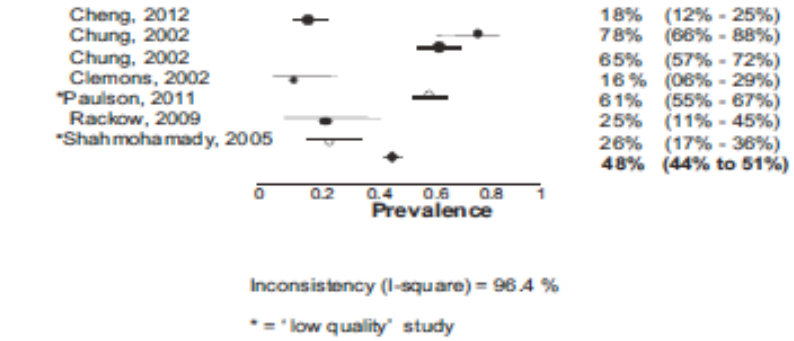


Fig. 3. Prevalence of bladder pain syndrome (BPS), endometriosis and co-existing BPS and endometriosis amongst women with chronic pelvic pain (CPP).

patients.[6,21,42] In 6 (67%) of the studies, the authors hip team had a special interest in urogynaecology.

We complied with PRISMA, searched comprehensively, selected studies and extracted data in duplicate, and synthesised results appropriately. This systematic review highlights the fact that almost two thirds of patients presenting with CPP have BPS, a finding that merits consideration. In all the studies, the diagnosis was made by the presence of urinary symptoms and positive cystoscopy findings. A limitation is that both cystoscopic normality and bladder lesions are poorly correlated with histopathology,[23] leading to the risk of misdiagnosis of patients. BPS has a wide symptom spectrum with imprecise clinical characterisation. Bladder pain or bladder filling pain is not captured in the commonly used questionnaires like OLS and PUF. The value of these questionnaires as a diagnostic tool is debatable.[24] There was limited information about the ethnicity of the participants in the included studies, which makes it difficult to apply the results of this review internationally. Literature shows that the prevalence of BPS does not vary with ethnicity although minority women appear to be symptomatic for longer than Caucasian women, while the prevalence of endometriosis appears to be higher in Asian women than other ethnicities.[25–27]

Identification of BPS is challenging, as the clinical presentation can be similar to several other conditions, which can lead to delays in diagnosis and inappropriate treatment. In 2011 the American Urological Association published guidelines for the diagnosis and management of IC and BPS, which recommended diagnosis by clinical history and physical examination, with cystoscopy only used as a diagnostic tool in complex presentations. Thus allowing initiation of conservative treatments, such as pain relief, behavioural modification and stress management.[23] We found an overlap between BPS and endometriosis. Clinicians need to be aware of the existence of co-existing pathology and actively investigate urinary symptoms and BPS as a cause of CPP and commence active management early.

Ethical approval

Not needed.

Funding

None.

Author contribution

SAT — Conception, design, search, study selection, data extraction, data synthesis and writing and revising the manuscript.

KK — Data extraction.

CC — Revising manuscript.

EB — Revising manuscript.

CM — Advice on search strategies, quality assessment, data analysis and presentation and revisions to manuscript.

KSK — Conception, design, data synthesis, writing and revising the manuscript.

Conflict of interest

None.

Acknowledgements

Ana Gutierrez for her help with translation of a foreign manuscript.

References

1. Tormi I, Wehrberger C, Riedl C, Pinholzer A, Marszalek M, Madersbacher S. Prevalence and correlates for interstitial cystitis symptoms in women participating in a health screening project. *Eur Urol* 2007;51(3):803–8. discussion 9.
2. Buttick CW. Interstitial cystitis and chronic pelvic pain: new insights in neuropathology, diagnosis, and treatment. *Clin Obstet Gynecol* 2003;46(4): 811–23.
3. 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. *Eur Urol* 2008;53(1): 60–7.
4. Fall M, Baranowski AP, Fowler CJ, Lepinard V, Malone-Lee JG, Messelink EJ, et al. EAU guidelines on chronic pelvic pain.
5. Kreklee KS, Berry SH, Elliott MN, Hilton L, Suttorp MJ, Clauw DJ, et al. Comparison of an interstitial cystitis/bladder pain syndrome clinical cohort with symptomatic community women from the RAND interstitial cystitis epidemiology study. *J Urol* 2012;187(2):508–12.
6. Chung MK, Chung RP, Gordon D. Interstitial cystitis and endometriosis in patients with chronic pelvic pain: the "evil twins" syndrome.
7. Chung MK, Chung RR, Gordon D, Jennings C. The evil twins of chronic pelvic pain syndrome: endometriosis and interstitial cystitis. *JSLS* 2002;6(4): 311–4.
8. Latthe P, Latthe M, Say L, Gülmezoglu M, Khan KS. WHO systematic review of prevalence of chronic pelvic pain: a neglected reproductive health morbidity. *BMC Public Health* 2006;6:177.
9. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PloS Med* 2009;6(7):e1000100.
10. Royal College of Obstetricians and Gynaecologists. *Management of chronic pelvic pain*. London April 2005.
11. Messing EM, Stamey TA. Interstitial cystitis: early diagnosis, pathology, and treatment. *Urology* 1978;12(4):381–92.
12. Hanno PM, Landis JR, Matthews-Cook Y, Kusek J, Nyberg L. The diagnosis of interstitial cystitis revisited: lessons learned from the National Institutes of Health Interstitial Cystitis Database study. *J Urol* 1999;161(2): 553–7.
13. Villegas-Echeverri, Lopez-Jaramillo, Leon-Avellaneda, Restrepo-Santa. The role of cystoscopy when studying patients suffering from chronic pelvic pain: an observational study. *Columbia: Rev Colomb Obstet Ginecol* 2011:161–6.
14. Shahmoradi S, Berker B, Lashay N, Sabeti N, Kazemnezhad T, Nezhat C. Interstitial cystitis in the setting of chronic pelvic pain. *Obstet Gynecol* 2005;105(4). 1015.
15. Glasziou P, Irwig L, Bain C, Colditz G. Frequency and rate. In: . *Systematic reviews in health care: a practical guide*. 2nd ed. Cambridge University Press; 2001. p. 67–73.
16. Khan KS, Kunz R, Kleijnen J, Antes G. Five steps to conducting a systematic review. *J R Soc Med* 2003;96(3):118–21.
17. Streiner DL, Norman GR. *Measurement*. London: PDQ Epidemiology; 1998.
18. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. *BMC Med Res Methodol* 2006;6:31.
19. Stanford EJ, Koziol J, Feng A. The prevalence of interstitial cystitis, endometriosis, adhesions, and vulvar pain in women with chronic pelvic pain. *J Minim Invasive Gynecol* 2005;12(1):43–9.
20. Cheng C, Rosamilia A, Healey M. Diagnosis of interstitial cystitis/bladder pain syndrome in women with chronic pelvic pain: a prospective observational study. *Int Urogynecol J* 2012;23(10):1361–6.
21. Paulson JD, Paulson JN. Anterior vaginal wall tenderness (AVWT) as a physical symptom in chronic pelvic pain. *JSLS* 2011;15(1):6–9.
22. Clemens JL, Arya LA, Myers DL. Diagnosing interstitial cystitis in women with chronic pelvic pain. *Obstet Gynecol* 2002;100(2):337–41.
23. Hanno PM, Burks DA, Clemens JQ, Dmochowski RR, Erickson D, Fitzgerald MP, et al. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. *J Urol* 2011;185(6):2162–70.
24. Kushner L, Moldwin RM. Efficiency of questionnaires used to screen for interstitial cystitis. *J Urol* 2006;176(2):587–92.
25. Clemens JQ, Link CL, Eggers PW, Kusek JW, Nyberg LM, McKinlay JB, et al. Prevalence of painful bladder symptoms and effect on quality of life in black, Hispanic and white men and women. *J Urol* 2007;177(4):1330–4.
26. Sant GR. Interstitial cystitis in minority women. *J Assoc Acad Minor Phys* 1993;4(3):89–92.
27. Jamby M, Fujimoto VY, Giudice LC, Kuppermann M, Washington AE. Racial and ethnic disparities in benign gynecologic conditions and associated surgeries. *Am J Obstet Gynecol* 2010;202(6):514–21.

Int Urogynecol J
DOI 10.1007/s00192-013-2091-1

REVIEW ARTICLE

Quality of information on the internet related to bladder pain syndrome: a systematic review of the evidence

S. A. Tirlapur · C. Leiu · K. S. Khan

Received: 11 February 2013 / Accepted: 9 March 2013

Abstract
Introduction and hypothesis Bladder pain syndrome (BPS) has an impact on quality of life and available treatments often only provide temporary symptomatic relief. The information provided by websites can be valuable for patient education and management. The hypothesis was to assess medical information available on the internet related to bladder pain syndrome in terms of accuracy, credibility, readability and quality.
Methods A search was performed in the meta-search engine Copernic Agent, using the search terms "bladder pain syndrome, interstitial cystitis, painful bladder syndrome and pelvic pain", which simultaneously captured websites from a range of engines. Websites in the English language that were open-access were included. The four quality assessments used were: credibility using a ten-point scale, accuracy based on the American Urological Association guidelines, quality using the DISCERN questionnaire and readability using the Flesch Reading Ease Score. Inter-rater agreement was tested by intra-class coefficient (ICC).
Results Eighteen suitable websites were identified; 7 (39%) were specialist or specific to BPS. The combined mean scores for accuracy, quality, credibility and readability ranged from 83 to 144 for specialist websites and 76 to 137 for non-specialist ones, with a maximum possible score of 208. There was good inter-observer agreement for the assessments performed with an ICC ranging from 0.80 for DISCERN to 0.53 for readability. Specialist websites had higher quality scores (median difference 10, $p=0.07$) and readability scores (median difference 5.4, $p=0.05$) compared with non-specialist websites whereas credibility and accuracy scores were no different.
Conclusion We found four websites that fulfilled our criteria for good quality information.

Keywords Accuracy · Bladder pain syndrome · Credibility · Internet · Interstitial cystitis · Readability

Abbreviations

AUA	American Urological Association
BPS	Bladder pain syndrome
CI	Confidence interval
DMSO	Dimethyl sulfoxide
FRE	Flesch Reading Ease test
ICC	Intra-class co-efficient
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PROSPERO	International Prospective Register for Systematic Reviews
SD	Standard deviation

Introduction

Bladder pain syndrome (BPS), formerly known as interstitial cystitis, is defined as chronic pelvic pain, pressure or discomfort related to the bladder along with at least one other urinary

Electronic supplementary material The online version of this article (doi:10.1007/s00192-013-2091-1) contains supplementary material, which is available to authorized users.

S. A. Tirlapur · C. Leiu · K. S. Khan
Women's Health Research Unit, Queen Mary, University of London, Turner Street, London E1 2AB, UK

S. A. Tirlapur · K. S. Khan
Barts Health NHS Trust, The Royal London Hospital, Whitechapel Road, London E1 1BB, UK

S. A. Tirlapur (✉)
Women's Health Research Unit, Barts and the London School of Medicine, Queen Mary, University of London, 58 Turner Street, London E1 2AB, UK
e-mail: s.a.tirlapur@qmul.ac.uk

Published online: 20 April 2013

Table 1 A description of the accuracy criteria used to assess the quality of information about bladder pain syndrome on the internet [2]

Criteria	Descriptor[a]
1	Definition: "Chronic pelvic pain, pressure or discomfort of greater than 6 weeks' duration perceived to be related to the urinary bladder accompanied by at least one other urinary symptom in the absence of any identifiable cause"
2	Assessment: history, symptom questionnaire, pain evaluation, physical examination and urine dipstick
3	First-line treatment: behavioural (stress management, relaxation, dietary modification, patient education)
4	Second-line treatment: physical (pelvic floor biofeedback, soft tissue massage)
5	Oral: analgesia, antihistamine, antidepressants. Intravesical: DMSO (dimethyl sulfoxide), heparin, lidocaine
6	Third-line treatment: cystoscopy with hydrodistension under anaesthesia
7	Fourth-line treatment: neuromodulation: posterior tibial nerve and sacral nerve stimulation
8	Fifth-line treatment: botulinum toxin or cyclosporin
9	Sixth-line treatment: surgical management: diversion with possible cystectomy

[a] Each of the 18 websites was evaluated for accuracy using the nine-point scoring system above which was derived from the 2010 American Urological Association guidelines for the diagnosis and management of interstitial cystitis/bladder pain syndrome

symptom, such as urinary urgency or frequency, in the absence of any other pathology [1]. Recently, the American Urological Association published guidelines for the diagnosis and management of BPS, but in practice BPS has imprecise clinical characterisation, which can lead to delays in diagnosis and initiation of treatment [2]. Patients often seek information on the worldwide web.

The internet can act as an effective tool, providing patients with information about their illness and allowing them to share experiences with others. Medical information on the internet is extremely variable in quality [3, 4]. In conditions such as BPS, which can have a large impact on quality of life, treatments may only provide temporary symptomatic relief, support networks and the information provided by websites can be valuable in patient education and management [5]. This review assessed the quality of medical information available on the internet related to BPS.

Materials and methods

The search strategy, inclusion criteria, methodology and analysis were documented in a protocol registered with the International Prospective Register of Systematic Reviews (PROSPERO) [6]. This review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [7].

Identification of websites

A list of search terms for BPS were obtained through the Google search engine, seeking websites for the terms "interstitial cystitis", "painful bladder syndrome" and "bladder pain syndrome". The first ten website links per keyword were evaluated and recurrent terms and symptoms were identified to develop a comprehensive search strategy. We performed the search using the meta-search engine Copernic Agent on 15 November 2012. Copernic combines multiple commonly used search engines, removes duplicate results and stores and manages the results obtained (http://www.copernic.com). It combined searches from the following search engines: Alta Vista, Ask.com, Bing, Blekko, Copernic, Dogpile, DuckDuckGo, Enhance Interactive, Exalead, Fast Search, Google, Incywincy, Lycos, Mamma.com, Open Directory Project, Yahoo! and Yippee. The search terms used were "bladder pain syndrome, interstitial cystitis, painful bladder syndrome, pelvic pain". Websites in the English language were included. Sites were excluded if they were not open access or required a password. Citations of scholarly scientific articles were also excluded.

Data extraction and quality assessment

Information on the websites were assessed for credibility, accuracy, readability and quality by two independent reviewers (SAT, CL). Credibility was defined as the power of inspiring belief based on ten criteria: source, content, currency, utility, editorial review process, hierarchy of evidence, statement of

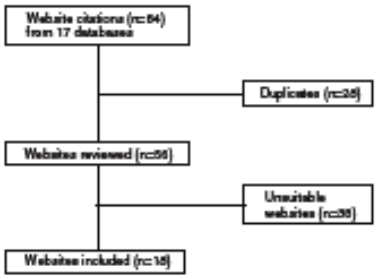


Fig. 1 Study selection for assessment of information on the internet related to bladder pain syndrome

Table 2 A summary of characteristics for the included websites

Website address	Country	Disease specific	Patient focused	Listed authors	Patient forum	Privacy statement
www.niddk.nih.gov	USA	No	Yes	No	No	Yes
www.wikipedia.org	International	No	No	No	No	Yes
www.essic.eu	International	Yes	No	Yes	No	Yes
www.associatedcontent.com	USA	No	Yes	Yes	No	Yes
www.womenshealth.gov	USA	No	Yes	No	No	Yes
www.webmd.com	USA	No	Yes	No	Yes	Yes
www.painful-bladder.org	International	Yes	Yes	Yes	No	Yes
www.mayoclinic.com	USA	No	Yes	Yes	No	Yes
www.ehow.com	USA	No	Yes	Yes	No	Yes
www.bladderandbowelfoundation.org	UK	Yes	Yes	No	Yes	Yes
www.medicinenet.com	USA	No	Yes	Yes	Yes	Yes
www.ichelp.org	USA	Yes	Yes	Yes	No	Yes
my.clevelandclinic.org	USA	No	Yes	No	No	Yes
www.ic-network.com	USA	Yes	Yes	Yes	Yes	Yes
www.localhealth.com	USA	No	Yes	Yes	Yes	Yes
www.intelihealth.com	USA	No	Yes	Yes	No	Yes
www.cobfoundation.org	UK	Yes	Yes	Yes	Yes	Yes
www.urologyhealth.org	USA	Yes	Yes	Yes	No	Yes

original source, disclaimer, which included ownership, sponsorship, funding and advertising, omissions and a feedback mechanism [8–14]. Each criterion was assigned a score 0 or 1: 0 if absent and 1 if present, giving a score ranging from 0 to 10. Accuracy of content consisted of nine items (Table 1), judged against rigorously developed peer-reviewed and published

Table 3 A summary of the outcome measures used to assess the included studies on bladder pain syndrome

Website address	DISCERN[a]		Accuracy[a]		Credibility[a]		Readability[a]	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
www.niddk.nih.gov	68.5	0.5	12.0	0	8.0	1.0	48.2	1.75
Wikipedia.org	53.2	5.0	17.0	0	2.0	0	31.7	0.35
www.essic.eu	34.0	8.0	2.5	0.5	4.0	2.0	42.3	11.0
www.associatedcontent.com	27.5	2.5	5.0	1.0	3.5	0.25	40.2	3.55
www.womenshealth.gov	55.0	3.0	10.5	0.5	6.5	0.5	69.1	0.05
www.webmd.com	46.5	0.5	10.5	2.5	5.5	1.5	56.3	1.0
www.painful-bladder.org	70.0	4.0	17.5	0.5	7.5	0.5	48.9	8.95
www.mayoclinic.com	63.5	11.5	15.0	0	7.0	0	43.2	0.8
www.ehow.com	40.5	4.5	8.0	1.0	3.0	0	44.2	0.6
www.bladderandbowelfoundation.org	59.0	3.0	10.5	0.5	6.0	1.0	45.6	1.25
www.medicinenet.com	61.0	2.0	11.5	3.5	8.0	0	32.8	4.3
www.ichelp.org	71.0	7.0	17.5	0.5	8.0	1.0	43.7	9.8
my.clevelandclinic.org	40.0	4.0	8.0	1.0	4.5	0.5	35.5	2.65
www.ic-network.com	74.5	4.5	14.0	0	9.0	0	45.0	6.2
www.localhealth.com	45.0	2.0	10.5	1.5	7.0	0	37.5	7.85
www.intelihealth.com	43.5	2.5	8.5	1.5	7.0	0	39.6	0.6
www.cobfoundation.org	52.0	3.0	10.0	2.0	6.0	2.0	47.4	0.6
www.urologyhealth.org	53.0	6.0	7.0	1.0	5.5	0.5	57.8	0

[a] DISCERN tool for quality assessment (maximum score 80), accuracy assessment based on American Urological Association 2011 guidelines (maximum score 18), credibility based on ten criteria (maximum score 10) and readability using the Flesch Reading Ease assessment (maximum score 100)

guidelines from the American Urological Association [2, 15]. Each item was scored 0, 1, 2; 0 if not or incorrectly mentioned, 1 if the item was mentioned and 2 if the item was mentioned satisfactorily, giving a score ranging from 0 to 18. Readability was assessed using two tools; the Flesch Reading Ease test with scores ranging from 0 to 100. Generally, the higher the score, the easier the website was to read, and the Flesch–Kincaid grade level, which ranged from 1 to 12 with a goal of <8, which would be understood by an 8th grade school child (i.e. aged around 13–14 years old) [16, 17]. Text on the first page of the website, giving an overview of the condition, was used to calculate readability scores, using an online readability calculator (www.readability-score.com). Quality assessment was performed using the DISCERN questionnaire, which assesses the quality of written information about treatment choices for a given condition, where 16 questions were rated 1–5 (1=no, 3=partial and 5=yes) with a maximum score of 80. This DISCERN questionnaire is a reliable and valid tool for analysing consumer health information in order to critically appraise and evaluate the information in a standardised manner. It assesses the reliability and quality of given information [18, 19].

Data analysis

Inter-rater reliability of assessments was tested for agreement using intra-class co-efficient (ICC) [18]. A score less than 0.2 indicated poor agreement, 0.6 to 0.8 good, and greater than 0.8 is very good agreement [20]. The mean score of the two observers was used for analysis. The Mann–Whitney *U* test was used to compare measures for specialist and non-specialist websites using the StatsDirect software package. Specialist websites were those specific to BPS and bladder-related conditions, in comparison to non-specialist websites.

Results

Eighteen suitable websites were identified in the search (Fig. 1). Concerning agreement in website assessment, the ICC for DISCERN was 0.75 (95% limits of agreement −14.8 to 21.8), for credibility it was 0.63 (95% limits of agreement −2.48 to 4.04), for accuracy it was 0.80 (95% limits of agreement −5.86 to 2.41) and for readability it was 0.53 (95% limits of agreement −−18.3 to 21.2).

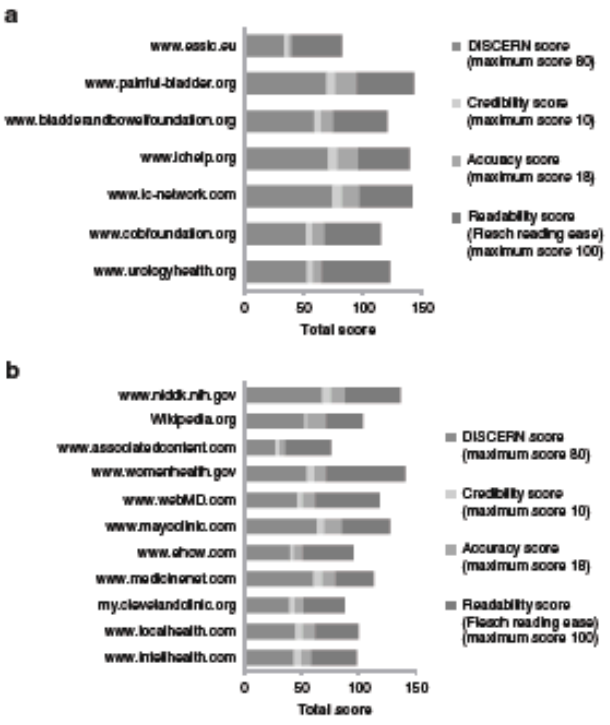


Fig. 2 Graphical summary of the outcome measures for the included websites. a Websites specific to bladder pain syndrome. b Websites not specific to bladder pain syndrome

Table 2 represents the website characteristics: 12 websites (67%) were based in America; 7 (39%) were specific to BPS; 6 (33%) had a patient forum; 11 (61%) were linked to social media platforms such as Facebook and Twitter.

Table 3 and Fig. 2 summarise measures of credibility, accuracy, readability and DISCERN scores for all included websites. The overall mean scores were: DISCERN 60 (maximum score 80), accuracy 11 (maximum score 18), credibility 6 (maximum score 10) and readability 45 (maximum score 100). The low readability scores were often due to the complexity of the medical terminology used in many websites, which did not make them easily readable to the general public. Several websites performed well on the four criteria of readability, accuracy, quality and credibility combined. In some cases, this was due to their high readability scores. While readability is important, quality, accuracy and credibility are necessary to provide useful information for patients. We found that the best information was provided by www.ic-network.com, www.ichelp.org, www.painful-bladder.org, and www.niddk.nih.gov. Three of these websites were specific to BPS. Specialty-specific websites tended to have higher DISCERN score (median difference 10, $p=0.07$) and readability scores (median difference 5.4, $p=0.05$) and no difference in credibility (median difference=1, $p=0.22$) and accuracy scores (median difference=0.5, $p=0.40$) compared with non-specialist websites.

Discussion

We believe this to be the first assessment of information on the internet related to BPS. This was a robust review of all identified websites associated with BPS. Four websites were identified as being easy to navigate and performed well across the measurements of accuracy, quality, credibility and readability and these could be recommended to patients as useful sources of information. There was good inter-rater agreement for DISCERN and credibility and very good agreement for accuracy. One weakness of this review was the exclusion of websites not in English or where a translation tool was unavailable.

Chronic pain syndromes, such as bladder pain syndrome, have a great impact on a patient's quality of life, interactions with their family and place a huge financial burden on the economy [21]. It is important that the information that we as clinicians have is transferred to our patients to empower them via understanding of their conditions and hence allowing improved disease awareness and self-management [22]. Although the American Medical Association has developed guidelines for the postings on websites, the usefulness of this information is extremely variable so it is important for clinicians to enquire about the type of information patients gain from the internet in order to clarify any inaccuracies [10, 23–25].

There can be great variation in how patients with BPS are managed so it is essential that patients understand the value of self-help [26]. As we have moved to an era where social media and the internet are a constant source of information and communication, it is important for clinicians to recognise the benefit that these resources can provide and embrace the good ones as valuable educational resources [27].

Acknowledgments None.

Funding None.

Ethics None.

Conflicts of interest None.

References

1. van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK et al (2008) Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol 53(1):60–67
2. Hanno PM, Burks DA, Clemens JQ, Dmochowski RR, Erickson D, Fitzgerald MP et al (2011) AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol 185(6):2162–2170
3. McMullan M (2006) Patients using the internet to obtain health information: how this affects the patient-health professional relationship. Patient Educ Couns 63(1–2):24–28
4. Benigeri M, Pluye P (2003) Shortcomings of health information on the internet. Health Promot Int 18(4):381–386
5. Tennstedt C, Wehrberger C, Riedl C, Posholzer A, Marszalek M, Madersbacher S (2007) Prevalence and correlates for interstitial cystitis symptoms in women participating in a health screening project. Eur Urol 51(3):803–808, discussion 809
6. Chien PF, Khan KS, Siassakos D (2012) Registration of systematic reviews: PROSPERO. BJOG 119(8):903–905
7. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP et al (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 62(10):e1–e34
8. Silberg WM, Lundberg GD, Musacchio RA (1997) Assessing, controlling, and assuring the quality of medical information on the internet: caveant lector et viewor–let the reader and viewer beware. JAMA 277(15):1244–1245
9. Lathe PM, Lathe M, Khan KS (2000) Quality of medical information about menorrhagia on the worldwide web. BJOG 107(1):39–43
10. Winker MA, Flanagin A, Chi-Lum B, White J, Andrews K, Kennett RL et al (2000) Guidelines for medical and health information sites on the internet: principles governing AMA web sites. Am Med Assoc JAMA 283(12):1600–1606
11. Groot D, ter Riet G, Khan KS, Misso K (2001) Comparison of search strategies and quality of medical information of the internet: a study relating to ankle sprain. Injury 32(6):473–476
12. Kunst H, Groot D, Lathe PM, Lathe M, Khan KS (2002) Accuracy of information on apparently credible websites: survey of five common health topics. BMJ 324(7337):581–582

13. Murphy R, Frost S, Webster P, Schmidt U (2004) An evaluation of web-based information. Int J Eat Disord 35(2):145–154
14. Ambre J, Guard R, Perveiler FM, Renner J, Rippen H (1997) White paper: Criteria for assessing the quality of health information on the internet
15. Hanno P, Lin A, Nordling J, Nyberg L, van Ophoven A, Ueda Tet al (2010) Bladder pain syndrome committee of the international consultation on incontinence. Neurourol Urodyn 29(1):191–198
16. Bernstam EV, Shelton DM, Walji M, Meric-Bernstam F (2005) Instruments to assess the quality of health information on the world wide web: what can our patients actually use? Int J Med Inform 74(1):13–19
17. Routh JC, Gong EM, Cannon GM, Nelson CP (2011) Does a controversial topic affect the quality of urologic information on the internet? Urology 78(5):1051–1056
18. Kaicker J, Debono VB, Dang W, Buckley N, Thabane L (2010) Assessment of the quality and variability of health information on chronic pain websites using the DISCERN instrument. BMC Med 8:59
19. Henderson EM, Rosser BA, Keogh E, Eccleston C (2012) Internet sites offering adolescents help with headache, abdominal pain, and dysmenorrhoea: a description of content, quality, and peer interactions. J Pediatr Psychol 37(3):262–271
20. Landis JR, Koch GG (1977) The measurement of observer agreement for categorical data. Biometrics 33(1):159–174
21. Davies L, Ganger K, Drummond M, Saunders D, Beard R (1992) The economic burden of intractable gynaecological pain. J Obstet Gynaecol 12 [Suppl 2]:S46–S54
22. Henry JL (2008) The need for knowledge translation in chronic pain. Pain Res Manag 13(6):465–476
23. Corcoran TB, Haigh F, Seabrook A, Schug SA (2009) The quality of internet-sourced information for patients with chronic pain is poor. Clin J Pain 25(7):617–623
24. de Boer MJ, Versteegen GJ, van Wijhe M (2007) Patients' use of the Internet for pain-related medical information. Patient Educ Couns 68(1):86–97
25. Sajadi KP, Goldman HB (2011) Social networks lack useful content for incontinence. Urology 78(4):764–767
26. Clemens JO, Calhoun EA, Litwin MS, Collins MM (2008) Primary care physician practice patterns in the management of interstitial cystitis/painful bladder syndrome. Neurourol Urodyn 27(2):140–141
27. Cline RJ, Haynes KM (2001) Consumer health information seeking on the internet: the state of the art. Health Educ Res 16(6):671–692

PROSPERO registration number

CRD42012003203

Tirlapur et al. Reproductive Health 2013, 10:61
http://www.reproductive-health-journal.com/content/10/1/61

REPRODUCTIVE HEALTH

STUDY PROTOCOL Open Access

Bladder pain syndrome: validation of simple tests for diagnosis in women with chronic pelvic pain: BRaVADO study protocol

Seema A Tirlapur[1*], Lee Priest[2], Daniel Wojdyla[3], Khalid S Khan[1,4] and On behalf of the MEDAL Study

Abstract

Background: Bladder pain syndrome (BPS), a condition with no gold standard diagnosis, comprises of a cluster of signs and symptoms. Bladder filling pain and bladder wall tenderness are two basic clinical features, present in a high number of sufferers. This study will validate the performance of these simple tests for BPS in women with chronic pelvic pain (CPP).

Methods/design: We will conduct a prospective test validation study amongst women with unexplained CPP presenting to gynaecology outpatient clinics. Two index tests will be performed: patient reported bladder filling pain and bladder wall tenderness on internal pelvic bimanual examination. A final diagnosis of BPS will be made by expert consensus panel. We will assess the rates of index tests in women with CPP; evaluate the correlation between index tests and Pelvic Pain Urgency/ Frequency (PUF) questionnaire results; and determine index test sensitivity and specificity using a range of analytical methods. Assuming a 50% prevalence of BPS and an 80% power approximately 152 subjects will be required exclude sensitivity of < 55% at 70% sensitivity.

Discussion: The results of this test validation study will be used to identify whether a certain combination of signs and symptoms can accurately diagnose BPS.

Trial registration: ISRCTN13028601

Keywords: Bladder pain syndrome, Chronic pelvic pain, Consensus panel, Latent class analysis, Test validation

Background

Bladder pain syndrome (BPS), formerly known as interstitial cystitis and painful bladder syndrome, is a cause of chronic pelvic pain (CPP) and is defined as CPP, bladder pressure or discomfort along with at least one other urinary symptom in the absence of any identifiable pathology or infection [1,2].

The reported prevalence of BPS is between 5 and 16 per 100,000 of the population with 61% of women presenting with CPP being diagnosed with BPS [3-5]. The condition has a large impact on sexual function and quality of life [6]. It has an unknown aetiology and imprecise characterisation, which makes it difficult to accurately diagnose clinically [7,8]. The diagnosis of BPS can be made by symptoms alone and further classified by cystoscopy findings and biopsy results, after exclusion of other confusable diseases like urinary tract infection or overactive bladder [2]. Symptoms include urinary frequency, urgency, nocturia and incomplete voiding [9]. Validated questionnaires may be used to help diagnose patients. The two commonly used are the O'Leary-Sant Interstitial Cystitis Symptom Index/Problem Index and the Pelvic Pain Urgency/ Frequency (PUF) questionnaire [10,11]. Neither questionnaire is considered a reliable predictor of disease or disease severity [11,12]. There is no gold standard test for BPS, which makes for difficulty in choice of study design for a diagnostic evaluation study (Figure 1).

The most commonly reported symptoms are bladder/ pelvic pain, urgency, frequency and nocturia but this symptom cluster is present in several other urinary conditions

* Correspondence: s.a.tirlapur@qmul.ac.uk
[1]Women's Health Research Unit, Barts and the London School of Medicine, Queen Mary, University of London, 58 Turner Street, London E1 2AB, UK
Full list of author information is available at the end of the article

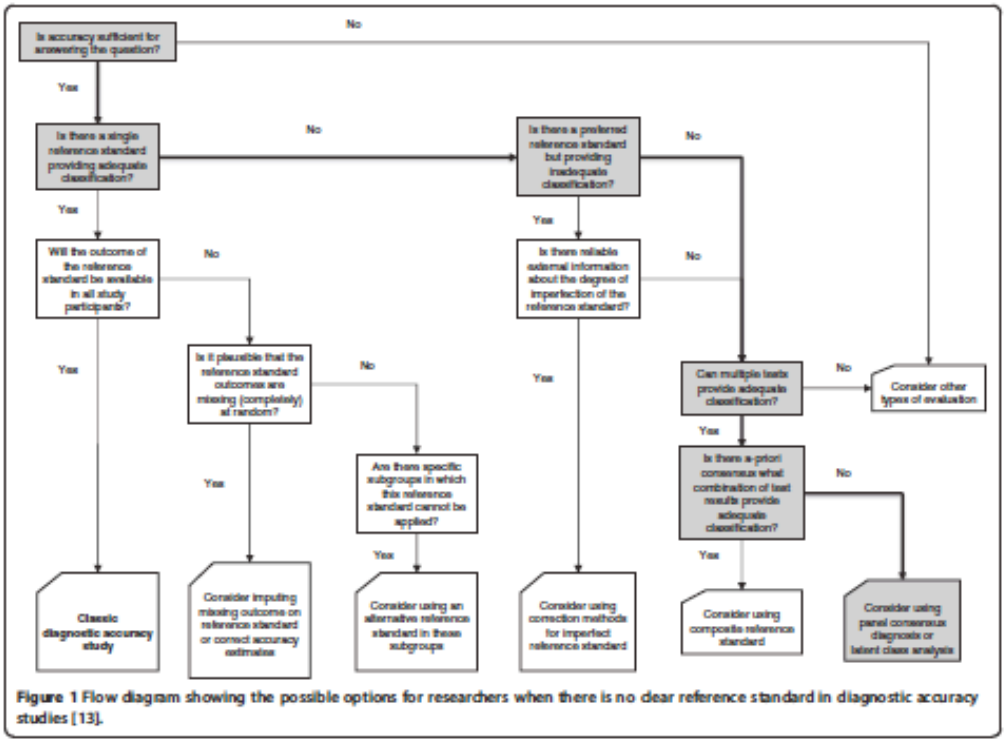


Figure 1 Flow diagram showing the possible options for researchers when there is no clear reference standard in diagnostic accuracy studies [13].

and is not discriminating of BPS [14]. In practice, the symptom of bladder filling pain and the sign of bladder wall tenderness on vaginal examination have been shown to be present in a high number of patients with BPS, but these have not been incorporated into existing tools [15,16]. This study will validate the use of these simple tests for BPS in women with CPP.

Methods/design

The BRaVADO study will be conducted prospectively and its protocol is reported in accordance with the SPIRIT guidelines [17]. This will be a sub-study of the MEDAL trial (MRI to Establish Diagnosis Against Laparoscopy), which is a multicentre diagnostic test accuracy study carried out in United Kingdom to investigate women with unexplained chronic pelvic pain.

Trial registration: Ethics and research and development approvals for this study are covered through the multicentre research ethics committee (REC no: 11/EM/0281). The study is sponsored by Queen Mary, University of London (Ref no: 007936 QM). Clinical trial registration no: ISRCTN13028601.

Objectives:

1. To determine the rates of the symptom of bladder filling pain and the sign of bladder wall tenderness in women with CPP.
2. To assess the correlation between bladder filling pain, bladder wall tenderness, and the PUF questionnaire (and several component questions within it) in the diagnosis of BPS in CPP.
3. To determine the prevalence of BPS in CPP, using consensus panel to establish reference standard diagnosis.
4. To estimate the accuracy with which a certain combination of signs and symptoms (index tests) can identify the diagnosis of BPS in CPP.

Design

Prospective test validation study with consensus panel to establish reference diagnosis.

Setting

Gynaecology outpatient clinics in the United Kingdom.

Participant eligibility

Women presenting to secondary care with unexplained CPP. The inclusion criteria are women aged 16 or older who are referred to secondary care with unexplained CPP and have the ability to understand adequate English to give informed consent. Exclusion criteria are pregnancy, a previous hysterectomy, a proven urinary tract infection on urine dipstick and a previous diagnosis of BPS.

Index tests:

1. Bladder filling pain will be assessed through a patient questionnaire (Figure 2). There is also assessment of pain when the bladder is full to discriminate the two.
2. Bladder base tenderness will be assessed by specialists in gynaecology as part of a routine vaginal examination. This is the sensation of pain when the bladder wall is palpated, rather than a sensation of discomfort.

Reference tests

There is no gold standard test for diagnosis. We will have an expert consensus panel in the study. The panel will be made of 3 national specialists in urogynaecology. The diagnosis determined by the panel will be a symptom-based diagnosis of BPS through patient self-reporting symptoms captured in a range of validated questionnaires. Figure 3 shows the proforma to be used for the consensus panels.

Recruitment

All eligible patients will be invited to participate in the study. They will be consented by named research staff at all participating centres, according to the MEDAL protocol version 1.2. There will be consecutive recruitment of all eligible patients to minimise selection bias (Figure 4).

Sample size

The power estimation for such test validation studies is not straightforward. Estimates of prevalence of BPS vary. A recent systematic review suggested the prevalence of BPS in women with CPP is as high as 61% [3,4]. Since the exact prevalence in unknown, a range of sample sizes have been calculated based on various levels of prevalence (Table 1). There are no published estimates of sensitivity, as defined as having a positive index test and actually having BPS. We use a 95% confidence interval and exact test to estimate sample sizes, excluding a sensitivity range of less than 45% to 65% with a power of 80%. For example, assuming a 50% prevalence of BPS and an 80% power approximately 152 subjects will be required exclude sensitivity of < 55% at 70% sensitivity.

Proposed time schedule

Table 2 shows the study timeline with recruitment commencing August 2012 and study end date of September 2014 [17].

Data collection

Data will be collected on the pre-designed data collection forms and inputted into the central database. Quality assurance testing will take place with double data entry, visual cross validation, data completeness checks and protocol adherence. All patients will undergo a diagnostic laparoscopy and cystoscopy, if deemed clinically necessary. Information will be collected about co-existing causes of CPP. The information collected will be represented in a STARD flow diagram (Figure 4).

Data analyses

Patient characteristics will be recorded. We will provide descriptive statistics with ranges and standard deviations as appropriate. Statistical analyses will compute sensitivity, specificity and predictive values using consensus panel

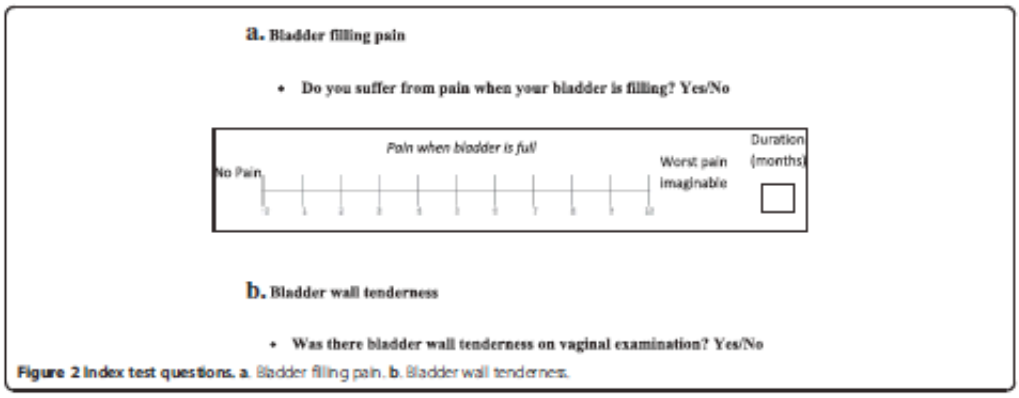


Figure 2 Index test questions. a. Bladder filling pain. **b.** Bladder wall tenderness.

Question	Answer
1. Negative urine dipstick?	Yes / No
2. Duration of pain	Answer in months
3. Location of pain and severity?	Description of location with pain score 1–10
4. Superficial/deep dyspareunia?	Yes / No
5. Pain on full bladder?	Yes / No
6. Urinary frequency?	Score 0 (3–6 times) to 4 (over 20 times)
7. Nocturia?	Score 0 (never) to 3 (always)
8. Post void urgency?	Yes / No
9. Degree of urgency?	Mild/ moderate/ severe
10. Pain associated with bladder, urethra, Vagina, perineum, pelvis?	Never/occ/usually/always
11. PUF score	0 – 35
12. **Do you think this patient has BPS?**	**Yes / No**
13. How certain are you? (0 = uncertain to 10 = very certain)	

Figure 3 Consensus panel assessment form for symptom-based diagnosis of bladder pain syndrome.

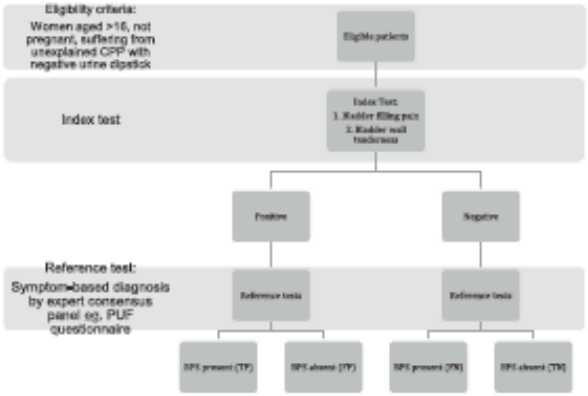


Figure 4 Study flow chart in accordance with the STARD reporting guidelines [18].

Table 1 Study power calculations at various assumptions

Sensitivity	Sensitivity to exclude	No. of patients with BPS	Sample size Total number of patients		
			40% prevalence	50% prevalence	60% prevalence
60%	45%	82	205	164	137
65%	50%	78	195	156	130
70%	55%	76	190	152	127
75%	60%	73	183	146	122
80%	65%	69	173	132	115

diagnosis as reference. We will consider several approaches to test validation [13]. The flow diagram in Figure 1 shows how we arrived at the proposed data analyses methodology. In the absence of a single reference standard to provide adequate diagnostic classification and the lack of information regarding the degree of imperfection of the reference standards, multiple tests can be used. As there is no consensus on pre-defined rules to define the target condition, we will use an expert panel diagnosis. Accuracy is concurrent criterion validity. In order to avoid incorporation bias, we will not include the index tests as part of the symptom based diagnosis. From the certainty scores of diagnosis we will calculate median and confidence interval scores, and kappa for inter-rater reliability. We will report all estimates of test performance with confidence intervals. We will also explore the use of latent class analysis, which is a statistical test that allows evaluation of a new test in the absence of a gold standard [19].

Data monitoring

Data monitoring will be undertaken in accordance with guidelines for diagnostic studies [20]. Quality testing with range checks for data values and standard operating procedures will be used to maintain accurate data reporting and monitoring. Regular data monitoring committee meetings will be scheduled with a group of independent experts.

Discussion

The results of this test validation study will be used to identify whether a certain combination of signs and symptoms can accurately predict the diagnosis of BPS. In 2011 the American Urological Association produced their guidelines for diagnosis and management of BPS, which are summarised in Figure 5 [21]. Since then, cystoscopic findings have been discredited as a negative cystoscopy does not exclude BPS and cystoscopic findings do not correlate well with disease severity or histopathology [22,23]. For

Table 2 A schematic diagram showing the timeline for study participation [17]

TIMEPOINT	$-t_1$ (July 2012)	0 (August 2012)	t_1	t_2	t_3	t_4	t_x
	Pre-study	Enrolment	Patient Visit 1	Patient Visit 2	Reference diagnosis	Analysis	Study end
ENROLMENT:							
Eligibility screen	X						
Informed consent		X					
Screening log		X					
Urine screen		X					
INTERVENTIONS:							
Bladder filling pain			X				
Bladder wall tenderness			X				
ASSESSMENTS:							
Validated questionnaires		X	X				
Vaginal examination			X				
Diagnostic laparoscopy				X			
Expert panel (reference diagnosis)					X		
DATA ANALYSIS						X	
COMPLETE REPORT							X

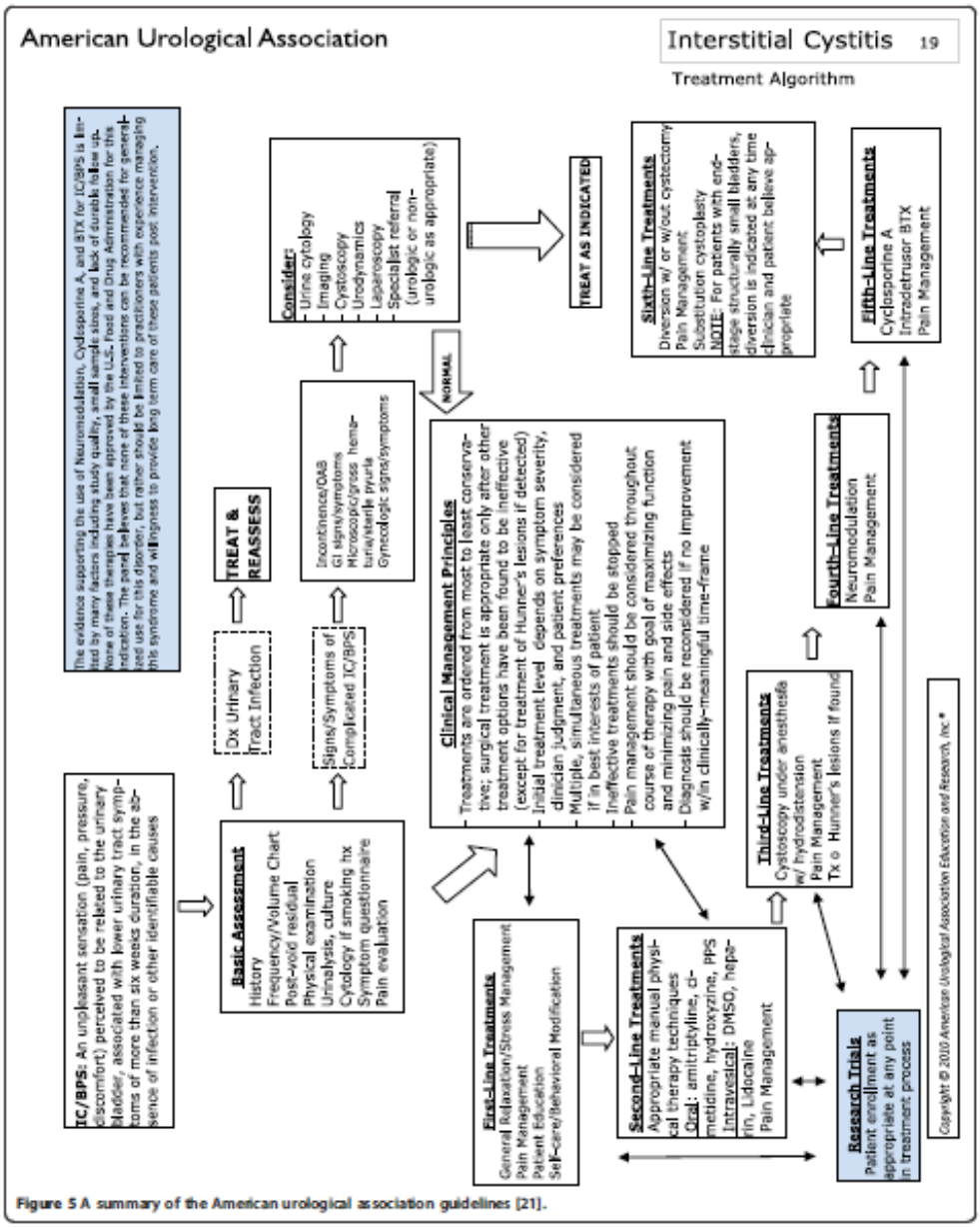


Figure 5 A summary of the American urological association guidelines [21].

this reason cystoscopy and bladder biopsy can no longer be used as a gold standard diagnostic tool for the condition. According to the 2011 guidelines, initial treatment with pain management, behavioural modifications, patient education and physical therapies can be commenced after basic assessment consisting of history, pain assessment, physical examination and urinalysis. Cystoscopy and hydrodistension are recommended as a fourth-line treatment for BPS as this investigation may provide limited diagnostic and therapeutic benefit [24]. If a cluster of signs and symptoms could accurately predict BPS this could be incorporated into the basic clinical assessment and would help clinicians diagnose the condition and initiate treatments without lengthy delays performing investigations, which are often not discriminatory.

Ethics approval

The study has ethical approval from the National Research Ethics Service (NRES) Committee East Midlands - Nottingham 1, United Kingdom (Ref 11/EM/0281).

Abbreviations

BPS: Bladder pain syndrome; CPP: Chronic pelvic pain; MEDAL: MRI to establish diagnosis against laparoscopy; NIHR: National Institute of health research; PUF: Pelvic pain urgency/ frequency.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SAT drafted and revised the protocol and manuscript. LP revised manuscript. DW provided statistical guidance on latent class analysis and sample size calculations. KSK conceived and designed the study and applied for funding. He revised the protocol and manuscript. All authors read and approved the final manuscript.

Author's information

Seema Anushka Tirlapur BSc, MBChB – Clinical research fellow in obstetrics and gynaecology at Queen Mary, University of London.
Lee Priest BSc (Hons), MPhil – Trial Coordinator at Birmingham Clinical Trials Unit, University of Birmingham.
Daniel Wojdyla MSc – Clinical statistician, Centro Rosarino de Estudios Perinatales, Argentina.
Khalid S Khan MSc, MRCOG, MMed - Professor of women's health and clinical epidemiology at Queen Mary, University of London.

Acknowledgements

The BRAVADO study is a sub-study within the MEDAL study (MRI to establish a diagnosis in chronic pelvic pain) (http://www.controlledtrials.com/ISRCTN13028601/medal), a project funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) (ref: 09/22/50). The views and opinions expressed are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or Department of Health. The MEDAL study management group includes Khalid Khan, Jane Daniels, Jon Deeks, Elizabeth Ball, Teresita Beeston, Lee Middleton, Lee Priest, Julia Seeley, Anushka Tirlapur and Julie Dodds.

Funding

SAT is a clinical research fellow, funded by the NIHR Health Technology Assessment Programme (ref: 09/22/50).

Author details

[1]Women's Health Research Unit, Barts and the London School of Medicine, Queen Mary, University of London, 58 Turner Street, London E1 2AB, UK. [2]Birmingham Clinical Trials Unit, School of Cancer Sciences, Robert Aitken Institute, University of Birmingham, Birmingham B15 2TT, UK. [3]Centro Rosarino de Estudios Perinatales (CREP), Moreno 878, Rosario S2000DKR, Santa Fe, Argentina. [4]WE1 2AB and Barts Health NHS Trust, The Royal London Hospital, Whitechapel Road, London E1 1BB, UK.

Received: 25 October 2013 Accepted: 15 November 2013
Published: 4 December 2013

References

1. Butrick CW: Interstitial cystitis and chronic pelvic pain: new insights in neuropathology, diagnosis, and treatment. *Clin Obstet Gynecol* 2003, 46(4):811–823.
2. 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. *Eur Urol* 2008, 53(1):60–67.
3. Konkle KS, Berry SH, Elliott MN, Hilton L, Suttorp MJ, Clauw DJ, *et al*: Comparison of an interstitial cystitis/bladder pain syndrome clinical cohort with symptomatic community women from the RAND interstitial cystitis epidemiology study. *J Urol* 2012, 187(2):508–512.
4. Tirlapur SA, Kuhrt K, Chaliha C, Ball E, Meads C, Khan KS: The 'evil twin syndrome' in chronic pelvic pain: a systematic review of prevalence studies of bladder pain syndrome and endometriosis. *Int J Surg* 2013, 11(3):233–237.
5. Berry SH, Monica S, Stoto MA, Elliott M, Suttorp M, Bogart L, *et al*: Prevalence of interstitial cystitis/painful bladder syndrome in the United States. *Journal of Urology* 2009, 181(4):20–21.
6. Temml C, Wehrberger C, Riedl C, Ponholzer A, Marszalek M, Madersbacher S: Prevalence and correlates for interstitial cystitis symptoms in women participating in a health screening project. *Eur Urol* 2007, 51(3):803–808. discussion 9.
7. Quillin RB, Erickson DR: Practical Use of the New American urological association interstitial cystitis guidelines. *Curr Urol Rep* 2012, 13(5):394–401.
8. Cheng C, Rosamilia A, Healey M: Diagnosis of interstitial cystitis/bladder pain syndrome in women with chronic pelvic pain: a prospective observational study. *Int Urogynecol J* 2012, 23(10):1361–1366.
9. Humphrey L, Arbuckle R, Moldwin R, Nordling J, van de Merwe JP, Mourier J, *et al*: The bladder pain/interstitial cystitis symptom score: development, validation, and identification of a cut score. *Eur Urol* 2012, 61(2):271–279.
10. Parsons CL, Dell J, Stanford EJ, Bullon 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):573–578.
11. O'Leary MP, Sant GR, Fowler FJ, Whitmore KE, Spolarich-Kroll J: The interstitial cystitis symptom index and problem index. *Urology* 1997, 49(5A Suppl):58–63.
12. Brower ME, White WM, Klein FA, Klein LM, Waters WB: Validity of pelvic pain, urgency, and frequency questionnaire in patients with interstitial cystitis/painful bladder syndrome. *Urology* 2007, 70(4):646–649.
13. Reitsma JB, Rutjes AW, Khan KS, Coomarasamy A, Bossuyt PM: A review of solutions for diagnostic accuracy studies with an imperfect or missing reference standard. *J Clin Epidemiol* 2009, 62(8):797–806.
14. Bogart LM, Berry SH, Clemens JQ: Symptoms of interstitial cystitis, painful bladder syndrome and similar diseases in women: a systematic review. *J Urol* 2007, 177(2):450–456.
15. Warren JW, Diggs C, Horne L, Greenberg P: Interstitial cystitis/painful bladder syndrome: what do patients mean by "perceived" bladder pain? *Urology* 2011, 77(2):309–312.
16. Paulson JD, Paulson JN: Anterior vaginal wall tenderness (AVWT) as a physical symptom in chronic pelvic pain. *JSLS* 2011, 15(1):6–9.
17. Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, *et al*: SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013, 346:e7586.
18. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, *et al*: Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ* 2003, 326(7379):41–44.
19. Pepe MS, Janes H: Insights into latent class analysis of diagnostic test performance. *Biostatistics* 2007, 8(2):474–484.
20. Daniels J, Gray J, Pattison H, Roberts T, Edwards E, Milner P, *et al*: Rapid testing for group B streptococcus during labour: a test accuracy study with evaluation of acceptability and cost-effectiveness. *Health Technol Assess* 2009, 13(42):1–154. iii-iv.

21. Hanno PM, Burks DA, Clemens JQ, Dmochowski RR, Erickson D, Fitzgerald MP, et al: AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol 2011, 185(6):2162–2170.
22. Messing E, Pauk D, Schaeffer A, Nieweglowski M, Nyberg LM, Landis JR, et al: Associations among cystoscopic findings and symptoms and physical examination findings in women enrolled in the interstitial cystitis data base (ICDB) study. Urology 1997, 49(5A Suppl):81–85.
23. Denson MA, Gribbling TL, Cohen MB, Kreder KJ: Comparison of cystoscopic and histological findings in patients with suspected interstitial cystitis. J Urol 2000, 164(6):1908–1911.
24. Ottem DP, Teichman JM: What is the value of cystoscopy with hydrodistension for interstitial cystitis? Urology 2005, 66(3):494–499.

doi:10.1186/1742-4755-10-61
Cite this article as: Tirlapur et al.: Bladder pain syndrome: validation of simple tests for diagnosis in women with chronic pelvic pain: BRaVADO study protocol. Reproductive Health 2013, 10:61.

AOGS
ACTA Obstetricia et Gynecologica Scandinavica

AOGS REVIEW ARTICLE

Nerve stimulation for chronic pelvic pain and bladder pain syndrome: a systematic review

SEEMA A. TIRLAPUR[1,2], ANTONIS VLISMAS[2], ELIZABETH BALL[2] & KHALID S. KHAN[1,2]

[1]Women's Health Research Unit, Queen Mary, University of London, and [2]Barts Health NHS Trust, Royal London Hospital, London, UK

Key words
Chronic pelvic pain, bladder pain syndrome, posterior tibial nerve stimulation, sacral nerve stimulation

Correspondence
Seema A. Tirlapur, Women's Health Research Unit, Barts and the London School of Medicine, Queen Mary, University of London, 58 Turner Street, London E1 2AB, UK.
E-mail: s.a.tirlapur@qmul.ac.uk

Conflicts of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Please cite this article as: Tirlapur SA, Vlismas A, Ball E, Khan KS. Nerve stimulation for chronic pelvic pain and bladder pain syndrome: a systematic review. Acta Obstet Gynecol Scand 2013; 92:881–887.

Received: 30 November 2012
Accepted: 19 May 2013

DOI: 10.1111/aogs.12184

Abstract

Chronic pelvic pain (CPP) and bladder pain syndrome (BPS) can have a negative impact on quality of life. Neuromodulation has been suggested as a possible treatment for refractory pain. To assess the effectiveness of tibial and sacral nerve stimulation in the treatment of BPS and CPP. We searched until July 2012: the Cochrane Library, EMBASE (1980–2012), Medline (1950–2012), Web of knowledge (1900–2012), LILACS (1982–2012) and SIGLE (1990–2012) with no language restrictions. We manually searched through bibliographies and conference proceedings of the International Continence Society. Randomized and prospective quasi-randomized controlled studies vs. sham nerve stimulation treatment or usual care of patients with CPP and BPS who underwent sacral or tibial nerve stimulation were included. Any studies involving transcutaneous stimulation were excluded. The outcome was a cure or improvement in symptoms. Three studies with 169 patients treated with tibial nerve stimulation were included; two for CPP and one for BPS. There were improvements in pain, urinary and quality of life scores. There were no reported data for sacral nerve stimulation. There is scanty literature reporting variable success of posterior tibial nerve stimulation in improving pain, urinary symptoms and quality of life in CPP and BPS. In view of the dearth of quality literature, a large multi-centered clinical trial investigating the effectiveness of electrical nerve stimulation to treat BPS and CPP along with the cost-analysis of this treatment is recommended.

Abbreviations: BPS, bladder pain syndrome; CPP, chronic pelvic pain; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; NIH CPSI, chronic prostatitis symptom index; PTNS, posterior tibial nerve stimulation; SNS, sacral nerve stimulation.

Introduction

Bladder pain syndrome (BPS), formerly known as interstitial cystitis and painful bladder syndrome, is defined as chronic pelvic pain (CPP), bladder pressure or discomfort with at least one other urinary symptom in the absence of any identifiable pathology or infection (1,2). CPP is an intermittent or constant pain in the lower abdomen for at least 6 months, not associated with pregnancy and not occurring exclusively with menstruation or sexual intercourse (3). BPS and CPP can have a negative impact on quality of life and sexual function (4). The prevalence of BPS is between 5 and 16 per 100 000 of the population and that of CPP is 3800 per 100 000 (5–7).

Key Message

Neuromodulation is a treatment for patients with chronic pelvic pain and bladder pain syndrome. This systematic review assessing the effectiveness of posterior tibial nerve and sacral nerve stimulation showed variable success and the need for a large multi-centered clinical trial.

As both BPS and CPP have an unknown etiology, symptomatic management is the mainstay of treatment. Standard treatments frequently fail (8). Minimally invasive treatments for refractory BPS and CPP, such as nerve stimulation, or neuromodulation, of the tibial or sacral nerves have been described. Both methods have been shown to be effective in other lower urinary tract disorders (9–11). Posterior tibial nerve stimulation (PTNS) involves insertion of a fine needle 5 cm cephalad from the medial malleolus and posterior to the margin of the tibia at the site of the posterior tibial nerve. The treatment regimen is usually weekly for 10–12 weeks (12). Sacral nerve stimulation (SNS) involves an initial test phase with insertion of a test lead tunneled under the skin transmitted onto the nerve roots exiting the S3 foramen, so stimulating the pelvic and pudendal nerves, and connected to a stimulator which is exchanged for a permanent implant if successful (13,14). There are contradictory published data about the effectiveness of neuromodulation. The authors of this report aim to assess the effectiveness of PTNS and SNS to treat BPS and CPP by systematically reviewing the available literature.

Material and methods

Our systematic review was conducted prospectively deploying a protocol based on contemporary methods and reported in accordance with the PRISMA statement (15).

Data sources

A search through the following databases was performed until July 2012: The Cochrane Library, EMBASE (1980–2012), Medline (1950–2012), PSYCHINFO (1806–2012), Web of knowledge (1900–2012), and LILACS (1982–2012). Grey literature was searched through SIGLE (1990–2012). There were no language restrictions. We used MeSH headings and keywords for "chronic pelvic pain" or "pelvic pain" or "interstitial cystitis" or "painful bladder syndrome" or "bladder pain syndrome" combined using the Boolean operator "and" with the terms "tibial nerve" or "sacral nerve" or "nerve stimulation" or "neuromodulation." A hand search of bibliographies from relevant articles and conference proceedings of the International Continence Society was performed to identify articles not electronically cited.

Study selection

Randomized trials and prospective quasi-randomized controlled studies vs. sham nerve stimulation treatment or usual care of patients with CPP and BPS who underwent sacral or tibial nerve stimulation were included. Any studies involving transcutaneous stimulation were excluded as this was not direct nerve stimulation. Participants were men and women suffering from BPS and/or CPP, not being pregnant or suffering from cancer (2,3). The outcome was a cure or improvement in symptoms.

Data extraction and quality assessment

The data were independently extracted by two reviewers (SAT, AV) using a pre-designed data collection form capturing information on the study characteristics, participant, intervention, comparator and outcomes. Two published indexes were used for quality assessment of studies included (16,17). They assessed the reporting, external validity, internal validity (Jadad scale) and power of each study. A quality score was calculated and each study was rated as poor quality (score <14), fair quality (score 15–19) or good quality (score >20) for the Downs and Black quality index. Good quality was associated with a score of ≥3 using the Jadad scale (18). The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach was also used to assess the quality of evidence for each outcome (19,20).

Data synthesis

The results were tabulated. It was not possible to perform statistical analysis on the data because of the variation in outcome scoring systems used. PROSPERO registration number: CRD42012002465.

Results

Figure 1 summarizes the selection of articles. The included studies' characteristics are listed in Table 1. There were three studies in our review with 169 patients (21–23). Lee and Lee (24) describe a different method of SNS using electroacupuncture, which involved stimulating acupuncture points in the second and third posterior sacral foramen on the sacrum with a frequency of 4 Hz and an intensity of 5–10 mA with continuous stimulation by the pulse generator along with deeper stimulation to reach the myofascial trigger point of the piriformis muscle. This paper was not included in the review because it did not use the traditional method of SNS, previously described (24).

Figure 2 illustrates the quality assessment of the studies. Using the Downs and Black quality index, there were no studies of "good" quality. According to the Jadad criteria, one study was found to be "good quality" (21,24). The populations studied were not homogeneous. The duration of treatment and the number of neuromodulation sessions per week along with the electrical parameters used varied.

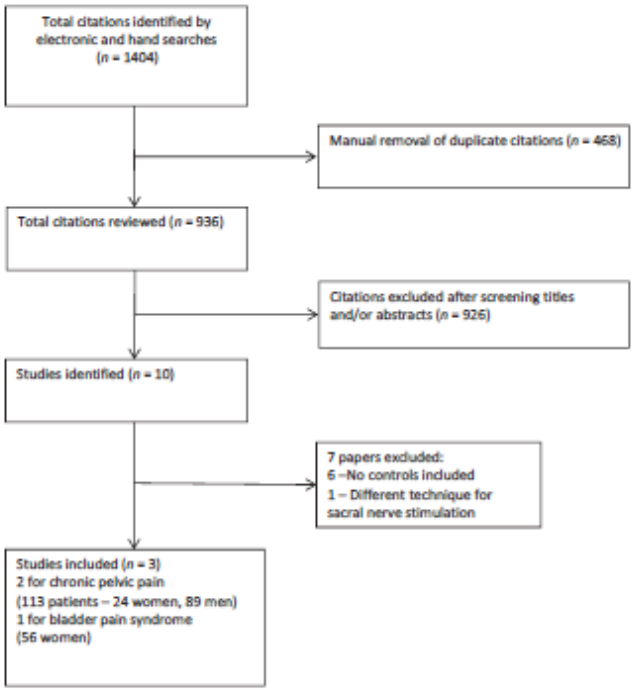


Figure 1. Study selection for a systematic review of the effectiveness of nerve stimulation in the treatment of chronic pelvic pain and bladder pain syndrome.

Two studies involved patients with CPP and one with BPS. Three studies used PTNS and there were no studies using SNS. Two of the studies had sham while one had usual care as a comparator. The symptom outcome measures used were pain, urinary symptoms and quality of life. The studies used different objective measurements of outcomes. Pain scores were measured using the McGill questionnaire (21), visual analog scale (21,23) and the National Institutes of Health chronic prostatitis symptom index (NIH CPSI) (23,24). Urinary symptoms were measured using the interstitial cystitis symptom index (22) and NIH CPSI (23,24). Quality of life outcomes were measured using the SF-36 questionnaire (22), female sexual function index (21) and NIH CPSI (23,24).

Table 2 represents the GRADE evaluation. There were limitations in the study design directness and precision, as different interventions and questionnaires were used in each study. The outcome measure of emotional quality of life performed best as the two papers that reported this used the same questionnaire. The evidence was found to be of "moderate" quality, indicating that further research is likely to have an important impact on the confidence of findings. One patient suffered from a hematoma at the needle site insertion but no other serious adverse effects were reported.

Discussion

There is scant literature, describing variable success of PTNS in improving pain, urinary symptoms and quality of life in patients with CPP and BPS. There were no studies assessing the effectiveness of SNS.

The main weakness of this review was the small number of studies that assessed the intervention with a comparator, which limits the inferences that can be drawn. A thorough literature search was performed with no language restrictions. At least 30 studies were found that did not have a comparator to allow meaningful assessment. The questionnaires used to measure outcomes varied between the included studies, making it difficult to directly compare scores for each symptom. There was a limited follow-up period of 12 weeks, so long-term

Table 1. Characteristics and summary of results for studies included in a systematic review of the effectiveness of neuromodulation for bladder pain syndrome and chronic pelvic pain.

Primary author, Publication date, Location	Participants	Methods and duration of follow-up	Treatment regimen	Outcome measures	Effectiveness	Complications
Gokyildiz 2012, Turkey	24 women with CPP randomized. No ages reported. Exclusion criteria: Pregnancy, heart disease, nerve damage, anticoagulant treatment, recurrent/active UTIs	PTNS vs. routine care, RCT. Ethics approval and informed consent. Follow up: end of treatment; randomization – envelopes; No blinding; ITT- 2 drop-outs	30 min × 12 weeks PTNS – 34 gauge needle 3–4 cm above inner malleolus to posterior tibial nerve. Needle connected to 9-V stimulator with adjustable current 0.5–10 mA.	Pain scores (VAS and McGill questionnaires), quality of life (SF-36), sexual function (FSFI)	Improvements in sensory and affective McGill scores, QoL factors and pain component of FSFI, no improvement in control group	1 hematoma, 2 patients suffered transient pain at the needle site
Kabay 2009, Turkey	89 men with CPP/chronic bacterial prostatis randomized. Mean age 37.9 PTNS and 38.5 years control. Exclusion criteria: Chronic prostatis, age <18 years, recurrent/active UTIs, malignancy, BPS, neurological, diabetes, heart disease	PTNS vs. sham treatment, RCT. Ethics approval and informed consent. Follow-up: end treatment; randomization method unknown; blinding of patients; ITT unknown	30 min × 12 weeks PTNS – 26-gauge needle 5 cm cephalad from medial malleolus and posterior to edge of tibia. Neutral electrode placed near arch foot. Electrode and needle connected to stimulator at pulse rate of 20 Hz. Sham device did not have electrical stimulation.	Pain scores (VAS), urinary and quality of life (NIH CPSI)	In PTNS group, objective response in 18/45 to pain and 30/45 to symptoms. Significant reduction in mean pain and urgency scores on – VAS and NIH CPSI. Scores were unchanged for sham treatment.	Not documented
O'Reilly 2004, Australia	56 women with IC randomized. No ages reported. Exclusion criteria: Age <18 years, malignancy, UTIs, neuropathy, detrusor overactivity	Transdermal posterior tibial nerve laser vs. sham RCT. Ethics approval and informed consent. Follow-up: end of treatment; randomization unknown method; double blind; ITT- unknown	30 s daily × 12 weeks TPTNL – 5 cm cephalad from medial malleolus, depth of penetration 2–3.5 cm. Inactivated sham device used in the same way.	Pain and urinary symptoms (ICPVSI) and quality of life (SF-36)	In the treatment group, significant decrease between baseline and 12 weeks follow-up in symptom severity, and quality of life scales.	Not documented

CPP, chronic pelvic pain; UTI, urinary tract infection; PTNS, posterior tibial nerve stimulation; VAS, visual analogue scale; ITT, intention to treat; QoL, quality of life; RCT, randomized controlled trial; FSFI, female sexual function index; NIH CPSI, chronic prostatitis symptom index; BPS, bladder pain syndrome; IC, interstitial cystitis; ICPVSI, interstitial cystitis problem index/symptom index.

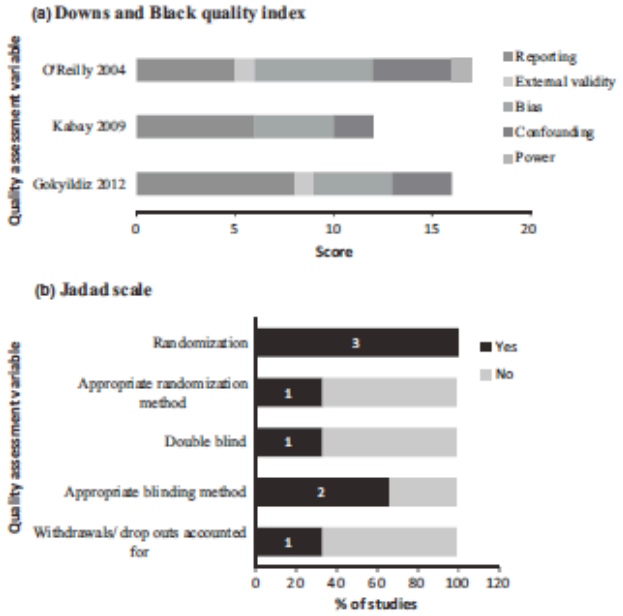


Figure 2. Quality assessment of included studies in a systematic review of the effectiveness of neuromodulation for bladder pain syndrome and chronic pelvic pain. (a) Downs and Black quality index; (b) Jadad scale.

Table 2. GRADE assessment of the evidence presented by outcomes in the studies included in a systematic review of the effectiveness of neuromodulation for bladder pain syndrome and chronic pelvic pain (38,39).

Quality assessment							No of patients		
Outcome (No. of studies)	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neuromodulation	Sham or no treatment	Importance
Pain (3)	Randomized trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	86	83	⊕OOO VERY LOW
Urinary symptoms (2)	Randomized trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	74	71	⊕OOO VERY LOW
Quality of Life (general) (3)	Randomized trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	86	83	⊕OOO VERY LOW
Quality of Life (emotional) (2)	Randomized trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[2]	None	41	39	⊕OOO VERY LOW

GRADE, Grading of Recommendations, Assessment, Development and Evaluations.
[1]Study design limitations – lack of blinding, no description of randomization, failure to document intention-to-treat analysis.
[2]Indirectness – indirect comparisons between interventions, comparators, outcome measurement tools.
[3]Imprecision – wide confidence intervals, few patients in studies.

effectiveness of nerve stimulation for CPP and BPS cannot be assessed.

Chronic pelvic pain and BPS affect large numbers of people across the world, often with unknown etiology and co-existing disease pathology, which makes the management of such patients difficult (25). Apart from the prevalence of BPS, there are uncertainties in the diagnosis and management of the condition. There is variation in the method of diagnosing BPS because patients may present with a wide spectrum of pain and urinary symptoms. Cystoscopy and bladder biopsies have traditionally been used as the "gold standard" to diagnose BPS.

Posterior tibial nerve stimulation can be performed in an outpatient setting (26). There is uncertainty about how often treatments need to be repeated and the frequency necessary to maintain good symptom control. In SNS there have been cases of sudden loss of function of the neuromodulator after trauma, due to lead avulsion (27). Both forms of nerve stimulation are generally well tolerated, although they may cause transient needle site pain, tingling in the legs and local infection. All complications were transient or resolved with removal of the neuromodulator (28).

After lifestyle, oral and intravesical treatments and cystoscopy with hydrodistension, nerve stimulation is recommended as a fourth-line treatment for BPS. According to the American and Japanese guidelines for the management of BPS, evidence for the treatment efficacy of nerve stimulation is level 2, indicating that data were drawn from well-designed nonrandomized or quasi-experimental studies. The grade of recommendation is C, where no clear recommendation for treatment is possible (29,30). However, studies show poor correlation between cystoscopy findings and diagnosis as glomerulations may be seen in asymptomatic patients, which has led to guidelines recommending treatment initiation after careful clinical history and physical assessment, to avoid delays in management (30). There are limited data about the natural course of BPS, which is needed to evaluate the effectiveness of therapies (31). The American Urological Association and the International Consultation on Incontinence have recommended further research into the prevalence of BPS and treatments to minimize patient symptoms and maximize quality of life (30,32).

In the USA, the Food and Drug Administration has not approved the use of nerve stimulation for the treatment of BPS. Current guidelines on diagnosis and management of BPS by the American Urological Association recommend a trial of nerve stimulation as a fourth-line treatment if conservative measures have failed (30,33). Even though the precise mode of action of nerve stimulation is unknown, it is minimally invasive and has the possibility to greatly improve the quality of life of patients with refractory pelvic pain (12,34). In view of the dearth of good quality literature shown in the current review, a thorough investigation of the therapeutic and cost effectiveness of nerve stimulation needs to be undertaken. Several papers have suggested the importance of a prospective, large multi-centered clinical trial investigating the effectiveness of electrical nerve stimulation to treat BPS and CPP to adequately assess this treatment, the long-term effects and produce reliable high-quality evidence (11,35–37).

References

1. Butrick CW. Interstitial cystitis and chronic pelvic pain: new insights in neuropathology, diagnosis, and treatment. Clin Obstet Gynecol. 2003;46(4):811–23.
2. 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. Eur Urol. 2008;53(1):60–7.
3. Royal College of Obstetricians and Gynaecologists. Initial management of chronic pelvic pain. London: RCOG, 2012.
4. Temml C, Wehrberger C, Riedl C, Ponholzer A, Marszalek M, Madersbacher S. Prevalence and correlates for interstitial cystitis symptoms in women participating in a health screening project. Eur Urol. 2007;51(3):803–8; discussion 9.
5. Latthe P, Latthe M, Say L, Gülmezoglu M, Khan KS. WHO systematic review of prevalence of chronic pelvic pain: a neglected reproductive health morbidity. BMC Public Health. 2006;6:177.
6. Fall M, Baranowski AP, Fowler CJ, Lepinard V, Malone-Lee JG, Messelink EJ, et al. EAU guidelines on chronic pelvic pain. Eur Urol. 2004;46(6):681–9.
7. Konkle KS, Berry SH, Elliott MN, Hilton L, Suttorp MJ, Clauw DJ, et al. Comparison of an interstitial cystitis/bladder pain syndrome clinical cohort with symptomatic community women from the RAND interstitial cystitis epidemiology study. J Urol. 2012;187(2):508–12.
8. Daniels JP, Khan KS. Chronic pelvic pain in women. BMJ. 2010;341:c4834.
9. Burton C, Sajja A, Latthe PM. Effectiveness of percutaneous posterior tibial nerve stimulation for overactive bladder: a systematic review and meta-analysis. Neurourol Urodyn. 2012;31(8):1206–16.
10. Giannantoni A, Bini V, Dmochowski R, Hanno P, Nickel JC, Proietti S, et al. Contemporary management of the painful bladder: a systematic review. Eur Urol. 2012;61(1):29–53.
11. Marcelissen T, Jacobs R, van Kerrebroeck P, de Wachter S. Sacral neuromodulation as a treatment for chronic pelvic pain. J Urol. 2011;186(2):387–93.
12. Bosch JL. Electrical neuromodulatory therapy in female voiding dysfunction. BJU Int. 2006;98(Suppl 1):43–8; discussion 49.

13. Hassouna MM, Siegel SW, Nyeholt A, Elhilali MM, van Kerrebroeck PEV, Das AK, et al. Sacral neuromodulation in the treatment of urgency–frequency symptoms: a multicenter study on efficacy and safety. J Urol. 2000; 163(6):1849–54.
14. Fariello JY, Whitmore K. Sacral neuromodulation stimulation for IC/PBS, chronic pelvic pain, and sexual dysfunction. Int Urogynecol J. 2010;21(12):1553–8.
15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100.
16. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52 (6):377–84.
17. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1–12.
18. Kennelley J. Methodological approach to assessing the evidence. Reducing racial and ethnic disparities in reproductive and perinatal outcomes: the evidence from population-based interventions. New York: Springer, 2011. pp. 7–20.
19. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–6.
20. Sharma M, Ansari MT, Abou-Setta AM, Soares-Weiser K, Ooi TC, Sears M, et al. Systematic review: comparative effectiveness and harms of combination therapy and monotherapy for dyslipidemia. Ann Intern Med. 2009;151 (9):622–30.
21. Gokyildiz S, Kizilkaya Beji N, Yalcin O, Istek A. Effects of percutaneous tibial nerve stimulation therapy on chronic pelvic pain. Gynecol Obstet Invest. 2012;73(2):99–105.
22. O'Reilly BA, Dwyer PL, Hawthorne G, Cleaver S, Thomas E, Rosamilia A, et al. Transdermal posterior tibial nerve laser therapy is not effective in women with interstitial cystitis. J Urol. 2004;172(5 Pt 1):1880–3.
23. Kabay S, Kabay SC, Yucel M, Ozden H. Efficiency of posterior tibial nerve stimulation in category IIIB chronic prostatitis/chronic pelvic pain: a Sham-Controlled Comparative Study. Urol Int. 2009;83(1):33–8.
24. Lee SH, Lee BC. Electroacupuncture relieves pain in men with chronic prostatitis/chronic pelvic pain syndrome: three-arm randomized trial. Urology. 2009;73 (5):1036–41.
25. Tirlapur SA, Kuhrt K, Chaliha C, Ball E, Meads C, Khan KS. The 'evil twin syndrome' in chronic pelvic pain: a systematic review of prevalence studies of bladder pain syndrome and endometriosis. Int J Surg. 2013;11(3):233–7.
26. Baxter C, Kim JH. Contrasting the percutaneous nerve evaluation versus staged implantation in sacral neuromodulation. Curr Urol Rep. 2010;11(5):310–4.
27. Diokno AC, Burgess S, Mulholland T. Complication of the sacral neuromodulator: lead avulsion and wire disruption. J Urol. 2003;169(1):283–4.
28. Mowatt G, Glazener C, Jarrett M. Sacral nerve stimulation for faecal incontinence and constipation in adults. Cochrane Database Syst Rev. 2007;CD004464.
29. Homma Y, Ueda T, Ito T, Takei M, Tomoe H. Japanese guideline for diagnosis and treatment of interstitial cystitis. Int J Urol. 2009;16(1):4–16.
30. Hanno PM, Burks DA, Clemens JQ, Dmochowski RR, Erickson D, Fitzgerald MP, et al. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol. 2011;185(6):2162–70.
31. van de Merwe JP. Interstitial cystitis and systemic autoimmune diseases. Nat Clin Pract Urol. 2007;4(9):484–91.
32. 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. Neurourol Urodyn. 2010;29(1):191–8.
33. Quillin RB, Erickson DR. Practical use of the new American Urological Association interstitial cystitis guidelines. Curr Urol Rep. 2012;13(5):394–401.
34. Bernstein AJ, Peters KM. Expanding indications for neuromodulation. Urol Clin North Am. 2005;32(1):59–63.
35. Butrick CW, Howard FM, Sand PK. Diagnosis and treatment of interstitial cystitis/painful bladder syndrome: a review. J Womens Health (Larchmt). 2010;19(6):1185–93.
36. Dudding TC. Future indications for sacral nerve stimulation. Colorectal Dis. 2011;13(Suppl 2):23–8.
37. van Balken MR, Vandoninck V, Messelink BJ, Vergunst H, Heesakkers J, Debruyne FMJ, et al. Percutaneous tibial nerve stimulation as neuromodulative treatment of chronic pelvic pain. Eur Urol. 2003;43(2):158–63; discussion 163.
38. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ, et al. What is "quality of evidence" and why is it important to clinicians? BMJ. 2008;336 (7651):995–8.
39. Brozek JL, Akl EA, Alonso-Coello P, Lang D, Jaeschke R, Williams JW, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy. 2009;64(5):669–77.

Int Urogynecol J
DOI 10.1007/s00192-013-2266-9

REVIEW ARTICLE

Grading of evidence for bladder pain syndrome: a comparative review of study quality assessment methods

S. A. Tirlapur · K. S. Khan

Received: 30 July 2013 / Accepted: 26 October 2013

Abstract
Introduction and hypothesis Clinical guidelines on bladder pain syndrome (BPS) report quality ratings for evidence based on study design. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system takes into account several domains in addition to limitations of study design for assigning quality ratings. We compared the quality of evidence described in current BPS literature.
Methods All existing systematic reviews and guidelines on BPS management were reviewed, and included evidence was rated according to GRADE on a four-point scale (1–4, from very low to high). These ratings were compared to the two reported quality assessments that assigned levels or strengths to evidence; both had a four-point scale: level of evidence 1–4 from meta-analysis of randomised studies to expert opinion; and strength of evidence 1–4 from very low to high.
Results Of the 19 treatments for BPS with GRADE ratings, comparison with level of evidence ratings showed that, on average, the latter overestimated quality by 1.8 points [1.1 v 2.9; 95 % confidence interval (CI) 1.2–2.3; p =<0.0001). Comparison of GRADE ratings with strength of evidence ratings showed that, on average, the latter overestimated quality by 1.7 points (1.1 v 2.8; 95 % CI 1.3–2.1; p =<0.0001).
Conclusion GRADE, a refined method of assigning quality to evidence, provided a more conservative gauge, giving a realistic assessment of the value of recommendations for consideration in practice.

S. A. Tirlapur (✉) · K. S. Khan
Women's Health Research Unit, Barts and the London School of Medicine, Queen Mary University of London, 58 Turner Street, London E1 2AB, UK
e-mail: s.a.tirlapur@qmul.ac.uk

K. S. Khan
Barts Health NHS Trust, The Royal London Hospital, Whitechapel Road, London E1 1BB, UK

Published online: 23 November 2013

Keywords Bladder pain syndrome · GRADE · Guidelines · Evidence · Quality

Abbreviations

AUA	American Urological Association
BCG	Bacillus Calmette-Guerin
BPS	Bladder pain syndrome
CPP	Chronic pelvic pain
CI	Confidence interval
DMSO	Dimethyl sulfoxide
EAU	European Association of Urology
EGF	Epidermal growth factor
GRADE	Grading, Recommendations, Assessment, Development and Evaluation
IC	Interstitial cystitis
PPS	Pentosan polysulfate sodium
RCT	Randomised controlled trials

Introduction

Bladder pain syndrome (BPS), formerly known as interstitial cystitis (IC), is a chronic condition defined as chronic pelvic pain (CPP), pressure or discomfort related to the bladder, along with at least one other urinary symptom, such as urgency or frequency, in the absence of any other pathology [1]. It is associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with lower urinary tract and sexual dysfunction [2]. There is often difficulty in assessing the value of treatments proposed for BPS. Different organisations use different scoring systems to rate quality of evidence, which can be confusing. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was developed in 2000 by the GRADE working group to establish transparency over the reporting

of evidence and strength of recommendations in systematic reviews and guidelines. The quality of evidence is assessed using several domains, including study design, indirectness, imprecision, inconsistency and risk of bias [3, 4]. Existing guidelines focus only on study design for summarising evidence quality [5, 6]: randomised controlled trials (RCTs) allocated a summary value with no distinction made between high- and low-quality RCTs. This is where the GRADE approach can be of greater use because it encompasses five different study domains to give a more robust quality of evidence rating [7, 8]. We assessed discrepancies between the different systems used to evaluate evidence and recommendations in relation to BPS and explored how guidelines may be affected if GRADE were to be used.

Methodology

Identifying evidence

Data sources

A search of MEDLINE and Embase databases was performed from inception to May 2013 using search terms and word variants for the concept "chronic pelvic pain" OR "interstitial cystitis" OR "painful bladder syndrome" OR "bladder pain syndrome" combined using the Boolean operator AND with "guideline" OR "systematic review". A manual search of bibliographies from relevant articles and conference proceedings of the International Continence Society (ICS) was performed to identify articles not electronically cited.

Study selection

Clinical guidelines and systematic reviews assessing the effectiveness of treatments for BPS were included. Individual effectiveness studies were excluded, as the aim of this article was to assess quality measures in existing guidelines in comparison with GRADE guidelines. Titles and abstracts captured in searches were reviewed, along with the full article where applicable. There were no language barriers.

Data extraction and synthesis

We compared quality of evidence using GRADE versus quality measures reported in recent guidelines. In 2009, the Japanese Guidelines for IC were produced that use level of evidence scores 1–4 [1 for an RCT; 4 for expert opinion] and strength of evidence scores A, B, C or D (from A for highly recommended treatment with evidence from good-quality studies, to D for not recommended treatments) [5]. The 2011 American Urological Association (AUA) produced their guidelines using strength of evidence scores [6]. Additional information was obtained from 2012 European Association of Urology (EAU) guidelines on CPP, which used both level and strength of evidence scores, a 2008 review and 2012 systematic review on managing PBS [9, 10, 11].

GRADE methodology

For each treatment option, evidence was assessed according to GRADE and incorporates the five domains of: study design, inconsistency, indirectness, imprecision and risk of bias. Randomised trials are usually considered high-quality studies and observational studies as low quality; hence, downgrading occurs when assigning a score for study design [4]. The domain of inconsistency is related to relative treatment effects. Scores for inconsistency may be downgraded if there are different point estimates, overlapping confidence intervals (CIs) and lack of heterogeneity [12]. Direct evidence compares important interventions in applicable populations, with important patient-related primary outcomes. Indirectness occurs when these factors are not correctly addressed in a study [13]. Imprecision may occur when there are large CIs or small sample sizes or numbers of events [14]. Study design limitations, leading to a high risk of bias, include failure to adequately conceal, blind, adhere to intention to treat analysis and account for losses to follow-up in RCTs; and selective reporting and inappropriate use of controls in observational studies [15]. Every time a deficiency occurred, the evidence was downgraded by one level, ranging from no deficiency to serious to very serious deficiencies. These assessments are subjective depending on the reviewer. Quality of evidence may also be graded from high (further research is unlikely to change our confidence in the effect), moderate, low and very low (any estimate of effect is very uncertain) (Table 1) [7].

Comparing GRADE with level of evidence in guidelines

Guidelines on diagnosis and management of BPS/IC from the USA [6], Japan [5], Europe [10] and a recent systematic review [9] were used to compare GRADE assessment with recommendations and levels of evidence in the guidelines. The guidelines assigned quality ratings using level of evidence with a four-point ordinal scale, where level 1a was a meta-analysis of a RCT and level 4 was expert opinion and for strength of evidence. A represented a highly recommended treatment; D indicated that treatment that was not recommended. Table 1 defines level of evidence scores used in the guidelines. Where discrepancy arose with rating scores between guidelines, evidence was reviewed and the most accurate score awarded. Statistical analysis was performed using the StatsDirect software programme to calculate mean and median differences with a 95% CI and probability for strength of evidence versus GRADE, and level of evidence versus

Table 1 Quality assessment methods used in different guidelines for bladder pain syndrom (BPS) management[6, 11]

Quality assessment method		
Level of evidence[a]		Numerical scale assigned for analysis
1a	Meta-analysis of randomised control trials (RCT)	4
1b	Evidence obtained from a single RCT	4
2a	Evidence obtained from one well-designed, controlled study without randomisation	3
2b	Evidence obtained from one other type of well-designed quasi-experimental study	3
3	Evidence obtained from nonexperimental studies (comparative, correlation or case reports)	2
4	Evidence obtained from expert committees, expert opinions or clinical practice	1
Strength of evidence[b]		
A	Highly recommended: clinical studies of good quality and consistency, including at least one RCT	4
B	Recommended: well-conducted clinical studies without randomised trials	3
C	No clear recommendation possible: absence of directly applicable clinical studies of good quality	2
D	Not recommended	1
Grading, Recommendations, Assessment, Development and Evaluation (GRADE)[c]		
4	High	4
3	Moderate	3
2	Low	2
1	Very low	1

[a] For example, Japanese Guidelines for Interstitial Cystitis, European Urology Association Guidelines for Chronic Pelvic Pain

[b] For example, American Urology Association Guidelines for Bladder Pain Syndrome

[c] See "Methodology" for details and Table 2 for a worked example of a GRADE table

GRADE. The mean difference was calculated using the unpaired *t* test and median difference using Wilcoxon's signed-rank test.

Results

From 88 citations, three suitable guidelines were identified: 2009 Japanese Urology Association Clinical Guidelines for Interstitial Cystitis, the 2011 AUA Guidelines for the Diagnosis and Management of IC/BPS and the 2012 EAU guidelines on CPP [5, 6, 11]. Seventy citations did not meet eligibility criteria, often because they discussed individual studies (Fig. 1).

Information from existing guidelines and systematic reviews was used to assess treatment options, along with their relative effectiveness, in order to assess quality of evidence. These have been categorised first- to sixth-line treatments according to the AUA classification, along with treatments that are not recommended.

First-line treatments

Self-care and behavioural modifications

A survey of 1,982 participants revealed 87.6 % patients had symptomatic improvement with an elimination diet and 86.1 % by completely avoiding these items, although treatment duration was not indicated; 65.2 % of patients gained symptomatic improvement with regular exercise [16].

Stress management

Patient survey showed symptomatic improvement in 76.4 % of patients using relaxation techniques, 66.8 % using meditation, 64.5 % listening to music and 80.5 % following stress reduction [16].

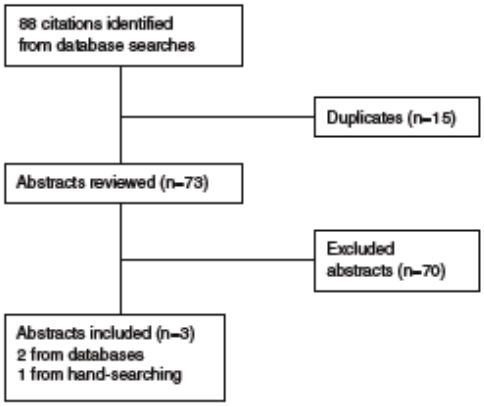


Fig. 1 Selected guidelines for managing bladder pain syndrome (BPS)

Second-line treatments

Manual physical therapy

An electronic questionnaire revealed that 74.2 % of patients experienced symptomatic improvement with massage therapy, 61.5 % with physical therapy and 66.1 % through physical therapy with internal treatment [16].

Analgesia

No data was available about the efficiency of different forms of analgesia.

Orally administered amitriptyline

We asked the question: Can an H1 receptor antagonist modify pain transmission in the central nervous system? One prospective randomised controlled double-blind study was undertaken on 50 patients treated with a self-titrating dose of amitriptyline over 4 months to a maximum of 100 mg. There was a decrease in mean O'Leary-Sant symptom score of 8.5 points in the treatment group and 3.5 in the control group. There were statistically significant improvements in pain and urgency symptoms [17]. A mean long-term follow-up of 19 months resulted in a 46 % patient satisfaction with treatment, with commonly noted side effects of dry mouth and weight gain [18].

Orally administered cimetidine

One randomised placebo-controlled double-blind study compared 36 patients treated with a 3-month course of 400 mg cimetidine orally versus placebo twice daily. The treatment group had marked improvement in symptoms, pain and nocturia; however, posttreatment cystoscopy and bladder biopsies showed no histological changes [19].

Orally administered hydroxyzine

One randomised study compared a treatment group of 31 patients taking 10–50 mg daily hydroxyzine titrated for 3 weeks then the highest dose for 21 weeks compared with the placebo group. The authors found a response rate in 31 % of treated patients compared with 20 % of the control group [20].

Orally administered pentosan polysulfate sodium (PPS)

Pentosan polysulfate sodium (PPS) is thought to repair the damaged glycosaminoglycan layer, which acts as a protective mechanism for the bladder mucosa [5]. Two prospective double-blind studies exist: one with 115 patients treated with 200 mg PPS twice daily for 4 months showed no difference in symptom or pain scores between treatment and placebo groups; another, with 148 patients treated with 100 mg PPS three times daily, showed a 32 % symptom improvement in the treatment group compared with 16 % in the placebo group [21, 22].

Intravesically administered dimethyl sulfoxide (DMSO)

Dimethyl sulfoxide (DMSO) has an analgesic, anti-inflammatory and muscle relaxant effect [5]. One prospective controlled crossover study reported on 33 patients who were randomised into treatment with 50 % DMSO or placebo (normal saline) for 2 weeks with two sessions each week; 93 % of the treatment group and 35 % of the placebo group had an objective improvement [23]. Reported side effects included a garlic-like odour and bladder spasm.

Intravesically administered heparin

One observational study evaluated 48 patients treated with 10,000 U heparin in 10 ml sterile water instilled three times a week for 3 months and reported that 56 % of patients achieved clinical remission over 3 months and 50 % of patients had symptomatic control after 1 year [24].

Intravesically administered lidocaine

This local anaesthetic blocks sensory nerve fibres in the bladder. One randomised double-blind study reported on 102 patients treated with a 5-day course of 200 mg intravesically administered lidocaine with alkalinised instillation of 8.4 % sodium bicarbonate to a final volume of 10 ml versus placebo; 30 % of the treatment group reported a moderate or marked symptom improvement compared with 9.6 % of the placebo group over a 29-day follow-up period [25].

Third-line treatments

Cystoscopy with short-duration, low-pressure hydrodistension

This method is now used as a treatment rather than solely as a diagnostic tool and can be used if conservative treatment measures fail. Three observational studies of 265 patients in total describe variable symptom improvement; however, within 6 months, symptoms had recurred in the majority of patients [26–28]. Rupture is a possible complication of prolonged distension of a diseased bladder; hence, low-pressure distension is advised [29].

Fulguration with or without triamcinolone for Hunner's lesions

Two observational studies reported success when using Nd:YAG laser under cystoscopic control in patients with BPS with Hunner's ulcers. Fifty-one patients were treated, resulting in 88 % symptomatic relief within 2–3 days of treatment; however, 45 % needed additional treatment within 23 months [30, 31].

Fourth-line treatment

Neurostimulation

There is limited data on the effectiveness of sacral and posterior tibial nerve stimulation for treating BPS, with no randomised trials comparing these treatments with a placebo. One study reported efficacy of posterior tibial nerve stimulation in 18 patients, and six studies reported on sacral nerve stimulation in 150 patients, both studies showing improvements in symptoms and quality of life [32–37]. Whereas both forms of neuromodulation are effective, they are invasive procedures, which may deter patients.

Fifth-line treatments

Cyclosporin A

Two RCTs compared a 6-month course of orally administered cyclosporin A (CSA) versus pentosan polysulfate sodium (PPS) [38–40]; 75 % of the treatment group and 19 % of the PPS group had symptomatic improvement, but as the intervention was not compared with a placebo, it was difficult to directly compare results. Comparing levels of urinary epidermal growth factor (EGF), a urinary marker shown to be higher in BPS patients, there was a significantly decreased level posttreatment in the CSA compared with the PPS group.

Botulinum toxin A

Botulinum toxin A is administered when other treatments fail control symptoms. A systematic review evaluating botulinum toxin A in BPS patients found three RCTs and seven prospective cohort studies with a total of 260 patients. Eight studies reported symptomatic improvement, although 7 % of patients needed posttreatment self-catheterisation [41].

Sixth-line treatment

Major surgery

Surgical management is often the last resort for refractory BPS. Total cystectomy and urinary diversion will lead to the need for self-catheterisation, and patients must be aware of persistent pelvic and pouch pain postsurgery [5]. A retrospective observational study of 47 patients who had reconstructive surgery for BPS found that 82 % of patients with Hunner's ulcerations had symptomatic relief after surgery compared with 23 % with nonulcer disease after an average 89-month follow-up period [42].

Treatments that should not be offered

Long-term orally administered antibiotics

Use of long-term rotating antibiotics is not recommended, as an RCT showed no significant benefit and a high proportion of adverse effects. One RCT compared sequential antibiotics versus placebo [43]: 50 patients were randomised to receive an 18-week course of antibiotics (rifampicin plus a sequence of doxycycline, erythromycin, metronidazole, clindamycin, amoxicillin and ciprofloxacin for 3 weeks each) or placebo; 48 % in the antibiotic and 24 % in the placebo group reported overall improvement ($p=0.14$), whereas ten and five patients, respectively, noticed improvement in pain and urgency ($p=0.22$). In the antibiotic group, 80 % had adverse effects compared with 40 % in the placebo group ($p=0.009$).

Intravesical instillation of Bacillus Calmette-Guerin (BCG)

This treatment is not recommended, as no clinical benefit was reported in an RCT, and serious adverse effects may occur. Two RCTs compared intravesical BCG with placebo over a 6-week course of treatment in a total of 282 patients [44, 45]. Mayer et al. found no statistically significant difference for symptomatic outcomes in the treatment arm and a large number of adverse outcomes, including arthralgia, headaches and infection. During an extended follow-up period of 68 weeks, 86 % of the treatment group and 75 % of the placebo group felt there was a marked or moderate symptomatic improvement [46]. The smaller RCT with 30 patients noted a 60 % symptomatic improvement in the treatment group compared with 27 % in the placebo group ($P=0.065$).

High-pressure, long-duration hydrodistension

A pressure >80–100 cm of water and prolonged duration >10 min may cause adverse effects, such as, bladder rupture or sepsis. Three observational studies showed a wide range of efficacy rates between 22–67 % with at least one case of bladder rupture in each study [6, 47, 48]. The risks of this treatment far outweigh the benefits, leading to guidelines recommending its avoidance.

Long-term, orally administered glucocorticoid

Administration of steroids, such as prednisolone, is not recommended due to the adverse effects of long-term use. There is limited data on the effectiveness of this treatment, as one study treated patients with prednisolone and hydrodistension simultaneously, and meaningful efficacy therefore could not be evaluated [49].

Rating of evidence with GRADE versus strength of evidence in guidelines

Table 2 shows an example of a GRADE table for second-line treatment of BPS created using GRADE computer software with a summary of findings and quality rating.

The level of evidence score is compared with GRADE in Fig. 2 and shows the overestimation in scores. Of the 19 comparable treatment options, all were downgraded, with six being downgraded by three points from "high" to "very low", four by two points and nine by one point. Mean overestimation score was 1.8 (1.1 v 2.9). The 95 % CI of mean difference was 2.3–1.2 (p =<0.0001) using unpaired t test, and median difference was 2 (95 % CI 2.0–1.0) using Wilcoxon's signed-rank test.

Figure 3 shows the overestimation in GRADE versus strength of evidence. Of the 21 treatment options, 19 were assigned GRADE scores. Of those 19, GRADE and strength of evidence scores could be compared. Eighteen treatment options were downgraded using GRADE, with a mean overestimation score of 1.7 (1.1 v 2.8), with a 95 % CI 2.2–1.3; p =<0.0001 and median difference of 1.5 (95 % CI 2.0–1.0). Nine were downgraded by one mark—for example, from low to very low quality—seven by two marks and two by three marks. Only one treatment option, intravesically administered lidocaine, had the same strength and GRADE scores.

Discussion

Main findings

Assessing the quality of information about treatment effectiveness for BPS varies depending on which guidelines are consulted. This can be confusing for clinicians who may not know the difference between such rating scales or how they were derived. Our review of the evidence for treatment options for BPS showed discrepancies between strength and level of evidence and GRADE ratings, with lower GRADE

Table 2 Sample Grading of Recommendations Assessment, Development and Evaluation (GRADE) table: second-line treatment for bladder pain syndrome (BPS)

Quality assessment								Quality
Treatment	No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	
Oral analgesia	0	NA	NA	NA	NA	NA	NA	NA
Oral hydroxyzine	1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias	⊕OOO Very low
Manual physical therapy	1	Observational studies	Very serious[a]	Very serious	No serious indirectness	No serious imprecision	Reporting bias[b]	⊕OOO Very low
Oral amitriptyline	1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[b]	⊕⊕OO Low
Oral cimetidine	1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[b]	⊕⊕OO Low
Oral pentosan polysulfate sodium (PPS)	2	Randomised trials	Serious[a]	No serious inconsistency	Serious[c]	No serious imprecision	Reporting bias[b]	⊕OOO Very low
Intravesical dimethyl sulfoxide (DMSO)	1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[b]	⊕OOO Very low
Intravesical heparin	1	Observational studies	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[b]	⊕OOO Very low
Intravesical lidocaine	1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[b]	⊕⊕OO Low

[a] Lack of blinding, failure to report intention to treat, method of randomisation, lack of allocation or concealment

[b] Evidence based on fewer than 10 trials

[c] Variations in outcome assessment tools, populations compared

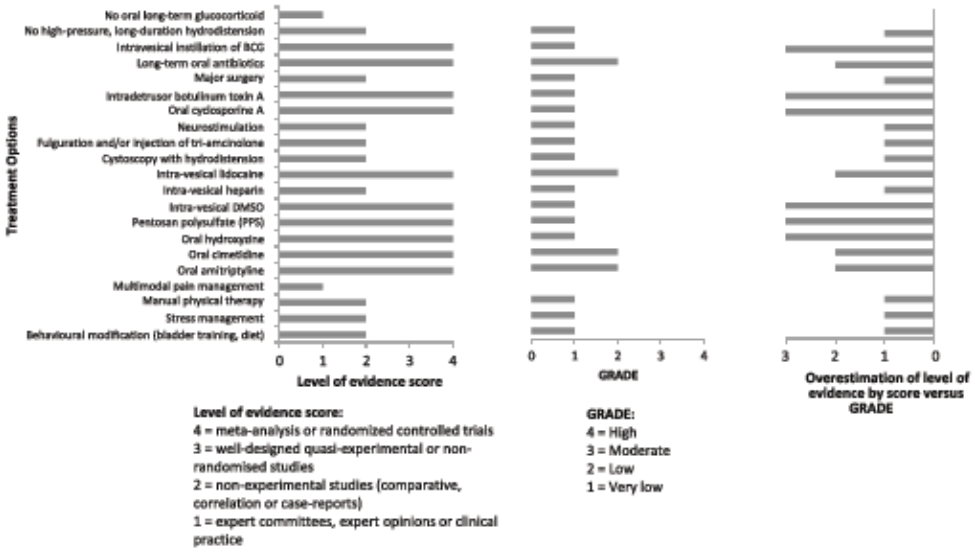


Fig. 2 Level of evidence score versus Grading of Recommendations Assessment, Development and Evaluation (GRADE) for managing bladder pain syndrome (BPS)

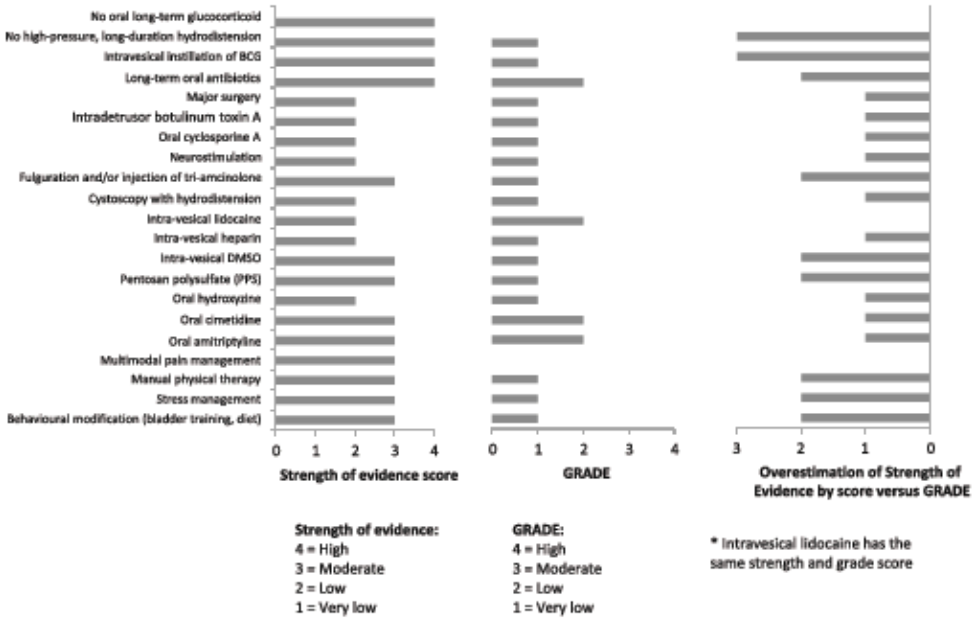


Fig. 3 Strength of evidence score versus Grading of Recommendations Assessment, Development and Evaluation (GRADE) for managing bladder pain syndrome (BPS)

scores overall. We downgraded most treatment options when we compared the with GRADE.

Study strengths and weaknesses

This review of the literature was thorough, incorporating several international guidelines and reviews. We believe GRADE provides the most comprehensive scoring system for quality as it combines information across five domains. One limitations of GRADE, however, is that the computer software programme automatically assigns only a a GRADE quality of evidence rating to randomised studies. The formation of GRADE tables and assignment of bias for study design, inconsistency, indirectness, imprecision and publication bias is subjective and assessor dependent [50]. GRADE tables assess several randomised studies across all domains. The overall quality of the information is dependent on combined data from all studies, so a very good-quality study may be downgraded by combining its data with a poor-quality study.

How do the findings affect clinical practice?

At present, there are several international guidelines on managing BPS that use a combination of level and strength of evidence to assess effectiveness. Our paper found an overestimation in the effectiveness of treatments compared with the GRADE approach for all but one treatment—strength of evidence versus GRADE for intravesically administered lidocaine—suggesting that clinicians should use caution when interpreting the effectiveness of treatment modalities that may not be as promising as suggested in current guidelines.

Conclusion

The GRADE system is an ideal quality assessment tool, as it provides an accurate appraisal of quality that is not limited solely by study design. It provides a summary of findings tables based on individual domains so the reader can identify specific areas of weakness in studies while also providing an overall quality of recommendation. A single, standardised reporting method would greatly help clinicians understand guidelines and communicate best treatment options to their patients with BPS.

Acknowledgments

Conflicts of interest None

References

1. van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK et al (2008) Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol 53(1):60–67
2. Baranowski A, Abrahms P, Berger R, Buffington, Collett B, Emmanuel A et al (2011) Classification of Chronic Pain. 2nd ed. International Association for the Study of Pain
3. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J et al (2011) GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 64(4):383–394
4. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A (2011) GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol 64(4):380–382
5. Homma Y, Ueda T, Ito T, Takei M, Tomoe H (2009) Japanese guideline for diagnosis and treatment of interstitial cystitis. Int J Urol 16(1):4–16
6. Hanno PM, Burks DA, Clemens JQ, Dmochowski RR, Erickson D, Fitzgerald MP et al (2011) AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol 185(6):2162–2170
7. Roos C, Bonowiack E, Kowalska M, Zapalska A, Mol B, Mignini L et al (2013) What do we know about tocolytic effectiveness and how do we use this information in guidelines? A comparison of evidence grading. BJOG 120(13):1588–1598
8. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S et al (2004) Grading quality of evidence and strength of recommendations. BMJ 328(7454):1490
9. Giannantoni A, Bini V, Dmochowski R, Hanno P, Nickel JC, Proietti S et al (2012) Contemporary management of the painful bladder: a systematic review. Eur Urol 61(1):29–53
10. Fall M, Oberpenning F, Peeker R (2008) Treatment of bladder pain syndrome/interstitial cystitis 2008: can we make evidence-based decisions? Eur Urol 54(1):65–75
11. Engeler D, Baranowski AP, Elneil S, Hughes J, Messelink EJ, Oliveira P et al (2012) Guidelines on Chronic Pelvic Pain
12. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M et al (2011) GRADE guidelines: 7. Rating the quality of evidence–inconsistency. J Clin Epidemiol 64(12):1294–1302
13. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M et al (2011) GRADE guidelines: 8. Rating the quality of evidence–indirectness. J Clin Epidemiol 64(12):1303–1310
14. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D et al (2011) GRADE guidelines 6. Rating the quality of evidence–imprecision. J Clin Epidemiol 64(12):1283–1293
15. Brozek JL, Akl EA, Alonso-Coello P, Lang D, Jaeschke R, Williams JW et al (2009) Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy 64(5):669–677
16. O'Hare PG, Hoffmann AR, Allen P, Gordon B, Salin L, Whitmore K (2013) Interstitial cystitis patients' use and rating of complementary and alternative medicine therapies. Int Urogynecol J 24(6):977–982
17. van Ophoven A, Pokupic S, Heinecke A, Hertle L (2004) A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. J Urol 172(2):533–536
18. Hertle L, van Ophoven A (2010) Long-term results of amitriptyline treatment for interstitial cystitis. Aktuelle Urol 41(Suppl 1):S61–S65
19. Thilagarajah R, Witherow RO, Walker MM (2001) Oral cimetidine gives effective symptom relief in painful bladder disease: a prospective, randomized, double-blind placebo-controlled trial. BJU Int 87(3):207–212
20. Sant GR, Propert KJ, Hanno PM, Burks D, Culkin D, Diokno AC et al (2003) A pilot clinical trial of oral pentosan polysulfate and oral

hydroxyzine in patients with interstitial cystitis. J Urol 170(3):810–815
21. Holm-Bentzen M, Jacobsen F, Nerstrøm B, Lose G, Kristensen JK, Pedersen RH et al (1987) A prospective double-blind clinically controlled multicenter trial of sodium pentosanpolysulfate in the treatment of interstitial cystitis and related painful bladder disease. J Urol 138(3):503–507
22. Parsons CL, Benson G, Childs SJ, Hanno P, Sant GR, Webster G (1993) A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosanpolysulfate. J Urol 150(3):845–848
23. Perez-Marrero R, Emerson LE, Feltis JT (1988) A controlled study of dimethyl sulfoxide in interstitial cystitis. J Urol 140(1):36–39
24. Parsons CL, Housley T, Schmidt JD, Lebow D (1994) Treatment of interstitial cystitis with intravesical heparin. Br J Urol 73(5):504–507
25. Matsuoka PK, Haddad JM, Pacetta AM, Baracat EC (2012) Intravesical treatment of painful bladder syndrome: a systematic review and meta-analysis. Int Urogynecol J 23(9):1147–1153
26. Erickson DR, Kunselman AR, Bentley CM, Peters KM, Rovner ES, Demers LM et al (2007) Changes in urine markers and symptoms after bladder distention for interstitial cystitis. J Urol 177(2):556–560
27. Cole EE, Scarpero HM, Dmochowski RR (2005) Are patient symptoms predictive of the diagnostic and/or therapeutic value of hydrodistention? Neurourol Urodyn 24(7):638–642
28. Ottem DP, Teichman JM (2005) What is the value of cystoscopy with hydrodistension for interstitial cystitis? Urology 66(3):494–499
29. Higson RH, Smith JC, Whelan P (1978) Bladder rupture: an acceptable complication of distension therapy? Br J Urol 50(7):529–534
30. Malloy TR, Shanberg AM (1994) Laser therapy for interstitial cystitis. Urol Clin North Am 21(1):141–144
31. Rofeim O, Hom D, Fazid RM, Moldwin RM (2001) Use of the neodymium: YAG laser for interstitial cystitis: a prospective study. J Urol 166(1):134–136
32. Zhao J, Bai J, Zhou Y, Qi G, Du L (2008) Posterior tibial nerve stimulation twice a week in patients with interstitial cystitis. Urology 71(6):1080–1084
33. Whitmore KE, Payne CK, Diokno AC, Lukban JC (2003) Sacral neuromodulation in patients with interstitial cystitis: a multicenter clinical trial. Int Urogynecol J Pelvic Floor Dysfunct 14(5):305–308, discussion 8–9
34. Maher CF, Carey MP, Dwyer PL, Schluter PL (2001) Percutaneous sacral nerve root neuromodulation for intractable interstitial cystitis. J Urol 165(3):884–886
35. Comiter CV (2003) Sacral neuromodulation for the symptomatic treatment of refractory interstitial cystitis: A prospective study. J Urol 169(4):1369–1373
36. Steinberg AC, Oyama IA, Whitmore KE (2007 Mar) Bilateral S3 stimulator in patients with interstitial cystitis. Urology 69(3):441–443
37. Powell CR, Kreder KJ (2010) Long-term outcomes of urgency-frequency syndrome due to painful bladder syndrome treated with sacral neuromodulation and analysis of failures. J Urol 183(1):173–176
38. Sairanen J, Leppilahti M, Tammela T, Ruutu M, Finn C, ICSIG (2007) Quality of life in patients with interstitial cystitis/painful bladder syndrome after treatment with DMSO, BCG, cyclosporine and pentosan polysulfate sodium. European Urol Suppl 6(2):169
39. Sairanen J, Hotakainen K, Tammela TL, Stenman UH, Ruutu M (2008) Urinary epidermal growth factor and interleukin-6 levels in patients with painful bladder syndrome/interstitial cystitis treated with cyclosporine or pentosan polysulfate sodium. Urology 71(4):630–633
40. Sairanen J, Leppilahti M, Tammela TL, Paananen I, Aaltomaa S, Tauri K et al (2009) Evaluation of health-related quality of life in patients with painful bladder syndrome/interstitial cystitis and the impact of four treatments on it. Scand J Urol Nephrol 43(3):212–219
41. Tirumuru S, Al Kurdi D, Latthe P (2010) Intravesical botulinum toxin a injections in the treatment of painful bladder syndrome/interstitial cystitis: a systematic review. Int Urogynecol J 21:S343–S344
42. Rössberger J, Fall M, Jonsson O, Peeker R (2007) Long-term results of reconstructive surgery in patients with bladder pain syndrome/interstitial cystitis: subtyping is imperative. Urology 70(4):638–642
43. Warren JW, Horne LM, Hebel JR, Marvel RP, Keay SK, Chai TC (2000) Pilot study of sequential oral antibiotics for the treatment of interstitial cystitis. J Urol 163(6):1685–1688
44. Peters K, Diokno A, Steinert B, Yuhico M, Mitchell B, Krohta S et al (1997) The efficacy of intravesical Tice strain bacillus Calmette-Guerin in the treatment of interstitial cystitis: a double-blind, prospective, placebo controlled trial. J Urol 157(6):2090–2094
45. Mayer R, Propert KJ, Peters KM, Payne CK, Zhang Y, Burks D et al (2005) A randomized controlled trial of intravesical bacillus calmette-guerin for treatment refractory interstitial cystitis. J Urol 173(4):1186–1191
46. Propert KJ, Mayer R, Nickel JC, Payne CK, Peters KM, Teal V et al (2008) Followup of patients with interstitial cystitis responsive to treatment with intravesical bacillus Calmette-Guerin or placebo. J Urol 179(2):552–555
47. McCahy PJ, Styles RA (1995) Prolonged bladder distension: experience in the treatment of detrusor overactivity and interstitial cystitis. Eur Urol 28(4):325–327
48. Glemain P, Rivière C, Lenormand L, Karam G, Bouchot O, Buzelin JM (2002) Prolonged hydrodistention of the bladder for symptomatic treatment of interstitial cystitis: efficacy at 6 months and 1 year. Eur Urol 41(1):79–84
49. Badenoch AW (1971) Chronic interstitial cystitis. Br J Urol 43(6):718–721
50. Sharma M, Ansari MT, Abou-Setta AM, Soares-Weiser K, Ooi TC, Sears M et al (2009) Systematic review: comparative effectiveness and harms of combination therapy and monotherapy for dyslipidemia. Ann Intern Med 151(9):622–630

European Journal of Obstetrics & Gynecology and Reproductive Biology 180 (2014) 61–67

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Review

Variations in the reporting of outcomes used in systematic reviews of treatment effectiveness research in bladder pain syndrome

Seema A. Tirlapur [a,*], Richeal Ni Riordain [b], Khalid S. Khan [a,c] on behalf of the EBM-CONNECT Collaboration

[a] Women's Health Research Unit, Barts and The London School of Medicine, Queen Mary, University of London, Turner Street, London E1 2AB, United Kingdom
[b] Barts and The London School of Medicine and Dentistry, London E1 2AB, United Kingdom
[c] Barts Health NHS Trust, The Royal London Hospital, Whitechapel Road, London E1 1BB, United Kingdom

ARTICLE INFO

Article history:
Received 10 January 2014
Received in revised form 6 May 2014
Accepted 4 June 2014

Keywords:
AMSTAR
Bladder pain syndrome
Core outcome set
Randomised controlled trials
Systematic review

ABSTRACT

This paper investigates the quality of outcomes reported in systematic reviews and randomised controlled trials (RCTs) of bladder pain syndrome and its relationship with study quality and journal impact factor. We searched until August 2013 the Cochrane Library, EMBASE, Medline, CINAHL, LILACS and SIGLE, without language restrictions. Quality of outcome reporting in systematic reviews and constituent RCTs was assessed using a 6-point scale. Overall study quality was assessed using the AMSTAR and Jadad scoring systems, and impact factor in the year of publication was noted. Spearman's rank correlation was calculated. There were 8 systematic reviews, with a total of 28 RCTs (1732 patients), reporting 5 outcomes using 19 different measurement scales. The outcomes reported in individual RCTs were urinary symptoms (100%), pain (64%), quality of life (39%), general wellbeing (36%) and bladder capacity (36%). The mean quality of outcomes reported was 1.63 (95% CI 0.29–2.96) for systematic reviews and 3.25 (95% CI 2.80–3.70) for RCTs. The quality of outcomes reported showed correlation with overall study quality (0.90, 95% CI 0.79–0.95, $p < 0.0001$) but not with journal impact factor (0.07, 95% CI −0.31–0.43, $p = 0.35$). Multivariable linear regression showed a relationship between quality of outcome reporting and study quality ($\beta = 0.05$, $p < 0.0001$), adjusting for effects of study type, impact factor and journal type. There is a need to generate consensus over a set of core outcomes in bladder pain syndrome using standardised reporting tools and to disseminate these through good publication practice.

Contents

Abbreviations: AMSTAR, assessment of multiple systematic reviews; BPS, bladder pain syndrome; CI, confidence intervals; COMET, core outcome measures in effectiveness trials; COS, core outcome sets; GRADE, grading, recommendations, assessment, development and evaluation; PRISMA, preferred reporting items for systematic reviews and meta-analyses; RCT, randomised controlled trial.

* Corresponding author. Tel.: +44 207 882 5883; fax: +44 207 882 2552.
E-mail address: s.a.tirlapur@qmul.ac.uk (S.A. Tirlapur).

http://dx.doi.org/10.1016/j.ejogrb.2014.06.003
0301-2115/

Introduction

Treatment effectiveness studies examine changes in outcomes. Inconsistencies in reported outcomes and the tools used to measure these, with missing outcome data and outcome reporting bias, are often seen across studies [1]. Consistency in outcomes is essential to allow direct comparison of effects. Inconsistency hinders evidence syntheses, limiting their usefulness with downstream negative impact on care quality. The use of core outcomes is required to improve the translation of evidence into practice [2].

We wanted to examine if quality of outcome reporting was linked to other publication features. Bladder pain syndrome (BPS) (formerly known as interstitial cystitis and painful bladder syndrome), a common condition associated with considerable disability [3,4], has trials and reviews evaluating various treatments to achieve symptomatic control. These outcomes are measured using a range of scales and scores. Any chronic condition would serve as a good exemplar to empirically address our questions, but we chose BPS as this condition is of particular interest to the authors who are assessing the evidence on efficacy of treatments in BPS. We acknowledge the lack of understanding around the aetiology of this condition and consensus on diagnosing and managing it, despite recent guidelines from the American Urological Association [5].

We systematically identified primary and secondary outcomes and assessed the variation in diversity and quality of outcome measures used to evaluate treatments for BPS in published systematic reviews and their constituent trials. We evaluated the relationship of quality of outcomes reported with overall study quality and journal impact factor in a controlled analysis adjusting for the effects of year of publication, commercial funding, study design and journal type.

Methods

Our systematic review was conducted prospectively deploying a protocol based on contemporary methods and reported in accordance with the PRISMA statement [6].

Search strategy

Literature searches were conducted in the following databases covering time period from database inception until August 2013: the Cochrane Library, EMBASE (1980–2013), Medline (1950–2013), CINAHL (1981–2013) and LILACS (1982–2013). Grey literature was searched through SIGLE (1990–2013). There were no language restrictions. We used MeSH headings, their keywords and variants for "interstitial cystitis" or "painful bladder syndrome" or "bladder pain syndrome" combined using the Boolean operator "and" with the term "systematic review" or its word variants in the title or abstract. A hand search of bibliographies from relevant articles and conference proceedings of the International Continence Society was performed to identify articles not electronically cited.

Study selection and data extraction

All systematic reviews, defined as those that searched in at least two databases and used PRISMA or predecessor guidelines for reporting, evaluating treatments for BPS were included. Primary and secondary outcomes were recorded along with the measurement tools or questionnaires used to capture the outcome. This was usually in the form of patient-rated improvement scales [5]. The type of journal (general or specialist) studies were published in was recorded, along with sources of pharmaceutical funding and any sample size calculations performed for randomised controlled trials (RCTs). The impact factor in the year of publication for both

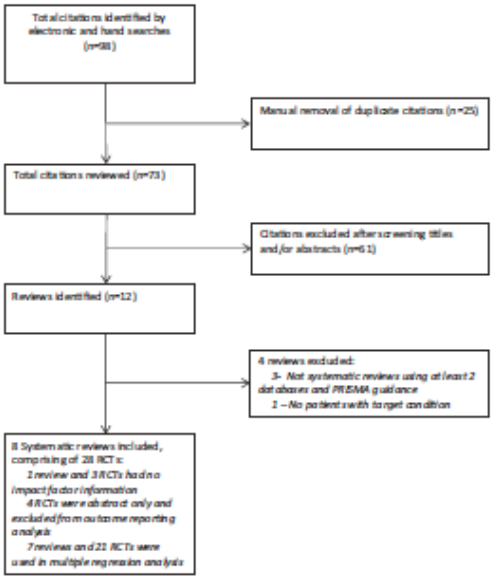


Fig. 1. Flow chart of systematic review selection.

systematic reviews and RCTs was noted. All data were extracted in duplicate by two independent researchers (SAT, RNR) using an electronic data extraction form. The results were discussed and disagreements resolved through consensus.

Quality assessments

Quality assessment for outcomes reported within each systematic review and RCT was assessed using the following six questions [7]: if a primary outcome was stated (1-point), if a clear definition was provided for reproducible measurement (1-point), if a secondary outcome was stated (1-point), if a clear definition was provided for reproducible measurement (1-point), if the authors explained the use of the outcomes (1-point) and if methods were used to enhance quality of measures, for example repeating measures or training in use of measurement tools (1-point). There is no rating system for the scores, so an arbitrary level of ≥4 was used by the authors to represent "good" quality. The development of core outcome sets is a relatively new concept. Much work has been done to develop specific questions to assess the chosen outcome measures, and so the six questions above were chosen, as used in published literature on core outcome development [7].

Study quality assessment was undertaken for all systematic reviews using an 11-point AMSTAR (assessment of multiple systematic reviews) measurement tool. This is a standardised checklist assessing the methodology of the systematic review,

Table 1
Characteristics of systematic reviews for treatments of bladder pain syndrome.

Systematic review (author, year)	Impact factor (AMSTAR)	Treatment	No. of RCTs (no. of patients)	Total no. of studies (total no. of patients)	Outcome	Measurement tool	No. of RCTs per outcome
Srivastava (2012) [15]	Not documented (3)	Sacral neuromodulation	1 (22)	11 (480)	Pain	VAS	1
					Quality of life	GRA, SF 36, BDI	0
					Urinary symptoms	ICPI, PUF	0
					Bladder capacity	Not documented	0
Dawson and Jamison (2007) [10]	4.65 (11)	Intravesical treatments	8 (586)	9 (616)	Pain	VAS, NRS	3
					Quality of life	ICSI, Rand 36	5
					Urinary symptoms	ICSI, GRA, PUF	4
					Bladder capacity	Voiding diary, urodynamics	4
					Economic outcomes	Not documented	0
Dimitrakov et al. (2007) [11]	8.39 (6)	Pharmacological	21 (1470)	21 (1470)	Urinary symptoms	ICSI/PI, voiding diary	21
					Global status	Not documented	0
Mangera et al. (2011) [12]	8.49 (4)	Botulinum toxin A	1 (20)	9 (231)	Pain	VAS	1
					Urinary frequency	Not documented	1
					Nocturia	Not documented	1
					Bladder capacity	Urodynamics	0
					Global quality of life	CPSI, PSS, GICS, AUA SI	1
Matsuoka et al. (2012) [13]	2.17 (5)	Intravesical treatments	5 (596)	5 (596)	Pain	VAS, PUF	3
					Quality of life	SF 36, Rand 36	0
					Urinary symptoms	GRA, ICSI	5
					Bladder capacity	Urodynamics	3
Mourtzoukou et al. (2012) [14]	2.38 (2)	Intravesical resiniferatoxin	3 (203)	6 (225)	Pain	VAS, PUF	3
					Quality of life	Not documented	0
					Urinary symptoms	GRA, ICSI, voiding diary	3
Tirlapur et al. (2013) [16]	1.85 (7)	Neuromodulation	1 (56)	1 (56)	Pain	ICSI/PI	1
					Quality of life	ICSI/PI	1
					Urinary symptoms	SF 36	1
Tirumuru et al. (2010) [17]	1.73 (7)	Intravesical Botulinum toxin A	3 (155)	10 (260)	Pain	VAS	2
					Urinary symptoms	BFLUTS, GRA, IIQ, ICSI, KHQ	2
					Bladder capacity	Urodynamics	2
					Quality of life	IPPS, UDI	2

AMSTAR: assessment of multiple systematic reviews; VAS: visual analogue scale; GRA: global response assessment; SF 36: short-form 36 quality of life survey; BDI: Beck's depression inventory; ICPI: interstitial cystitis problem index; PUF: pelvic pain urgency/frequency; NRS: numeric rating scale; ICSI: interstitial cystitis symptom index; RAND 36: research and development health survey; CPSI: chronic prostatitis symptom index; PSS: perceived stress scale; GICS: global interstitial cystitis score; AUA SI: American Urological Association symptom index; BFLUTS: Bristol female lower urinary tact symptoms; IIQ: incontinence impact questionnaire; KHQ: King's health questionnaire; IPPS: international prostate symptom score; UDI: urogenital distress inventory.

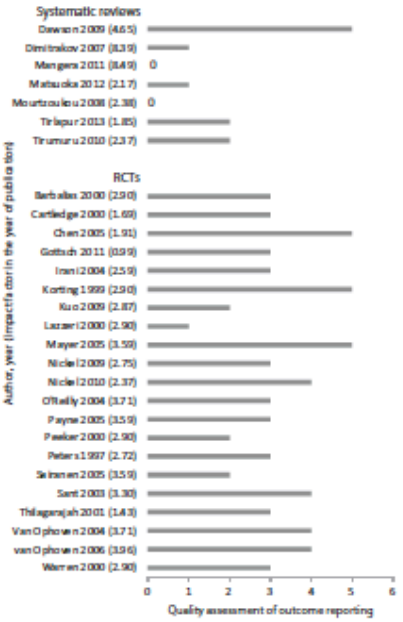


Fig. 2. Quality of outcomes reported for systematic reviews and randomised controlled trials (RCTs).

along with study characteristics, quality assessment, publication bias assessment and conflict of interest declaration, where all 11 questions can be answered as yes, no, cannot be answered or not applicable. 'High' quality is assigned to scores 8–11, 'medium' quality to scores 4–7 and 'low' quality to 0–3 [8]. The Jadad criteria were used to assess quality in RCTS. This is a commonly used scoring system, which evaluates randomisation and blinding along with the methodology used and accounts for patient who drop out of the study, where all five questions are answered as yes or no. Scores ranged from 0–5, with 'good' quality assigned to scores ≥3 [9]. Both study quality assessment scores were transformed into a scale from 0–100 for graphical representation and correlation analysis.

Data synthesis

Descriptive characterisations of studies were tabulated. Graphical representations were prepared. Spearman's rank correlation with 95% confidence intervals (CI) was calculated for quality of reporting outcomes versus overall study quality assessment and journal impact factor in the year of publication. Multiple regression analysis was undertaken using StatsDirect version 2.7.9 to assess the relationship of quality of outcomes reported with study quality adjusting for impact factor, year of publication, commercial funding and study and journal type.

Results

Fig. 1 summarises the selection of articles, which were all in english. Eight systematic reviews were included with a total of 1732 patients [10–17]. Four articles were excluded; three did not adhere to the definition of a systematic review, and one did not affect patients with BPS [18–21]. There were various outcomes and measurement tools within each study (Table 1). There were 28 unique RCTs [22–47]. Five outcomes were identified; urinary symptoms, pain, quality of life, general wellbeing and bladder capacity. Seven outcome tools were used to measure urinary symptoms in 28 RCTs (100%), five to measure pain in 18 RCTs (64%), six for quality of life in 11 RCTs (39%), one for general wellbeing in 10 RCTS (36%) and one for bladder capacity in 12 RCTs (43%). In quality of life measurement tools, we used the general or 'physical' component, rather than the emotional or 'mental' component referred to in the SF 36 questionnaire. The AMSTAR tool for quality of systematic reviews scored a mean of 5.63 (95% CI 3.26–7.99). The Jadad criteria for quality in RCTS scored mean of 3.13 (95% CI 2.58–3.67).

Half of the systematic reviews were published in specialists' urology or urogynaecology journals ($n=4$), 13% ($n=1$) in a general obstetrics and gynaecology journal and 38% ($n=3$) in non-women's health journals. All of the RCTs were published in specialty urology or urogynaecology journals ($n=28$). In 46% ($n=15$) of RCTS a sample size calculation was performed. None of systematic reviews and 33% ($n=8$) of RCTs had pharmaceutical company funding.

The quality of outcomes reporting was assessed in 21 RCTs and seven systematic reviews (Fig. 2). Four original RCT papers could not be obtained despite all attempts to contact the authors, so were excluded from this analysis, as accurate quality assessment could not be performed from the limited information in the study abstract [28,36,48,49]. The mean score for quality of outcomes reported was 1.63 (95% CI 0.29–2.96) for systematic reviews and 3.25 (95% CI 2.80–3.70) for RCTs. The quality of outcome reporting in 13% ($n=1$) of systematic reviews was deemed good quality and

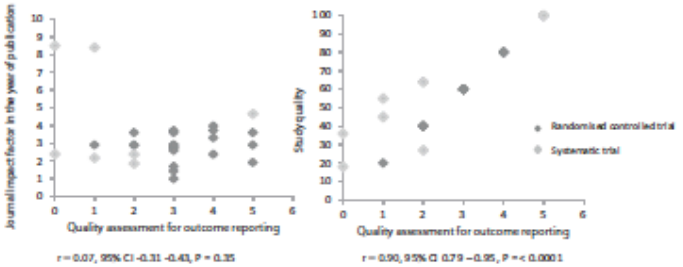


Fig. 3. Relationship of quality of outcomes reporting with journal impact factors at publication and overall study quality.

Table 2
Multiple linear regression analysis to determine factors associated with quality of outcome reporting.

Factor	Univariable		Multivariable[b]	
	β	p	β	p
Study quality[a]	0.05	<0.0001	0.05	<0.0001
Impact factor at publication	−0.08	0.02	−0.07	0.02
Type of study (systematic review/RCT)	−1.20	<0.0001	−1.24	<0.0001
Journal type (specialist/general)	−0.40	0.05	−0.41	0.03
Year of publication	−0.01	0.70	–	–
Commercial funding	−0.01	0.93	–	–

[a] Measurement details in methodology section.
[b] Based on best sub-set regression.

33% ($n=8$) of RCTS (Fig. 2). Primary outcome reporting was no different (4 versus 21, 50% versus 88%, $p=0.51$), but secondary outcomes were more frequently reported in RCTs compared to systematic reviews (1 versus 11, 13% versus 46%, $p=0.003$).

Fig. 3 shows the relationship between quality of outcomes reporting with impact factor in the year of publication and study quality in included systematic reviews and RCTs. One systematic review and three RCTs were excluded, as information about the journal impact factor in the year of publication could not be obtained [15,22,35,45]. The quality of outcomes reported showed correlation with study quality (0.90, 95% CI 0.79–0.95, $p=<0.0001$) but not with journal impact factor (0.07, 95% CI −0.31–0.43, $p=0.35$) using Spearman's rank coefficient. Multivariable linear regression analysis confirmed the positive relationship between outcome reporting quality and study quality ($\beta=0.05$, $p<0.0001$) with adjusting for effects of study type, impact factor and journal type (Table 2). Systematic reviews versus RCTs ($\beta=-1.24$, $p<0.0001$), specialist versus general journals ($\beta=-0.41$, $p=0.03$), and lower versus higher impact factor ($\beta=-0.07$, $p=0.02$) were associated with outcome reporting quality.

Discussion

Various outcomes and measurement tools were used to assess treatment effectiveness in BPS. There is a general lack of RCTs for treatment effectiveness in BPS with the majority of studies being observational. There was poor quality of outcomes reporting. Reporting of secondary outcomes was better in individual RCTs compared to systematic reviews. The quality of included systematic reviews and RCTs was variable. The highest quality systematic review was by Dawson and Jamison [10] assessing intravesical treatments for BPS, which clearly stated outcome measures and performed well using the quality assessment tools, but this may be explained by the fact that it is a Cochrane collaboration publication which needs to adhere to the Cochrane guidance and hence, incorporates all expected elements of reporting a systematic review. Conversely, the publication in the highest impact journal by Mangera et al. [12] had the lowest quality assessment score as it did not describe primary or secondary outcomes. There was a relationship between the quality of outcomes reported and the quality of a study but not with journal impact factor at publication. This relationship remained significant in a multivariable analysis. It is interesting to note the lack of correlation with journal impact factor which may suggest the authors with good quality studies do not aim to publish in high impact journals, resorting for speciality specific, often lower ranking journals.

This review performed systematic assessment of all available literature with no language barriers. All five outcomes were assessed using a variety of patient-reported questionnaires, which comprised of composite symptom and sign scores, along with visual analogue scales. This heterogeneity would make comparison of effects on treatment very difficult with an inability to evaluate their impact on disease [50]. Many patient-reported questionnaires lack the ability to be truthful, are unfeasible to replicate and do not have discriminative power to gauge the reliability and sensitivity of the measurement tool [51]. The relationship we observed between quality of outcomes reporting and overall study quality merits consideration. The RCTs were international with different patient populations, so no meaningful comparisons could be made relating to ethnicity.

This review has identified five different outcomes to assess treatments for BPS which can serve as a starting point for the development of a core outcome set involving a Delphi panel survey of stakeholders, including patient representatives, through consensus and would enable prioritisation of outcomes [52]. Outcome measures can be prioritised using the Grading, Recommendations, Assessment, Development and Evaluation (GRADE) working group recommendation scale. This enables improved standardisation and transparency of results by prioritising outcomes from 'critically important' to 'not important' [53,54].

There is an attempt to standardise terminology in urogynaecology [55,56]. Standardised, validated tools with clear reporting on time of testing will be needed to allow repeatable results when developing an inventory of core outcomes [7]. There is a need for a set of core outcomes for common gynaecological conditions in addition to explicitness of intended primary and secondary outcomes in order to improve the transparency of results in trials, reviews and guidelines. Symptom severity and general physical and mental quality of life are important outcome measures. There are several validated disease-specific questionnaires used for BPS but no single internationally adopted one. Delphi panels of specialists may be used to develop a single symptom-based questionnaire, which incorporates the five core outcomes identified in this paper.

Methods of measuring outcomes, and the reporting of frequency of incomplete outcomes in results, are necessary in order to minimise reporting bias and improve the reliability of outputs from evidence syntheses [57–59]. The Core Outcomes in Women's Health (CROWN) initiative is a working group, recently established, led by journal editors to minimise inconsistencies in the reporting of outcomes and avoid reporting bias in women's health.

Conflict of interest

None.

Funding

We received funding from the European Union made available to the EBM-CONNECT Collaboration through its Seventh

Framework Programme, Marie Curie Actions, International Staff Exchange Scheme (Proposal no. 101377; Grant Agreement no. 247613); EBM-CONNECT Canadian Collaborators received funding from the Canadian Institutes of Health Research. No funders played a role in the planning and execution of this work or in drafting of the manuscript.

Acknowledgments

The EBM-CONNECT (Evidence-Based Medicine Collaboration: Network for systematic reviews and guideline development research and dissemination) Collaboration (in alphabetical order by country) includes: L. Mignini (Centro Rosarino de Estudios Perinatales, Argentina); P. von Dadelszen, L. Magee, D. Sawchuck (University of British Columbia, Canada); E. Gao (Shanghai Institute of Planned Parenthood Research, China); B. W. Mol, K. Oude Rengerink (Academic Medical Centre, The Netherlands); J. Zamora (Ramon y Cajal, Spain); C. Fox, J. Daniels (University of Birmingham, UK); and K. S. Khan, S. Thangaratinam, C. Meads, S.A. Tirlapur (Barts and the London School of Medicine, Queen Mary University of London, UK).

References

[1] Kirkham JJ, Gargon E, Clarke M, Williamson PR. Can a core outcome set improve the quality of systematic reviews? – a survey of the Co-ordinating Editors of Cochrane Review Groups. Trials 2013;14:21.
[2] Williamson PR, Altman DG, Blazeby JM, et al. Developing core outcome sets for clinical trials: issues to consider. Trials 2012; 13:132.
[3] Berry SH, Monica S, Stoto MA, et al. Prevalence of interstitial cystitis/painful bladder syndrome in the United States. J Urol 2009;181(4):20–1.
[4] Bogart LM, Berry SH, Clemens JQ. Symptoms of interstitial cystitis, painful bladder syndrome and similar diseases in women: a systematic review. J Urol 2007; 177(2):450–6.
[5] Hanno PM, Burks DA, Clemens JQ, et al. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol 2011;185 (6):2162–70.
[6] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009;62(10):e1–e34.
[7] Harman NL, Bruce IA, Callery P, et al. MOMENT – Management of Otitis Media with Effusion in Cleft Palate: protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. Trials 2013; 14:70.
[8] Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 2007; 7: 10.
[9] Kennelley J. Methodological approach to assessing the evidence. Reducing racial and ethnic disparities in reproductive and perinatal outcomes the evidence from population-based interventions. US: Springer; 2011. p. 7–20.
[10] Dawson TE, Jamison J. Intravesical treatments for painful bladder syndrome/interstitial cystitis. Cochrane Database Syst Rev 2007; 17(4):CD006113.
[11] Dimitrakov J, Kroenke K, Steers WD, et al. Pharmacologic management of painful bladder syndrome/interstitial cystitis: a systematic review. Arch Intern Med 2007; 167(18): 1922–9.
[12] Mangera A, Andersson KE, Apostolidis A, et al. Contemporary management of lower urinary tract disease with botulinum toxin A: a systematic review of botox (onabotulinumtoxinA) and dysport (aboborulinumtoxinA). Eur Urol 2011;60(4):784–95.
[13] Matsuoka PK, Haddad JM, Pacetta AM, Baracat EC. Intravesical treatment of painful bladder syndrome: a systematic review and meta-analysis. Int Urogynecol J 2012; 23(9):1147–53.
[14] Mourtzoukou EG, Iavazzo C, Falagas ME. Resiniferatoxin in the treatment of interstitial cystitis: a systematic review. Int Urogynecol J 2012; 23(9): 1147–53.
[15] Srivastava D. Efficacy of sacral neuromodulation in treating chronic pain related to painful bladder syndrome/interstitial cystitis in adults. J Anaesthesiol Clin Pharmacol 2012;28(4):428–35.
[16] Tirlapur SA, Vlismas A, Ball E, Khan KS. Nerve stimulation for chronic pelvic pain and bladder pain syndrome: a systematic review. Acta Obstet Gynecol Scand 2013;92(8):881–7.
[17] Tirumuru S, Al-Kurdi D, Latthe P. Intravesical botulinum toxin A injections in the treatment of painful bladder syndrome/interstitial cystitis: a systematic review. Int Urogynecol J 2010;21(10): 1285–300.
[18] Cody JD, Nabi G, Dublin N, et al. Urinary diversion and bladder reconstruction/replacement using intestinal segments for intractable incontinence or following cystectomy. Cochrane Database Syst Rev 2012;2:CD003306.
[19] Vilar DC, Fadrique GG, Martin JJP, et al. Hypebaric oxygen treatment in urology. Arch Esp Urol 2011;64(9):869–74.
[20] Yokoyama T, Chancellor MB, Oguma K, et al. Botulinum toxin type A for the treatment of lower urinary tract disorders. Int J Urol 2012;19(3):202–15.
[21] Giannantoni A, Bini V, Dmochowski R, et al. Contemporary management of the painful bladder: a systematic review. Eur Urol 2012; 61(1):29–53.
[22] Bade JJ, Laseur M, Nieuwenburg A, van der Weele LT, Mensink HJ. A placebo-controlled study of intravesical pentosanpolysulphate for the treatment of interstitial cystitis. Br J Urol 1997;79(2):168–71.
[23] Barbalias GA, Liatsikos EN, Athanasopoulos A, Nikiforidis G. Interstitial cystitis: bladder training with intravesical oxybutynin. J Urol 2000;163(6):1818–22.
[24] Chen TY, Corcos J, Camel M, Ponsot Y, Tu le M. Prospective, randomized, double-blind study of safety and tolerability of intravesical resiniferatoxin (RTX) in interstitial cystitis (IC). Int Urogynecol J Pelvic Floor Dysfunct 2005; 16 (4):293–7.
[25] Mayer R, Propert KJ, Peters KM, et al. A randomized controlled trial of intravesical bacillus Calmette–Guerin for treatment refractory interstitial cystitis. J Urol 2005; 173(4):1186–91.
[26] Payne CK, Mosbaugh PG, Forrest JB, et al. Intravesical resiniferatoxin for the treatment of interstitial cystitis: a randomized, double-blind, placebo controlled trial. J Urol 2005; 173(5):1590–4.
[27] Peeker R, Haghsheno MA, Holmäng S, Fall M. Intravesical bacillus Calmette–Guerin and dimethyl sulfoxide for treatment of classic and nonulcer interstitial cystitis: a prospective, randomized double-blind study. J Urol 2000; 164(6) 1912–6 Discussion 5–6.
[28] Perez-Marrero R, Emerson LE, Feltis JT. A controlled study of dimethyl sulfoxide in interstitial cystitis. J Urol 1988;140(1):36–9.
[29] Peters K, Diokno A, Steinert B, et al. The efficacy of intravesical Tice strain bacillus Calmette–Guerin in the treatment of interstitial cystitis: a double-blind, prospective, placebo controlled trial. J Urol 1997;157(6):2090–4.
[30] Kuo HC, Chancellor MB. Comparison of intravesical botulinum toxin type A injections plus hydrodistention with hydrodistention alone for the treatment of refractory interstitial cystitis/painful bladder syndrome. BJU Int 2009; 104 (5):657–61.
[31] Nickel JC, Moldwin R, Lee S, Davis EL, Henry RA, Wyllie MG. Intravesical alkalinized lidocaine (PSD597) offers sustained relief from symptoms of interstitial cystitis and painful bladder syndrome. BJU Int 2009; 103(7):910–8.
[32] Irani D, Heidari M, Khezri AA. The efficacy and safety of intravesical Bacillus-Calmette–Guerin in the treatment of female patients with interstitial cystitis: a double-blinded prospective placebo controlled study. Urol J 2004; 1(2):90–3.
[33] Lazzeri M, Beneforti P, Spinelli M, Zanollo A, Barbagli G, Turini D. Intravesical resiniferatoxin for the treatment of hypersensitive disorder: a randomized placebo controlled study. J Urol 2000; 164(3 Pt 1):676–9.
[34] O'Reilly BA, Dwyer PL, Hawthorne G, et al. Transdermal posterior tibial nerve laser therapy is not effective in women with interstitial cystitis. J Urol 2004;172(5):1880–3.
[35] El-Bahnasy A, Farahat Y, El-Bendary M, Taha M, El-Damhogy M, Mourad S. A randomized controlled trial of bacillus Calmette–Guerin and botulinum toxin-A for the treatment of refractory interstitial cystitis. UroToday Int J 2009; 2(1).
[36] Manning JA, Dwyer P, Rosamilia A, Murray C, Thomas E, Beattie K. Prospective randomized double blind study of the effectiveness of botulinum a toxin for treatment of refractory painful bladder syndrome. Int Urogynecol J 2009; 20: 587–8.
[37] van Ophoven A, Pokupic S, Heinecke A, Hertle L. A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. J Urol 2004; 172(2):533–6.
[38] van Ophoven A, Rossbach G, Pajonk F, Hertle L. Safety and efficacy of hyperbaric oxygen therapy for the treatment of interstitial cystitis: a randomized, sham controlled, double-blind trial. J Urol 2006;176(4 Pt 1): 1442–6.
[39] Warren JW, Horne LM, Hebel JR, Marvel RP, Keay SK, Chai TC. Pilot study of sequential oral antibiotics for the treatment of interstitial cystitis. J Urol 2000;163(6):1685–8.
[40] Thilagarajah R, Witherow RO, Walker MM. Oral cimetidine gives effective symptom relief in painful bladder disease: a prospective, randomized, double-blind placebo-controlled trial. BJU Int 2001;87(3):207–12.
[41] Sairanen J, Tammela TL, Leppilahti M, et al. Cyclosporine A and pentosan polysulfate sodium for the treatment of interstitial cystitis: a randomized comparative study. J Urol 2005; 174(6): 2235–8.
[42] Sant GR, Propert KJ, Hanno PM, et al. A pilot clinical trial of oral pentosan polysulfate and oral hydroxyzine in patients with interstitial cystitis. J Urol 2003; 170(3): 810–5.
[43] Korting GE, Smith SD, Wheeler MA, Weiss RM, Foster HE. A randomized double-blind trial of oral L-arginine for treatment of interstitial cystitis. J Urol 1999; 161(2):558–65.
[44] Cartledge JJ, Davies AM, Eardley I. A randomized double-blind placebo-controlled crossover trial of the efficacy of L-arginine in the treatment of interstitial cystitis. BJU Int 2000;85(4):421–6.
[45] Mulholland SG, Hanno P, Parsons CL, Sant GR, Staskin DR. Pentosan polysulfate sodium for therapy of interstitial cystitis. A double-blind placebo-controlled clinical study. Urology 1990; 35(6): 552–8.
[46] Gottsch HP, Yang CC, Berger RE. A pilot study of botulinum toxin A for male chronic pelvic pain syndrome. Scand J Urol Nephrol 2011;45(1):72–6.
[47] Nickel JC, Egerdie RB, Steinhoff G, Palmer B, Hanno P. A multicenter, randomized, double-blind, parallel group pilot evaluation of the efficacy and safety of intravesical sodium chondroitin sulfate versus vehicle control in patients with interstitial cystitis/painful bladder syndrome. Urology 2010;76 (4):804–9.

[48] Holm-Bentzen M, Jacobsen F, Nerstrøm B, et al. A prospective double-blind clinically controlled multicenter trial of sodium pentosanpolysulfate in the treatment of interstitial cystitis and related painful bladder disease. J Urol 1987;138(3):503–7.
[49] Parsons CL, Mulholland SG. Successful therapy of interstitial cystitis with pentosanpolysulfate. J Urol 1987;138(3):513–6.
[50] Simpson R, Thomas K, Murphy R. Outcome measures for vulval skin conditions: a systematic review of randomised controlled trials. Br J Dermatol 2013; 169(September (3)):494–501.
[51] Tugwell P, Boers M, Brooks P, Simon L, Strand V, Idzerda L. OMERACT: an international initiative to improve outcome measurement in rheumatology. Trials 2007;8:38.
[52] Williamson P, Clarke M. The COMET (Core Outcome Measures in Effectiveness Trials) initiative: its role in improving Cochrane reviews. Cochrane Database Syst Rev 2012;5:ED000041.
[53] Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. What is "quality of evidence" and why is it important to clinicians? BMJ 2008;336 (7651):995–8.
[54] Rahn DD, Abed H, Sung VW, et al. Systematic review highlights difficulty interpreting diverse clinical outcomes in abnormal uterine bleeding trials. J Clin Epidemiol 2011;64(3):293–300.
[55] Haylen BT, Freeman RM, Swift SE, et al. An International Urogynecological Association (IUGA) / International Continence Society (ICS) joint terminology and classification of the complications related directly to the insertion of prostheses (meshes, implants, tapes) & grafts in female pelvic floor surgery. Int Urogynecol J 2011;22(1):3–15.
[56] Toozs-Hobson P, Freeman R, Barber M, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for reporting outcomes of surgical procedures for pelvic organ prolapse. Neurourol Urodyn 2012;31(4):415–21.
[57] Smyth RM, Kirkham JJ, Jacoby A, Altman DG, Gamble C, Williamson PR. Frequency and reasons for outcome reporting bias in clinical trials: interviews with trialists. BMJ 2011;342:c7153.
[58] Dwan K, Gamble C, Williamson PR, Altman DG. Reporting of clinical trials: a review of research funders' guidelines. Trials 2008;9:66.
[59] Kirkham JJ, Dwan KM, Altman DG, et al. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. BMJ 2010;340:c365.

References

1. Hunner GL. A rare type of bladder ulcer in women: A report of cases. Boston Medical and Surgical Journal. 1915(172):660-5.
2. Messing EM, Stamey TA. Interstitial cystitis: early diagnosis, pathology, and treatment. Urology. 1978;12(4):381-92.
3. Gillenwater JY, Wein AJ. Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis, National Institutes of Health, Bethesda, Maryland, August 28-29, 1987. J Urol. 1988;140(1):203-6.
4. Hanno PM, Landis JR, Matthews-Cook Y, Kusek J, Nyberg L. The diagnosis of interstitial cystitis revisited: lessons learned from the National Institutes of Health Interstitial Cystitis Database study. J Urol. 1999;161(2):553-7.
5. Butrick CW. Interstitial cystitis and chronic pelvic pain: new insights in neuropathology, diagnosis, and treatment. Clin Obstet Gynecol. 2003;46(4):811-23.
6. Hanno P, Keay S, Moldwin R, Van Ophoven A. International Consultation on IC - Rome, September 2004/Forging an International Consensus: progress in painful bladder syndrome/interstitial cystitis. Report and abstracts. Int Urogynecol J Pelvic Floor Dysfunct. 2005;16 Suppl 1:S2-S34.
7. 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. Eur Urol. 2008;53(1):60-7.
8. Homma Y, Ueda T, Ito T, Takei M, Tomoe H. Japanese guideline for diagnosis and treatment of interstitial cystitis. International Journal of Urology. 2009;16(1):4-16.
9. Baranowski A, Abrams P, Berger R, Buffington T, Collett B, Emmanuel A, et al. Classification of Chronic Pain. 2 ed. International Association for the Study of Pain. 2011.
10. Oravisto KJ. Epidemiology of interstitial cystitis. Ann Chir Gynaecol Fenn. 1975;64(2):75-7.
11. Temml C, Wehrberger C, Riedl C, Ponholzer A, Marszalek M, Madersbacher S. Prevalence and correlates for interstitial cystitis symptoms in women participating in a health screening project. Eur Urol. 2007;51(3):803-8; discussion 9.
12. Ito T, Miki M, Yamada T. Interstitial cystitis in Japan. BJU Int. 2000;86(6):634-7.
13. Homma Y, Yamaguchi O, Hayashi K, Committee NBS. An epidemiological survey of overactive bladder symptoms in Japan. BJU Int. 2005;96(9):1314-8.
14. Ito T, Ueda T, Honma Y, Takei M. Recent trends in patient characteristics and therapeutic choices for interstitial cystitis: analysis of 282 Japanese patients. Int J Urol. 2007;14(12):1068-70.
15. Konkle KS, Berry SH, Elliott MN, Hilton L, Suttorp MJ, Clauw DJ, et al. Comparison of an Interstitial Cystitis/Bladder Pain Syndrome Clinical Cohort With Symptomatic Community Women From the RAND Interstitial Cystitis Epidemiology Study. J Urol. 2012;187(2):508-12.
16. Dyer AJ, Twiss CO. Painful bladder syndrome: an update and review of current management strategies. Curr Urol Rep. 2014;15(2):384.
17. Parsons CL, Lilly JD, Stein P. Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). J Urol. 1991;145(4):732-5.
18. Peeker R, Enerbäck L, Fall M, Aldenborg F. Recruitment, distribution and phenotypes of mast cells in interstitial cystitis. J Urol. 2000;163(3):1009-15.

19. Ochs RL, Stein TW, Peebles CL, Gittes RF, Tan EM. Autoantibodies in interstitial cystitis. J Urol. 1994;151(3):587-92.
20. Pontari MA, Hanno PM, Ruggieri MR. Comparison of bladder blood flow in patients with and without interstitial cystitis. J Urol. 1999;162(2):330-4.
21. Cheng C, Rosamilia A, Healey M. Diagnosis of interstitial cystitis/bladder pain syndrome in women with chronic pelvic pain: a prospective observational study. Int Urogynecol J. 2012. Oct;23(10):1361-6
22. Wyndaele JJ, Van Dyck J, Toussaint N. Cystoscopy and bladder biopsies in patients with bladder pain syndrome carried out following ESSIC guidelines. Scand J Urol Nephrol. 2009;43(6):471-5.
23. Hanno PM, Burks DA, Clemens JQ, Dmochowski RR, Erickson D, Fitzgerald MP, et al. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol. 2011;185(6):2162-70.
24. Fall M, Oberpenning F, Peeker R. Treatment of bladder pain syndrome/interstitial cystitis 2008: can we make evidence-based decisions? Eur Urol. 2008;54(1):65-75.
25. Castro-Diaz D, Cardozo L, Chapple CR, Espuña M, Kelleher C, Kirby M, et al. Urgency and pain in patients with overactive bladder and bladder pain syndrome. What are the differences? Int J Clin Pract. 2014;68(3):356-62.
26. O'Leary MP, Sant GR, Fowler FJ, Whitmore KE, Spolarich-Kroll J. The interstitial cystitis symptom index and problem index. Urology. 1997;49(5A Suppl):58-63.
27. Lubeck DP, Whitmore K, Sant GR, Alvarez-Horine S, Lai C. Psychometric validation of the O'leary-Sant interstitial cystitis symptom index in a clinical trial of pentosan polysulfate sodium. Urology. 2001;57(6 Suppl 1):62-6.
28. 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.
29. Brewer ME, White WM, Klein FA, Klein LM, Waters WB. Validity of Pelvic Pain, Urgency, and Frequency questionnaire in patients with interstitial cystitis/painful bladder syndrome. Urology. 2007;70(4):646-9.
30. 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. Neurourol Urodyn. 2010;29(1):191-8.
31. Rapariz-González M, Castro-Díaz D, Mejía-Rendón D, EURCIS. Evaluation of the impact of the urinary symptoms on quality of life of patients with painful bladder syndrome/chronic pelvic pain and radiation cystitis: EURCIS study. Actas Urol Esp. 2014;38(4):224-31.
32. Fall M, Baranowski AP, Fowler CJ, Lepinard V, Malone-Lee JG, Messelink EJ, et al. EAU guidelines on chronic pelvic pain.
33. Chung MK, Chung RP, Gordon D. Interstitial cystitis and endometriosis in patients with chronic pelvic pain: The "Evil Twins" syndrome. JSLS. 2005 Jan-Mar;9(1):25-9.
34. Chung MK, Chung RR, Gordon D, Jennings C. The evil twins of chronic pelvic pain syndrome: endometriosis and interstitial cystitis. JSLS. 2002;6(4):311-4.
35. Latthe P, Latthe M, Say L, Gülmezoglu M, Khan KS. WHO systematic review of prevalence of chronic pelvic pain: a neglected reproductive health morbidity. BMC Public Health. 2006;6:177.

36. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100.
37. Royal College of Obstetricians and Gynaecologists. Green-top guideline: Management of Chronic Pelvic Pain. London. April 2005.
38. Villegas-Echeverri, Lopez-Jaramillo, Leon-Avellaneda, Restrepo-Santa. The role of cystoscopy when studying patients suffering from chronic pelvic pain:an observational study. . Columbia: *Rev Colomb Obstet Ginecol*; 2011. p. 161-6.
39. Shahmohamady B, Berker B, Lashay N, Saberi N, Kazerooni T, Nezhat C. Interstitial cystitis in the setting of chronic pelvic pain. Obstetrics and Gynecology. 2005;105(4):101S-S.
40. Glasziou P, Irwig L, Bain C, Colditz G. Frequency and Rate. In systematic Reviews in Health Care: A practical guide. 2nd edition: Cambridge University Press; 2001. p. 67-73.
41. Khan KS, Kunz R, Kleijnen J, Antes G. Five steps to conducting a systematic review. J R Soc Med. 2003;96(3):118-21.
42. Streiner DL, Norman GR. Measurement. London: PDQ Epidemiology; 1998.
43. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. BMC Med Res Methodol. 2006;6:31.
44. Chung MK, Chung RP, Gordon D. Interstitial cystitis and endometriosis in patients with chronic pelvic pain: The "Evil Twins" syndrome. JSLS. 2005;9(1):25-9.
45. Blum M, Rho M. A multidisciplinary approach to managing lumbar radiculopathy throughout pregnancy: A unique case report. PM&R. 2012; vol 4 (10) suppl 263.
46. Paulson JD, Paulson JN. Anterior vaginal wall tenderness (AVWT) as a physical symptom in chronic pelvic pain. JSLS. 2011;15(1):6-9.
47. Rackow BW, Novi JM, Arya LA, Pfeifer SM. Interstitial cystitis is an etiology of chronic pelvic pain in young women. J Pediatr Adolesc Gynecol. 2009;22(3):181-5.
48. Stanford EJ, Koziol J, Feng A. The prevalence of interstitial cystitis, endometriosis, adhesions, and vulvar pain in women with chronic pelvic pain. J Minim Invasive Gynecol. 2005;12(1):43-9.
49. Clemons JL, Arya LA, Myers DL. Diagnosing interstitial cystitis in women with chronic pelvic pain. Obstet Gynecol. 2002;100(2):337-41.
50. Cao W, Zhang D, Gan J. [Effects of microwave baking on the immunological cells in primary lymphedema patients]. Chung-Hua Cheng Hsing Shao Shang Wai Ko Tsa Chih - Chinese Journal of Plastic Surgery & Burns.15(5):357-9.
51. Kushner L, Moldwin RM. Efficiency of questionnaires used to screen for interstitial cystitis. J Urol. 2006;176(2):587-92.
52. Clemens JQ, Link CL, Eggers PW, Kusek JW, Nyberg LM, McKinlay JB, et al. Prevalence of painful bladder symptoms and effect on quality of life in black, Hispanic and white men and women. J Urol. 2007;177(4):1390-4.
53. Sant GR. Interstitial cystitis in minority women. J Assoc Acad Minor Phys. 1993;4(3):89-92.
54. Jacoby VL, Fujimoto VY, Giudice LC, Kuppermann M, Washington AE. Racial and ethnic disparities in benign gynecologic conditions and associated surgeries. Am J Obstet Gynecol. 2010;202(6):514-21.
55. Suskind AM, Berry SH, Suttorp MJ, Elliott MN, Hays RD, Ewing BA, et al. Health-related quality of life in patients with interstitial cystitis/bladder pain syndrome and frequently associated comorbidities. Qual Life Res. 2013;22(7):1537-41.

56. Cervigni M, Natale F. Gynecological disorders in bladder pain syndrome/interstitial cystitis patients. Int J Urol. 2014;21 Suppl 1:85-8.
57. Tirlapur SA, Kuhrt K, Chaliha C, Ball E, Meads C, Khan KS. The 'evil twin syndrome' in chronic pelvic pain: a systematic review of prevalence studies of bladder pain syndrome and endometriosis. Int J Surg. 2013. 2013;11(3):233-7
58. McMullan M. Patients using the Internet to obtain health information: how this affects the patient-health professional relationship. Patient Educ Couns. 2006;63(1-2):24-8.
59. Benigeri M, Pluye P. Shortcomings of health information on the Internet. Health Promot Int. 2003;18(4):381-6.
60. Temml C, Wehrberger C, Riedl C, Ponholzer A, Marszalek M, Madersbacher S. Prevalence and correlates for interstitial cystitis symptoms in women participating in a health screening project. Eur Urol. 2007;51(3):803-8; discussion 9.
61. Chien PF, Khan KS, Siassakos D. Registration of systematic reviews: PROSPERO. BJOG. 2012;119(8):903-5.
62. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62(10):e1-34.
63. Silberg WM, Lundberg GD, Musacchio RA. Assessing, controlling, and assuring the quality of medical information on the Internet: Caveant lector et viewor--Let the reader and viewer beware. JAMA. 1997;277(15):1244-5.
64. Latthe PM, Latthe M, Khan KS. Quality of medical information about menorrhagia on the worldwide web. BJOG. 2000;107(1):39-43.
65. Winker MA, Flanagin A, Chi-Lum B, White J, Andrews K, Kennett RL, et al. Guidelines for medical and health information sites on the internet: principles governing AMA web sites. American Medical Association. JAMA. 2000;283(12):1600-6.
66. Groot D, ter Riet G, Khan KS, Misso K. Comparison of search strategies and quality of medical information of the Internet: a study relating to ankle sprain. Injury. 2001;32(6):473-6.
67. Kunst H, Groot D, Latthe PM, Latthe M, Khan KS. Accuracy of information on apparently credible websites: survey of five common health topics. BMJ. 2002;324(7337):581-2.
68. Murphy R, Frost S, Webster P, Schmidt U. An evaluation of web-based information. Int J Eat Disord. 2004;35(2):145-54.
69. Ambre J, Guard R, Perveiler FM, Renner J, Rippen H. White paper: Criteria for assessing the quality of health information on the internet. 1997.
70. Bernstam EV, Shelton DM, Walji M, Meric-Bernstam F. Instruments to assess the quality of health information on the World Wide Web: what can our patients actually use? Int J Med Inform. 2005;74(1):13-9.
71. Routh JC, Gong EM, Cannon GM, Nelson CP. Does a controversial topic affect the quality of urologic information on the Internet? Urology. 2011;78(5):1051-6.
72. Kaicker J, Debono VB, Dang W, Buckley N, Thabane L. Assessment of the quality and variability of health information on chronic pain websites using the DISCERN instrument. BMC Med. 2010;8:59.
73. Henderson EM, Rosser BA, Keogh E, Eccleston C. Internet sites offering adolescents help with headache, abdominal pain, and dysmenorrhoea: a description of content, quality, and peer interactions. J Pediatr Psychol. 2012;37(3):262-71.

74. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.
75. Henry JL. The need for knowledge translation in chronic pain. Pain Res Manag. 2008;13(6):465-76.
76. Corcoran TB, Haigh F, Seabrook A, Schug SA. The quality of internet-sourced information for patients with chronic pain is poor. Clin J Pain. 2009;25(7):617-23.
77. de Boer MJ, Versteegen GJ, van Wijhe M. Patients' use of the Internet for pain-related medical information. Patient Educ Couns. 2007;68(1):86-97.
78. Sajadi KP, Goldman HB. Social networks lack useful content for incontinence. Urology. 2011;78(4):764-7.
79. Clemens JO, Calhoun EA, Litwin MS, Collins MM. Primary care physician practice patterns in the management of interstitial cystitis/painful bladder syndrome. Neurourology and Urodynamics. 2008;27(2):140-1.
80. Cline RJ, Haynes KM. Consumer health information seeking on the Internet: the state of the art. Health Educ Res. 2001;16(6):671-92.
81. Tirlapur SA, Vlismas A, Ball E, Khan KS. Nerve stimulation for chronic pelvic pain and bladder pain syndrome: a systematic review. Acta Obstet Gynecol Scand. 2013;92(8):881-7.
82. Tincello DG, Walker AC. Interstitial cystitis in the UK: results of a questionnaire survey of members of the Interstitial Cystitis Support Group. Eur J Obstet Gynecol Reprod Biol. 2005;118(1):91-5.
83. Tirlapur SA, Khan KS. Grading of evidence for bladder pain syndrome: a comparative review of study quality assessment methods. Int Urogynecol J. 2013.
84. Poldrack RA. Can cognitive processes be inferred from neuroimaging data? Trends Cogn Sci. 2006;10(2):59-63.
85. Kelley K, Clark B, Brown V, Sitzia J. Good practice in the conduct and reporting of survey research. Int J Qual Health Care. 2003;15(3):261-6.
86. Latthe PM, Braunholtz DA, Hills RK, Khan KS, Lilford R. Measurement of beliefs about effectiveness of laparoscopic uterosacral nerve ablation. BJOG. 2005;112(2):243-6.
87. Mahendru AA, Al-Taher H. Cystodistension: certainly no standards and possibly no benefits--survey of UK practice. Int Urogynecol J. 2010;21(2):135-9.
88. Keller JJ, Chen YK, Lin HC. Comorbidities of bladder pain syndrome/interstitial cystitis: a population-based study. BJU Int. 2012;110(11 Pt C):E903-9.
89. Hepner KA, Watkins KE, Elliott MN, Clemens JQ, Hilton LG, Berry SH. Suicidal ideation among patients with bladder pain syndrome/interstitial cystitis. Urology. 2012;80(2):280-5.
90. Watkins KE, Eberhart N, Hilton L, Suttorp MJ, Hepner KA, Clemens JQ, et al. Depressive disorders and panic attacks in women with bladder pain syndrome/interstitial cystitis: a population-based sample. Gen Hosp Psychiatry. 2011;33(2):143-9.
91. Clemens JQ, Calhoun EA, Litwin MS, Walker-Corkery E, Markossian T, Kusek JW, et al. A survey of primary care physician practices in the diagnosis and management of women with interstitial cystitis/painful bladder syndrome. Urology. 2010;76(2):323-8.
92. Mishra N, Meijlink J. International survey on interstitial cystitis. Int J Urol. 2003;10 Suppl:S59-60.
93. Bogart LM, Berry SH, Clemens JQ. Symptoms of interstitial cystitis, painful bladder syndrome and similar diseases in women: a systematic review. J Urol. 2007;177(2):450-6.

94. Warren JW, Diggs C, Horne L, Greenberg P. Interstitial cystitis/painful bladder syndrome: what do patients mean by "perceived" bladder pain? Urology. 2011;77(2):309-12.
95. Reitsma JB, Rutjes AW, Khan KS, Coomarasamy A, Bossuyt PM. A review of solutions for diagnostic accuracy studies with an imperfect or missing reference standard. J Clin Epidemiol. 2009;62(8):797-806.
96. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. BMJ. 2003;326(7379):41-4.
97. Liu B, Su M, Zhan H, Yang F, Li W, Zhou X. Adding a Sexual Dysfunction Domain to UPOINT System Improves Association With Symptoms in Women With Interstitial Cystitis and Bladder Pain Syndrome. Urology. 2014. Oct 11.
98. Bogart LM, Suttorp MJ, Elliott MN, Clemens JQ, Berry SH. Validation of a quality-of-life scale for women with bladder pain syndrome/interstitial cystitis. Qual Life Res. 2012;21(9):1665-70.
99. Chung SD, Liu SP, Li HC, Lin HC. Health care service utilization among patients with bladder pain syndrome/interstitial cystitis in a single payer healthcare system. PLoS One. 2014;9(1):e87522.
100. Tirlapur SA, Priest L, Wojdyla D, Khan KS. Bladder pain syndrome: validation of simple tests for diagnosis in women with chronic pelvic pain: BRaVADO study protocol. Reprod Health. 2013;10(1):61.
101. Zondervan KT, Yudkin PL, Vessey MP, Dawes MG, Barlow DH, Kennedy SH. Prevalence and incidence of chronic pelvic pain in primary care: evidence from a national general practice database. Br J Obstet Gynaecol. 1999;106(11):1149-55.
102. Royal College of Obstetricians and Gynaecologists. Initial management of chronic pelvic pain. 2012.
103. Engeler D, Baranowski AP, Elneil S, Hughes J, Messelink EJ, Oliveira P, et al. Guidelines on Chronic Pelvic Pain. 2012.
104. Howard FM. The role of laparoscopy in chronic pelvic pain: promise and pitfalls. Obstet Gynecol Surv. 1993;48(6):357-87.
105. Hebbar S, Chawla C. Role of laparoscopy in evaluation of chronic pelvic pain. J Minim Access Surg. 2005;1(3):116-20.
106. Tirlapur SA, Khan KS, Ball E. The role of laparoscopy and cystoscopy in the diagnosis and management of pelvic and bladder pain. In: Ledger, editor. Recent advances in obstetrics and gynaecology. 1. 1 ed2014. p. 1-8.
107. Wykes CB, Clark TJ, Khan KS. Accuracy of laparoscopy in the diagnosis of endometriosis: a systematic quantitative review. BJOG. 2004;111(11):1204-12.
108. Freedman J, Ganeshan A, Crowe PM. Pelvic congestion syndrome: the role of interventional radiology in the treatment of chronic pelvic pain. Postgrad Med J. 2010;86(1022):704-10.
109. Munday PE. Clinical aspects of pelvic inflammatory disease. Hum Reprod. 1997;12(11 Suppl):121-6.
110. Ahmad G, O'Flynn H, Duffy JM, Phillips K, Watson A. Laparoscopic entry techniques. Cochrane Database Syst Rev. 2012;2:CD006583.
111. Ball E, Koh C, Janik G, Davis C. Gynaecological laparoscopy: 'see and treat' should be the gold standard. Curr Opin Obstet Gynecol. 2008;20(4):325-30.
112. Okaro E, Condous G, Khalid A, Timmerman D, Ameye L, Huffel SV, et al. The use of ultrasound-based 'soft markers' for the prediction of pelvic pathology in women with chronic pelvic pain--can we reduce the need for laparoscopy? BJOG. 2006;113(3):251-6.

113. Byrne H, Ball E, Davis C. The role of magnetic resonance imaging in minimal access surgery. Curr Opin Obstet Gynecol. 2006 Aug;18(4):369-73.
114. Griffiths AN, Koutsouridou RN, Penketh RJ. Rectovaginal endometriosis -- a frequently missed diagnosis. J Obstet Gynaecol. 2007;27(6):605-7.
115. Wright J, Lotfallah H, Jones K, Lovell D. A randomized trial of excision versus ablation for mild endometriosis. Fertil Steril. 2005;83(6):1830-6.
116. Swank DJ, Swank-Bordewijk SC, Hop WC, van Erp WF, Janssen IM, Bonjer HJ, et al. Laparoscopic adhesiolysis in patients with chronic abdominal pain: a blinded randomised controlled multi-centre trial. Lancet. 2003;361(9365):1247-51.
117. Dunker MS, Bemelman WA, Vijn A, Jansen FW, Peters AA, Janss RA, et al. Long-term outcomes and quality of life after laparoscopic adhesiolysis for chronic abdominal pain. J Am Assoc Gynecol Laparosc. 2004;11(1):36-41.
118. Elcombe S, Gath D, Day A. The psychological effects of laparoscopy on women with chronic pelvic pain. Psychol Med. 1997;27(5):1041-50.
119. Levy G, Dehaene A, Laurent N, Lernout M, Collinet P, Lucot JP, et al. An update on adenomyosis. Diagn Interv Imaging. 2013;94(1):3-25.
120. Yasmin H, Bombieri L, Hollingworth J. What happens to women with chronic pelvic pain after a negative [normal] laparoscopy? J Obstet Gynaecol. 2005;25(3):283-5.
121. Offiah I, McMahon SB, O'Reilly BA. Interstitial cystitis/bladder pain syndrome: diagnosis and management. Int Urogynecol J. 2013. Aug;24(8):1243-56.
122. Latthe P, Mignini L, Gray R, Hills R, Khan K. Factors predisposing women to chronic pelvic pain: systematic review. BMJ. 2006;332(7544):749-55.
123. Butrick CW. Patients with chronic pelvic pain: endometriosis or interstitial cystitis/painful bladder syndrome? JSLS. 2007;11(2):182-9.
124. Baranowski AP, Lee J, Price C, Hughes J. Pelvic pain: a pathway for care developed for both men and women by the British Pain Society. Br J Anaesth. 2014;112(3):452-9.
125. Daniels JP, Khan KS. Chronic pelvic pain in women. BMJ. 2010;341:c4834.
126. Burton C, Sajja A, Latthe PM. Effectiveness of percutaneous posterior tibial nerve stimulation for overactive bladder: A systematic review and meta-analysis. Neurourol Urodyn. 2012. Nov;31(8):1206-16.
127. Giannantoni A, Bini V, Dmochowski R, Hanno P, Nickel JC, Proietti S, et al. Contemporary management of the painful bladder: a systematic review. Eur Urol. 2012;61(1):29-53.
128. Marcelissen T, Jacobs R, van Kerrebroeck P, de Wachter S. Sacral Neuromodulation as a Treatment for Chronic Pelvic Pain. Journal of Urology. 2011;186(2):387-93.
129. Bosch J. Electrical neuromodulatory therapy in female voiding dysfunction. Bju International. 2006;98:43-8.
130. Hassouna MM, Siegel SW, Nyeholt A, Elhilali MM, van Kerrebroeck PEV, Das AK, et al. Sacral neuromodulation in the treatment of urgency-frequency symptoms: A multicenter study on efficacy and safety. Journal of Urology. 2000;163(6):1849-54.
131. Fariello JY, Whitmore K. Sacral neuromodulation stimulation for IC/PBS, chronic pelvic pain, and sexual dysfunction. International Urogynecology Journal. 2010;21(12):1553-8.
132. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52(6):377-84.

133. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12.
134. Kennelley J. Methodological approach to assessing the evidence. Reducing racial and ethnic disparities in reproductive and perinatal outcomes: the evidence from population-based interventions. 2011. p. 7-20.
135. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.
136. Sharma M, Ansari MT, Abou-Setta AM, Soares-Weiser K, Ooi TC, Sears M, et al. Systematic review: comparative effectiveness and harms of combination therapy and monotherapy for dyslipidemia. Ann Intern Med. 2009;151(9):622-30.
137. Gokyildiz S, Kizilkaya Beji N, Yalcin O, Istek A. Effects of percutaneous tibial nerve stimulation therapy on chronic pelvic pain. Gynecol Obstet Invest. 2012;73(2):99-105.
138. O'Reilly BA, Dwyer PL, Hawthorne G, Cleaver S, Thomas E, Rosamilia A, et al. Transdermal posterior tibial nerve laser therapy is not effective in women with interstitial cystitis. Journal of Urology. 2004;172(5):1880-3.
139. Kabay S, Kabay SC, Yucel M, Ozden H. Efficiency of posterior tibial nerve stimulation in category IIIB chronic prostatitis/chronic pelvic pain: a Sham-Controlled Comparative Study. Urol Int. 2009;83(1):33-8.
140. Lee SH, Lee BC. Electroacupuncture relieves pain in men with chronic prostatitis/chronic pelvic pain syndrome: three-arm randomized trial. Urology. 2009;73(5):1036-41.
141. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ, et al. What is "quality of evidence" and why is it important to clinicians? BMJ. 2008;336(7651):995-8.
142. Brozek JL, Akl EA, Alonso-Coello P, Lang D, Jaeschke R, Williams JW, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy. 2009;64(5):669-77.
143. Baxter C, Kim JH. Contrasting the percutaneous nerve evaluation versus staged implantation in sacral neuromodulation. Curr Urol Rep. 2010;11(5):310-4.
144. Diokno AC, Burgess S, Mulholland T. Complication of the sacral neuromodulator: lead avulsion and wire disruption. J Urol. 2003;169(1):283-4.
145. Mowatt G, Glazener C, Jarrett M. Sacral nerve stimulation for faecal incontinence and constipation in adults. Cochrane Database of Systematic Reviews. 2007(3). Jul 18;(3):CD004464.
146. van de Merwe JP. Interstitial cystitis and systemic autoimmune diseases. Nat Clin Pract Urol. 2007;4(9):484-91.
147. Quillin RB, Erickson DR. Practical Use of the New American Urological Association Interstitial Cystitis Guidelines. Curr Urol Rep. 2012. Oct;13(5):394-401.
148. Bernstein AJ, Peters KM. Expanding indications for neuromodulation. Urologic Clinics of North America. 2005;32(1):59.
149. Peters K, Carrico D, Burks F. Validation of a Sham for Percutaneous Tibial Nerve Stimulation (PTNS). Neurourology and Urodynamics. 2009;28(1):58-61.
150. Butrick CW, Howard FM, Sand PK. Diagnosis and treatment of interstitial cystitis/painful bladder syndrome: a review. Journal of Women's Health (15409996). 2010;19(6):1185-94.

151. Dudding TC. Future indications for sacral nerve stimulation. Colorectal Dis. 2011 Mar;13 Suppl 2:23-8
152. van Balken MR, Vandoninck V, Messelink BJ, Vergunst H, Heesakkers J, Debruyne FMJ, et al. Percutaneous tibial nerve stimulation as neuromodulative treatment of chronic pelvic pain. European Urology. 2003;43(2):158-63.
153. Kirkham JJ, Gargon E, Clarke M, Williamson PR. Can a core outcome set improve the quality of systematic reviews?--a survey of the Co-ordinating Editors of Cochrane Review Groups. Trials. 2013;14:21.
154. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, et al. Developing core outcome sets for clinical trials: issues to consider. Trials. 2012;13:132.
155. Harman NL, Bruce IA, Callery P, Tierney S, Sharif MO, O'Brien K, et al. MOMENT - Management of Otitis Media with Effusion in Cleft Palate: protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. Trials. 2013;14:70.
156. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10.
157. Dawson TE, Jamison J. Intravesical treatments for painful bladder syndrome/ interstitial cystitis. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD006113.
158. Dimitrakov J, Kroenke K, Steers WD, Berde C, Zurakowski D, Freeman MR, et al. Pharmacologic management of painful bladder syndrome/interstitial cystitis: a systematic review. Arch Intern Med. 2007;167(18):1922-9.
159. Mangera A, Andersson KE, Apostolidis A, Chapple C, Dasgupta P, Giannantoni A, et al. Contemporary management of lower urinary tract disease with botulinum toxin A: a systematic review of botox (onabotulinumtoxinA) and dysport (abobotulinumtoxinA). Eur Urol. 2011 Oct;60(4):784-95.
160. Matsuoka PK, Haddad JM, Pacetta AM, Baracat EC. Intravesical treatment of painful bladder syndrome: a systematic review and meta-analysis. Int Urogynecol J. 2012;23(9):1147-53.
161. Mourtzoukou EG, Iavazzo C, Falagas ME. Resiniferatoxin in the treatment of interstitial cystitis: A systematic review. Int Urogynecol J Pelvic Floor Dysfunct. 2008 Nov;19(11):1571-6.
162. Srivastava D. Efficacy of sacral neuromodulation in treating chronic pain related to painful bladder syndrome/interstitial cystitis in adults. J Anaesthesiol Clin Pharmacol. 2012 Oct;28(4):428-35.
163. Tirlapur SA, Vlismas A, Ball E, Khan KS. Nerve stimulation for chronic pelvic pain and bladder pain syndrome: a systematic review. Acta Obstet Gynecol Scand. 2013 Aug;92(8):881-7.
164. Tirumuru S, Al-Kurdi D, Latthe P. Intravesical botulinum toxin A injections in the treatment of painful bladder syndrome/interstitial cystitis: a systematic review. Int Urogynecol J. 2010;21(10):1285-300.
165. Cody JD, Nabi G, Dublin N, McClinton S, Neal DE, Pickard R, et al. Urinary diversion and bladder reconstruction/replacement using intestinal segments for intractable incontinence or following cystectomy. Cochrane Database Syst Rev. 2012 Feb 15;2:CD003306
166. Vilar DG, Fadrique GG, Martin IJP, Aguado JM, Perello CG, Verdu LS, et al. Hypebaric oxygen treatment in urology. Arch Esp Urol. 2011 Nov;64(9):869-74.

167. Yokoyama T, Chancellor MB, Oguma K, Yamamoto Y, Suzuki T, Kumon H, et al. Botulinum toxin typeA for the treatment of lower urinary tract disorders. Int J Urol. 2012 Mar;19(3):202-15.
168. Bade JJ, Laseur M, Nieuwenburg A, van der Weele LT, Mensink HJ. A placebo-controlled study of intravesical pentosanpolysulphate for the treatment of interstitial cystitis. Br J Urol. 1997;79(2):168-71.
169. Barbalias GA, Liatsikos EN, Athanasopoulos A, Nikiforidis G. Interstitial cystitis: bladder training with intravesical oxybutynin. J Urol. 2000;163(6):1818-22.
170. Chen TY, Corcos J, Camel M, Ponsot Y, Tu lM. Prospective, randomized, double-blind study of safety and tolerability of intravesical resiniferatoxin (RTX) in interstitial cystitis (IC). Int Urogynecol J Pelvic Floor Dysfunct. 2005;16(4):293-7.
171. Mayer R, Propert KJ, Peters KM, Payne CK, Zhang Y, Burks D, et al. A randomized controlled trial of intravesical bacillus calmette-guerin for treatment refractory interstitial cystitis. J Urol. 2005;173(4):1186-91.
172. Payne CK, Mosbaugh PG, Forrest JB, Evans RJ, Whitmore KE, Antoci JP, et al. Intravesical resiniferatoxin for the treatment of interstitial cystitis: a randomized, double-blind, placebo controlled trial. J Urol. 2005;173(5):1590-4.
173. Peeker R, Haghsheno MA, Holmäng S, Fall M. Intravesical bacillus Calmette-Guerin and dimethyl sulfoxide for treatment of classic and nonulcer interstitial cystitis: a prospective, randomized double-blind study. J Urol. 2000;164(6):1912-5; discussion 5-6.
174. Perez-Marrero R, Emerson LE, Feltis JT. A controlled study of dimethyl sulfoxide in interstitial cystitis. J Urol. 1988;140(1):36-9.
175. Peters K, Diokno A, Steinert B, Yuhico M, Mitchell B, Krohta S, et al. The efficacy of intravesical Tice strain bacillus Calmette-Guerin in the treatment of interstitial cystitis: a double-blind, prospective, placebo controlled trial. J Urol. 1997;157(6):2090-4.
176. Kuo HC, Chancellor MB. Comparison of intravesical botulinum toxin type A injections plus hydrodistention with hydrodistention alone for the treatment of refractory interstitial cystitis/painful bladder syndrome. BJU Int. 2009;104(5):657-61.
177. Nickel JC, Moldwin R, Lee S, Davis EL, Henry RA, Wyllie MG. Intravesical alkalinized lidocaine (PSD597) offers sustained relief from symptoms of interstitial cystitis and painful bladder syndrome. BJU Int. 2009;103(7):910-8.
178. Irani D, Heidari M, Khezri AA. The efficacy and safety of intravesical Bacillus-Calmette-Guerin in the treatment of female patients with interstitial cystitis: a double-blinded prospective placebo controlled study. Urol J. 2004;1(2):90-3.
179. Lazzeri M, Beneforti P, Spinelli M, Zanollo A, Barbagli G, Turini D. Intravesical resiniferatoxin for the treatment of hypersensitive disorder: a randomized placebo controlled study. J Urol. 2000;164(3 Pt 1):676-9.
180. El-Bahnasy A, Farahat Y, El-Bendary M, Taha M, El-Damhogy M, Mourad S. A Randomized Controlled Trial of Bacillus Calmette-Guerin and Botulinum Toxin-A for the Treatment of Refractory Interstitial Cystitis. UroToday International Journal [Internet]. 2009; 2(1).
181. Manning JA, Dwyer P, Rosamilia A, Murray C, Thomas E, Beattie K. Prospective randomized double blind study of the effectiveness of botulinum a toxin for treatment of refractory painful bladder syndrome. International Urogynecology Journal. 2009;20:S87-S8.
182. van Ophoven A, Pokupic S, Heinecke A, Hertle L. A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. J Urol. 2004;172(2):533-6.

183. van Ophoven A, Rossbach G, Pajonk F, Hertle L. Safety and efficacy of hyperbaric oxygen therapy for the treatment of interstitial cystitis: a randomized, sham controlled, double-blind trial. J Urol. 2006;176(4 Pt 1):1442-6.
184. Warren JW, Horne LM, Hebel JR, Marvel RP, Keay SK, Chai TC. Pilot study of sequential oral antibiotics for the treatment of interstitial cystitis. J Urol. 2000;163(6):1685-8.
185. Thilagarajah R, Witherow RO, Walker MM. Oral cimetidine gives effective symptom relief in painful bladder disease: a prospective, randomized, double-blind placebo-controlled trial. BJU Int. 2001;87(3):207-12.
186. Sairanen J, Tammela TL, Leppilahti M, Multanen M, Paananen I, Lehtoranta K, et al. Cyclosporine A and pentosan polysulfate sodium for the treatment of interstitial cystitis: a randomized comparative study. J Urol. 2005;174(6):2235-8.
187. Sant GR, Propert KJ, Hanno PM, Burks D, Culkin D, Diokno AC, et al. A pilot clinical trial of oral pentosan polysulfate and oral hydroxyzine in patients with interstitial cystitis. J Urol. 2003;170(3):810-5.
188. Korting GE, Smith SD, Wheeler MA, Weiss RM, Foster HE. A randomized double-blind trial of oral L-arginine for treatment of interstitial cystitis. J Urol. 1999;161(2):558-65.
189. Cartledge JJ, Davies AM, Eardley I. A randomized double-blind placebo-controlled crossover trial of the efficacy of L-arginine in the treatment of interstitial cystitis. BJU Int. 2000;85(4):421-6.
190. Mulholland SG, Hanno P, Parsons CL, Sant GR, Staskin DR. Pentosan polysulfate sodium for therapy of interstitial cystitis. A double-blind placebo-controlled clinical study. Urology. 1990;35(6):552-8.
191. Gottsch HP, Yang CC, Berger RE. A pilot study of botulinum toxin A for male chronic pelvic pain syndrome. Scand J Urol Nephrol. 2011;45(1):72-6.
192. Nickel JC, Egerdie RB, Steinhoff G, Palmer B, Hanno P. A multicenter, randomized, double-blind, parallel group pilot evaluation of the efficacy and safety of intravesical sodium chondroitin sulfate versus vehicle control in patients with interstitial cystitis/painful bladder syndrome. Urology. 2010;76(4):804-9.
193. Holm-Bentzen M, Jacobsen F, Nerstrøm B, Lose G, Kristensen JK, Pedersen RH, et al. A prospective double-blind clinically controlled multicenter trial of sodium pentosanpolysulfate in the treatment of interstitial cystitis and related painful bladder disease. J Urol. 1987;138(3):503-7.
194. Parsons CL, Mulholland SG. Successful therapy of interstitial cystitis with pentosanpolysulfate. J Urol. 1987;138(3):513-6.
195. Simpson R, Thomas K, Murphy R. Outcome measures for vulval skin conditions: A systematic review of randomised controlled trials. British Journal of Dermatology. 2013;In press.
196. Tugwell P, Boers M, Brooks P, Simon L, Strand V, Idzerda L. OMERACT: an international initiative to improve outcome measurement in rheumatology. Trials. 2007;8:38.
197. Williamson P, Clarke M. The COMET (Core Outcome Measures in Effectiveness Trials) Initiative: Its Role in Improving Cochrane Reviews. Cochrane Database Syst Rev. 2012;5:ED000041.
198. Rahn DD, Abed H, Sung VW, Matteson KA, Rogers RG, Morrill MY, et al. Systematic review highlights difficulty interpreting diverse clinical outcomes in abnormal uterine bleeding trials. J Clin Epidemiol. 2011;64(3):293-300.

199. Haylen BT, Freeman RM, Swift SE, Cosson M, Davila GW, Deprest J, et al. An International Urogynecological Association (IUGA) / International Continence Society (ICS) joint terminology and classification of the complications related directly to the insertion of prostheses (meshes, implants, tapes) & grafts in female pelvic floor surgery. Int Urogynecol J. 2011;22(1):3-15.
200. Toozs-Hobson P, Freeman R, Barber M, Maher C, Haylen B, Athanasiou S, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for reporting outcomes of surgical procedures for pelvic organ prolapse. Neurourol Urodyn. 2012;31(4):415-21.
201. Smyth RM, Kirkham JJ, Jacoby A, Altman DG, Gamble C, Williamson PR. Frequency and reasons for outcome reporting bias in clinical trials: interviews with trialists. BMJ. 2011;342:c7153.
202. Dwan K, Gamble C, Williamson PR, Altman DG. Reporting of clinical trials: a review of research funders' guidelines. Trials. 2008;9:66.
203. Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R, et al. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. BMJ. 2010;340:c365.
204. Khan K. The CROWN Initiative: journal editors invite researchers to develop core outcomes in women's health. BJOG. 2014. Sep;121(10):1181-2.
205. Tirlapur SA, Riordain RN, Khan KS, Collaboration E-C. Variations in the reporting of outcomes used in systematic reviews of treatment effectiveness research in bladder pain syndrome. Eur J Obstet Gynecol Reprod Biol. 2014;180C:61-7.
206. 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. J Clin Epidemiol. 2011;64(4):383-94.
207. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;64(4):380-2.
208. Roos C, Borowiack E, Kowalska M, Zapalska A, Mol B, Mignini L, et al. What do we know about tocolytic effectiveness and how do we use this information in guidelines? A comparison of evidence grading. BJOG. 2013 Dec;120(13):1588-96
209. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. J Clin Epidemiol. 2011;64(12):1294-302.
210. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. J Clin Epidemiol. 2011;64(12):1303-10.
211. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol. 2011;64(12):1283-93.
212. O'Hare PG, Hoffmann AR, Allen P, Gordon B, Salin L, Whitmore K. Interstitial cystitis patients' use and rating of complementary and alternative medicine therapies. Int Urogynecol J. 2013. Jun;24(6):977-82.
213. Hertle L, van Ophoven A. Long-term results of amitriptyline treatment for interstitial cystitis. Aktuelle Urol. 2010;41 Suppl 1:S61-5.
214. Parsons CL, Benson G, Childs SJ, Hanno P, Sant GR, Webster G. A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosanpolysulfate. J Urol. 1993;150(3):845-8.

215. Parsons CL, Housley T, Schmidt JD, Lebow D. Treatment of interstitial cystitis with intravesical heparin. Br J Urol. 1994;73(5):504-7.
216. Erickson DR, Kunselman AR, Bentley CM, Peters KM, Rovner ES, Demers LM, et al. Changes in urine markers and symptoms after bladder distention for interstitial cystitis. J Urol. 2007;177(2):556-60.
217. Cole EE, Scarpero HM, Dmochowski RR. Are patient symptoms predictive of the diagnostic and/or therapeutic value of hydrodistention? Neurourol Urodyn. 2005;24(7):638-42.
218. Ottem DP, Teichman JM. What is the value of cystoscopy with hydrodistension for interstitial cystitis? Urology. 2005;66(3):494-9.
219. Higson RH, Smith JC, Whelan P. Bladder rupture: an acceptable complication of distension therapy? Br J Urol. 1978;50(7):529-34.
220. Malloy TR, Shanberg AM. Laser therapy for interstitial cystitis. Urol Clin North Am. 1994;21(1):141-4.
221. Rofeim O, Hom D, Freid RM, Moldwin RM. Use of the neodymium: YAG laser for interstitial cystitis: a prospective study. J Urol. 2001;166(1):134-6.
222. Zhao J, Bai J, Zhou Y, Qi G, Du L. Posterior tibial nerve stimulation twice a week in patients with interstitial cystitis. Urology. 2008;71(6):1080-4.
223. Whitmore KE, Payne CK, Diokno AC, Lukban JC. Sacral neuromodulation in patients with interstitial cystitis: a multicenter clinical trial. Int Urogynecol J Pelvic Floor Dysfunct. 2003;14(5):305-8; discussion 8-9.
224. Maher CF, Carey MP, Dwyer PL, Schluter PL. Percutaneous sacral nerve root neuromodulation for intractable interstitial cystitis. J Urol. 2001;165(3):884-6.
225. Comiter CV. Sacral neuromodulation for the symptomatic treatment of refractory interstitial cystitis: A prospective study. Journal of Urology. 2003;169(4):1369-73.
226. Steinberg AC, Oyama IA, Whitmore KE. Bilateral S3 Stimulator in Patients with Interstitial Cystitis. Urology. 2007 Mar;69(3):441-3.
227. Powell CR, Kreder KJ. Long-Term Outcomes of Urgency-Frequency Syndrome Due to Painful Bladder Syndrome Treated With Sacral Neuromodulation and Analysis of Failures. Journal of Urology. 2010;183(1):173-6.
228. Sairanen J, Leppilahti M, Tammela T, Ruutu M, Finn ICSG. Quality of life in patients with interstitial cystitis/painful bladder syndrome after treatment with DMSO, BCG, cyclosporine and pentosan polysulfate sodium. European Urology Supplements. 2007;6(2):169-.
229. Sairanen J, Hotakainen K, Tammela TL, Stenman UH, Ruutu M. Urinary epidermal growth factor and interleukin-6 levels in patients with painful bladder syndrome/interstitial cystitis treated with cyclosporine or pentosan polysulfate sodium. Urology. 2008;71(4):630-3.
230. Sairanen J, Leppilahti M, Tammela TL, Paananen I, Aaltomaa S, Taari K, et al. Evaluation of health-related quality of life in patients with painful bladder syndrome/interstitial cystitis and the impact of four treatments on it. Scand J Urol Nephrol. 2009;43(3):212-9.
231. Tirumuru S, Al Kurdi D, Latthe P. Intravesical botulinum toxin a injections in the treatment of painful bladder syndrome/interstitial cystitis: a systematic review. International Urogynecology Journal. 2010;21:S343-S4.
232. Rössberger J, Fall M, Jonsson O, Peeker R. Long-term results of reconstructive surgery in patients with bladder pain syndrome/interstitial cystitis: subtyping is imperative. Urology. 2007;70(4):638-42.

233. Propert KJ, Mayer R, Nickel JC, Payne CK, Peters KM, Teal V, et al. Followup of patients with interstitial cystitis responsive to treatment with intravesical bacillus Calmette-Guerin or placebo. J Urol. 2008;179(2):552-5.
234. McCahy PJ, Styles RA. Prolonged bladder distension: experience in the treatment of detrusor overactivity and interstitial cystitis. Eur Urol. 1995;28(4):325-7.
235. Glemain P, Rivière C, Lenormand L, Karam G, Bouchot O, Buzelin JM. Prolonged hydrodistention of the bladder for symptomatic treatment of interstitial cystitis: efficacy at 6 months and 1 year. Eur Urol. 2002;41(1):79-84.
236. Badenoch AW. Chronic interstitial cystitis. Br J Urol. 1971;43(6):718-21.
237. Tirlapur SA, Khan KS. Grading of evidence for bladder pain syndrome: a comparative review of study quality assessment methods. Int Urogynecol J. 2014;25(8):1005-13.
238. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.