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Patient-Reported Outcomes in Bladder Pain Syndrome: *Qui Auget Dolorem, Auget et Scientiam* (As Pain Increases, So Increases Knowledge)

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Bladder pain syndrome/interstitial cystitis (BPS/IC) is a chronic disease characterized by bladder pain and increased urinary frequency and urge to urinate [1]. It still represents a major problem for patients and physicians because its pathogenesis is elusive and treatment remains challenging. To date, the diagnosis of BPS/IC mainly relies on symptoms because we still lack objective evidence of the disease. The need to identify patients with BPS according to symptom-based diagnostic criteria is problematic. Physicians have to take into account any confusable disease whose symptoms can overlap those in BPS patients.

A great effort has been made recently to create and apply symptom- and problem-based instruments in the diagnosis and treatment of BPS/IC. One of the most important concerns is the identification and evaluation of the appropriate population to treat. The O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI) were proposed in 1997 as outcome measures in BPS/IC. They both demonstrated an excellent ability to discriminate characteristics between patients and controls [2]. Psychometric properties of ICSI, including variability, test-retest reliability (intraclass correlation coefficient), internal consistency (the Cronbach α), construct validity responsiveness, and clinically meaningful change, were found to be helpful [3]. To date, ICSI and ICPI are recognized among the most reliable and valid instruments to identify the most prominent voiding and pain symptoms in patients with BPS/IC and the extent of the perceived problem, although they do not address dyspareunia or pelvic pain other than bladder pain [4]. Other widely distributed questionnaires for the evaluation of patients with suspected BPS/IC are the Pelvic Pain and Urgency/Frequency Patient Symptom Scale (PUF) and the University of Wisconsin Interstitial Cystitis Scale (UW-IC scale) [5,6]. The PUF questionnaire pays equal attention to pelvic pain, urinary urgency/frequency, and symptoms associated with sexual intercourse. It also correlates well with the results of the intravesical potassium sensitivity test, which is positive in about 80% of individuals with BPS/IC [5]. Similarly, the UW-IC scale shows psychometric properties analogous to other measurement instruments used in clinical research, with a Cronbach α of 0.84 [6].

In their paper, "The Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS): Development, Validation, and Identification of a Cut Score" [7], Humphrey et al discuss a new patient-friendly reported measure with good sensitivity and specificity. They began with the assumption that the existing measures do not meet the current standards aimed at identifying BPS patients eligible for clinical trials [7]. The authors developed and validated the Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS) according to the standards established by the US Food and Drug Administration for patient-reported outcomes (PRO) development [8]. The new questionnaire was found to be a reliable, valid, and appropriate instrument to select BPS/IC patients for clinical trials. A first-stage investigation offered BPS patients concept elicitation interviews to gather information about their BPS symptoms. The interviews were also offered to patients with overactive bladder syndrome (OAB) to aid in understanding how BPS differs from OAB, particularly with regard to the urge to urinate and compared with healthy controls. Following the analysis of the interviews, a cognitive debriefing was performed

by administering the questionnaire and asking detailed questions about comprehension and relevance to ensure it adequately measured the concepts and that items were understood and interpreted correctly. Finally, researchers generated a 15-item questionnaire, and cut scores and psychometric validation of the questionnaire were performed. The BPIC-SS appeared more discriminating than the PUF or the ICSI in identifying patients affected by BPS [7]. The authors accomplished an impressive body of work to generate the new questionnaire in a difficult field of research, for which they deserve congratulations.

Although the process to identify the more correct items describing patients' experience regarding pain, urge to urinate, and urinary frequency was well conducted and adhered to the psychometric properties of a PRO measure, I have some reservations about the inclusion criteria of patients in the present study. The authors classified patients as affected by BPS on the basis of "urologist-confirmed diagnosis of BPS with exclusion of confusable diseases." The inclusion of patients in the so-called BPS/IC population was thus performed without applying any criteria from any current guideline, which is not completely correct or adequate, particularly to generate a valid self-reported questionnaire. Thus the established cut-off using a receiver operating characteristic curve provided sensitivity and specificity about subjects who were only approximately diagnosed as having BPS. Another problem arises when considering the description of the results. In Table 1 the authors list the statistical methods they used to determine the structure and cut scores of the BPIC-SS and to perform the psychometric validation of the final version, but they do not show the results of their analysis [7]. Thus we have to presume the results were good or excellent and that the more appropriate items were identified and included in the new questionnaire. Finally, the BPIC-SS did not address patients' negative experience related to sexual activity, which is one of the most distressing complaints affecting quality of life in BPS patients.

I believe that some additional concepts should be included when deciding to use a self-reported measure in clinical trials to evaluate outcomes or treatment effects. A patient-reported outcome should come directly from the patient without interpretation by physicians or others about how a patient experiences a pathologic condition and its treatment [9]. This is particularly important because some effects of a pathologic condition and its therapy are known only to patients. Properly developed and evaluated PRO instruments also provide more sensitive and specific measurements of the benefits of therapies, thereby increasing the efficiency of clinical trials that measure the effects of those therapeutic interventions [9]. Inadequate instruments, in contrast, may offer wrong interpretations and conclusions. Thus PRO instruments should present with appropriate reliability and validity, which should be tested repeatedly along different phases of

clinical trials. Several guidelines are recommended for establishing sufficient evidence of reliability and validity [9]. For clinical trials, a minimum reliability threshold of 0.70 is required. Sample sizes for testing should include at least 200 cases, and results should be repeated in at least one additional sample [9]. In the case of using a PRO instrument to evaluate patients affected by a pathologic condition with pain, it should mainly consider pain and its associated, often severe, sensorial and emotional effects. To analyze pain requires a complete understanding of the mechanisms underlying tissue damage and a rigorous research process to adequately analyze any individual painful experience. Applying BPIC-SS in future clinical trials will test the real ability of the questionnaire to detect BPS symptoms and changes over time, and perhaps it will allow us to better identify effective treatments.

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