available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Neuro-urology

Editorial by Antonella Giannantoni on pp. 280–281 of this issue

The Bladder Pain/Interstitial Cystitis Symptom Score: Development, Validation, and Identification of a Cut Score

Louise Humphrey [a,*], *Rob Arbuckle* [a], *Rob Moldwin* [b], *Jorgen Nordling* [c,d], *Joop P. van de Merwe* [e], *Juliette Meunier* [f], *Tim Crook* [g], *Lucy Abraham* [g]

[a] *Mapi Values, Adelphi Mill, Bollington, Cheshire SK10 5JB, United Kingdom;* [b] *Hofstra University School of Medicine, Pelvic Pain Treatment Center, The Arthur Smith Institute for Urology, North Shore-LIJ Healthcare System, New Hyde Park, NY 11040, USA;* [c] *University of Copenhagen, Copenhagen, Denmark;* [d] *Department of Urology, Herlev Hospital, Herlev, Denmark;* [e] *Department of Immunology and Internal Medicine, Erasmus MC, Rotterdam, The Netherlands;* [f] *Mapi Values, Lyon, France;* [g] *Pfizer Ltd, Walton Oaks, Walton on the Hill, Tadworth, Surrey KT20 7NS, United Kingdom*

Article info

Article history:
Accepted October 6, 2011
Published online ahead of print on October 17, 2011

Keywords:
Bladder pain syndrome
Painful bladder syndrome
Interstitial cystitis
Screener
Qualitative research
Cut score
Receiver operating characteristic (ROC) curve
Questionnaire

Abstract

Background: There is a need to develop a self-report measure that reliably identifies moderate to severe bladder pain syndrome (BPS) patients for inclusion into clinical trials to assess the efficacy of new BPS treatments.
Objective: To develop and validate a patient-reported symptom-based instrument, the Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS), for clinical trial eligibility of BPS patients.
Design, setting, and participants: Stage 1: Qualitative concept elicitation (CE) interviews were conducted with BPS patients in France ($n = 12$), Germany ($n = 12$), and the United States (US) ($n = 20$), and overactive bladder (OAB) ($n = 10$) patients in the US for comparison. Stage 2: Cognitive debriefing (CD) interviews were performed with US BPS patients ($n = 20$). Stage 3: An observational study with 99 BPS, 99 OAB, and 100 healthy participants in the US was used to perform item reduction, identify cut scores, and validate the measure. A cut score was defined using logistic regression and receiver operating characteristic curves. Psychometric properties, including test-retest reliability, were assessed.
Measurements: In addition to the BPIC-SS, the Pelvic Pain and Urgency/Frequency Patient Symptom Scale, the Interstitial Cystitis Symptom Index, a Clinician Global Impression of Severity, and a Patient Global Impression of Change were included in the observational study.
Results and limitations: In CE, reported symptoms were bladder pain, persistent urge to urinate, and high urinary frequency. In CD, 13 items were deleted, and 15 were retained. Based on validation analyses, qualitative findings, and clinical relevance, the instrument was reduced to eight items that had strong sensitivity (0.72) and specificity (0.86) with a cut score $\geq$19 to determine clinical trial inclusion. Psychometric properties were strong.
Conclusions: The BPIC-SS is a reliable, valid, and appropriate questionnaire to select BPS/interstitial cystitis patients for clinical trials.

* Corresponding author. Mapi Values, Adelphi Mill, Bollington, Cheshire SK10 5JB, United Kingdom. Tel. +1 625 577245; Fax: +1 625 5787328.
E-mail address: Louise.Humphrey@mapivalues.com (L. Humphrey).

1. Introduction

Bladder pain syndrome (BPS), also referred to as *interstitial cystitis* (IC) or *painful bladder syndrome* [1,2], is a chronic bladder condition characterized by bladder pain, increased urinary frequency, and urge to urinate [1]. Prevalence estimates vary from 67 to 230 per 100 000 women [3]; 5–10% of diagnosed patients are men [4,5].

0302-2838/$ – see back matter doi:10.1016/j.eururo.2011.10.004

BPS represents a high unmet medical need because there is a lack of effective treatments for this condition. Many challenges confront clinical trials for novel therapies. A key one is the identification of an appropriate population. Research criteria developed at the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) IC Workshop [6], which includes "objective" evidence of disease indicated by glomerulations or Hunner ulcer, are widely used to diagnose BPS. However, these criteria were devised to define a homogeneous population for research rather than diagnosis [2]. Approximately two-thirds of patients whom experienced clinicians regard as definitely or very likely to have BPS would not meet the NIDDK criteria [7,8]. Additionally, the presence of glomerulations or ulcer has no relationship to symptom severity. Consequently, the urologic community has moved towards symptom-based diagnostic criteria for BPS (alongside exclusion of confusable diseases) [1,2], although this also presents challenges due to overlapping symptoms with other conditions. For example, frequency and urge to urinate are also part of the symptom complex for overactive bladder (OAB), a condition often confused with BPS.

BPS clinical trials for investigational medicines need to recruit a confirmed BPS population with moderate to severe symptom burden, to ensure efficient statistical design and adequate benefit-risk ratio. A daily patient-completed symptom diary during a 1- to 2-wk screening period may identify this population, but those not meeting the symptom criteria may be excluded from the trial, causing additional burden to patients and investigators. Thus it is more efficient to identify these patients at initial entry to the study using a 7-d recall self-report symptom measure prior to further screening using a diary.

A review of existing patient-completed measures (eg, Pelvic Pain and Urgency/Frequency Patient Symptom Scale [PUF] and the Interstitial Cystitis Symptom Index [ICSI]) concluded that existing measures do not meet current standards for the development of patient reported measures and there is a need to develop a new patient-friendly measure with good sensitivity and specificity [9–12]. Thus the aim of the present study was to develop a new measure of BPS symptoms that could be used to screen patients into trials. The measure has been developed with patient and clinical input and using methods that meet standards for patient-completed measures [9–12].

2. Patients and methods

2.1. Inclusion and exclusion criteria

For all stages, eligible BPS patients had to have received a urologist-confirmed diagnosis of BPS with exclusion of confusable diseases (eg, OAB, endometriosis, or cervical, uterine, and ovarian cancer); experienced chronic pelvic pain (>6 mo); and reported pressure or discomfort related to the urinary bladder and one or more other urinary symptom. BPS patients had to have had a cystoscopy within 2 yr to confirm absence of other significant lower urinary tract pathology and to assess for cystoscopic features of BPS, although the presence of BPS features was not required for inclusion. Patients with significant physical or psychiatric comorbidities, confusable conditions, or passive urinary incontinence were excluded.

In stage 1, OAB patients provided information to inform how BPS symptoms differ from OAB symptoms, the most relevant confusable condition. In stage 3, OAB patients were included to evaluate the specificity and sensitivity of the measure for distinguishing between confusable conditions. In both stages, OAB patients had to have a physician-based diagnosis of OAB with symptoms ≥6 mo. OAB patients with any neurologic condition, pelvic organ prolapse, urinary tract infection (≤6 wk), or a history of BPS or bladder pain were excluded. Of note, it is not generally necessary for patients to be treatment free or under steady treatment for patient-reported outcome (PRO) development [9]. Healthy controls (HCs) in stage 3 were ≥18 yr of age, with no self-reported history of BPS or OAB (not physician verified). All participants provided written informed consent.

2.2. Stage 1: Concept elicitation and item generation

Forty-four exploratory interviews were conducted with BPS patients in France ($n = 12$), Germany ($n = 12$), and the US ($n = 20$) to gather information about experiences of BPS symptoms. Ten OAB patients in the US were interviewed to understand how BPS differs from OAB, particularly with regard to the urge to urinate. Concept elicitation (CE) interviews included open-ended questions with direct follow-up probes if key topics were not mentioned. Interviews in all stages were audiotaped and transcribed verbatim. Qualitative analysis was conducted in the original language by a native speaker. Using grounded theory methods [13] and ATLAS.ti software [14], quotes were assigned a code determined by the underlying concept and grouped into higher level concepts. Conceptual saturation was assessed [15].

Following analysis, researchers from all countries met to generate questionnaire items using a conceptual framework developed from the qualitative data. Clinical BPS experts were present to ensure the items were relevant and no clinically important symptoms were missed (authors RM, JN, and JM).

2.3. Stage 2: Cognitive debriefing

Twenty BPS patients in the US were administered the questionnaire and asked detailed questions about comprehension and relevance to ensure it adequately measured the concepts and items were understood and correctly interpreted. As per CE, analysis was conducted using ATLAS.ti software [14].

2.4. Stage 3: Development of cut scores and psychometric validation

An observational noninterventional study was conducted in the US with 300 participants (100 with BPS, 100 with OAB, and 100 HCs) to identity a cut score to differentiate between BPS and non-BPS patients and for psychometric validation. The newly developed Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS), ICSI [16], and PUF [17], as well two single-item measures (Clinician Global Impression of Severity [CGI-S] and Patient Global Impression of Change [PGI-C]), were mailed to participants for completion. All participants completed the questionnaires at baseline, and the first 50% in each patient group who returned their questionnaires were mailed a second package for completion 7–14 d later.

The sample was divided into a test sample ($n = 150$) for item reduction and scoring, and a validation sample ($n = 150$) for validation of the scores. The test-retest sample included patients in the BPIC-SS baseline sample who completed one or more BPIC-SS item at follow-up and reported "no change" on the PGI-C ($n = 89$). Table 1 details the analyses performed to determine the structure of the BPIC-SS