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A REVIEW OF THE DEVELOPMENT AND VALIDATION OF THE NATIONAL INSTITUTES OF HEALTH CHRONIC PROSTATITIS SYMPTOM INDEX

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ABSTRACT

Chronic nonbacterial prostatitis or chronic pelvic pain syndrome (CPPS) causes morbidity, both through symptoms and associated impairment in health-related quality of life, both of which illustrate the importance of patient-centered outcomes. Despite preliminary work by several investigators, research and clinical efforts to provide help for men afflicted with CPPS have been hampered by the absence of a widely accepted, reliable, and valid instrument to measure symptoms and quality-of-life impact. Investigators from the National Institutes of Health (NIH)-funded Chronic Prostatitis Collaborative Research Network (CPCRN) sought to remedy this problem by developing a psychometrically valid index of symptoms and quality-of-life impact in men with chronic prostatitis. This instrument, now validated in English, Spanish, German, and Korean, is known as the NIH Chronic Prostatitis Symptom Index (NIH-CPSI). It contains 13 items that are scored in 3 discrete domains: pain, urinary symptoms, and quality-of-life impact. In early studies, the NIH-CPSI has been shown to be reliable, valid, and responsive to change. Further work is needed to determine whether it performs as well in minority populations, men seeking care in nonreferral centers, and other diverse populations. UROLOGY **60** (Suppl 6A): 14–19, 2002. © 2002, Elsevier Science Inc.

Chronic nonbacterial prostatitis or chronic pelvic pain syndrome (CPPS) represents one of the greatest challenges in clinical medicine, largely because it consists of a constellation of symptoms that are subjectively evaluated by both the patient and his physician. CPPS causes morbidity both through symptoms and associated quality-of-life impairment. These components represent patient-centered outcomes on which research attention should be focused. Although related, symptoms and bother (quality-of-life impact) are theoretically and practically discrete, and must be assessed separately.[1] Thus, to diagnose and treat patients with CPPS, we need to obtain accurate measurements of those symptoms at baseline and longitudinally with or without treatment. Before we can develop or select appropriate instruments, we must have a clear understanding of patients' own perceptions of their symptoms and the impact of these symptoms.

The traditional goal in the treatment of genitourinary diseases has been to maximize survival. However, in patients with non–life-threatening conditions, symptoms and quality of life take on paramount importance. Hence, the various components of well-being must be addressed when treating individual patients with CPPS and when conducting clinical trials.[2] Recently, there has been greater interest in patient-centered endpoints; the current popularity of medical outcomes and quality-of-life assessment is based in part on the World Health Organization's long-standing definition of health as not merely the absence of disease, but a state of complete physical, psychologic, and social well-being.[3]

In 1996, Wenninger *et al.*[4] used the sickness impact profile (SIP) and a separate series of nonvalidated pain questions to profile the health-related quality-of-life (HRQOL) impact of the disorder in 39 men clinically diagnosed with CPPS (chronic genital pain with no evidence of malignancy or infection). Mean total SIP scores placed CPPS patients in the same range as those with myocardial infarction, angina, or Crohn's disease. Multiple lo-

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gistic regression suggested that the SIP physical summary scale explained 43% of the variance in overall HRQOL. The informal pain items explained 65% of the variance in overall HRQOL.

Other research has suggested that psychosocial problems are associated with impairment in overall HRQOL in men with CPPS. In 1981, Keltikangas-Jarvinen *et al.*[5] assessed mental health in CPPS patients with 2 well-validated instruments: the Minnesota Multiphasic Personality Inventory and the Beck Depression Inventory. Of 42 men in the sample, nearly 66% reported anxiety and >50% reported depression. Longitudinal follow-up evaluation of the same sample revealed that anxiety and stress increased with time, while overall physical well-being and social functioning decreased.[6] Subsequent studies by Egan and Krieger[7] and de la Rosette *et al.*[8] have confirmed that men with CPPS are more likely to show signs of depression and impairment in their intimate relationships.

Several investigators have derived lists of patient symptoms in CPPS. Barbalias[9] reported a summary of patient-derived complaints in 60 men with prostatodynia, in whom he performed video pressure urodynamic assessments. Patients in his sample complained of penile pain (45%), perineal discomfort (40%), suprapubic discomfort (30%), urinary frequency (25%), and orchialgia (25%). Although he made no significant neurourologic observations, he did find his patients' symptoms comparable to a historic series of men with pyriformis syndrome, levator anispasm syndrome, proctalgia fugax, and coccygodynia,[10] all of which are likely similar, if not identical, to what we presently call CPPS.

In 1993, de la Rosette *et al.*[11] continued the process of defining patients' experience with prostatitis by collecting another inventory of symptoms. This study combined men with chronic bacterial prostatitis and those with CPPS to look for frequent presenting symptoms. The investigators produced an extensive list of complaints in this population. Common symptoms included penoscrotal pain (49%), urinary frequency (39%), stranguria (36%), dribbling (35%), suprapubic pain (36%), and perineal and groin pain (22%). Although this project did not attempt to develop a symptom score or HRQOL impact index, it laid important groundwork by documenting symptoms in a large sample.

In a more recent study, Alexander and Trissel[12] added a modern technologic twist by surveying Internet users to develop an inventory of symptoms. The investigators posted the American Urological Association (AUA) Symptom Index[13] (a validated measure of obstructive voiding symptoms), several questions about sexual practices, and several family history items on their Web site. They also collected an inventory of symptoms and a measure of depression. A predominantly white (95%) sample of 161 subjects responded to the 54-item electronic questionnaire. Common symptoms included nonurinary pelvic pain (80%), urinary frequency (71%), fatigue (39%), lower back pain (38%), aggravation by urination (37%), and myalgias (32%). More common symptoms were associated with greater severity. Of the respondents, 78% reported depression from their symptoms, whereas very few reported associated erectile difficulties. Although the sample was highly selected and not generalizable, the exploratory work accomplished by the investigators will be valuable in directing the current project.

In 1994, Neal and Moon[14] reported data from a small pilot study, in which they set out to develop a symptom score among 25 patients with nonbacterial prostatitis. Their instrument consisted of the Boyarsky symptom score[15] (a historic index of primarily obstructive urinary symptoms), which was enhanced with 4 additional questions thought to reflect issues of concern to men with CPPS. These 4 questions included issues of (1) perineal/thigh pain, (2) orchialgia, (3) abdominal/inguinal pressure, and (4) urethral discomfort. Their 4-level response set covered both frequency and intensity, including (1) no pain, (2) occasional pain, (3) usual but does not stop activity, and (4) incapacitating. The questions combined assessment of frequency and impact into a single item for each symptom. They reported an internal consistency level of 0.77, suggesting that their 4 items addressed similar concepts. They also compared scores from their CPPS patients with those of 20 men in a benign prostatic hyperplasia (BPH) study and 10 men presenting for vasectomy. Their instrument showed high sensitivity and specificity levels at discriminating patients with CPPS from those with BPH and those presenting for vasectomy. They went on to use this pilot-tested instrument to measure responses to α-blocker therapy for CPPS and showed that the 4 questions did demonstrate the ability to discriminate symptomatic change among responders. Their data showed for the first time that the symptoms of men with CPPS could be "quantified and differentiated from those of normal controls and men with BPH." This important early study laid a foundation for subsequent formal development of a CPPS symptom score and HRQOL impact index. These items are presently being pilot tested in the NIH-funded Medical Treatment of Prostate Symptoms (MTOPS) Study, an ongoing investigation of pharmacologic therapies for obstructive urinary symptoms. Because this questionnaire involved only a handful of subjects, and physicians, not patients, created its 4 additional items, no conclusions can

be drawn about its validity. Test-retest reliability for these items has not been assessed, so no conclusions can be drawn about the reproducibility of the data. Nonetheless, this effort was an important first step toward creating a CPPS symptom index (see Figure 1).

In 1996, Nickel[16] presented a new symptom index, pilot tested in 20 Canadian men with a clinical diagnosis of chronic nonbacterial prostatitis and 30 men with clinical BPH. This 20-item, self-administered instrument included 2 scales designed to measure the frequency (10 items) and the severity (10 items) of various symptoms. In the frequency questionnaire, the investigators altered the AUA Symptom Index by replacing its obstructive symptoms with genital pain symptoms that they obtained from the literature. In the severity questionnaire, the investigators listed the same symptoms and applied visual analog scales to estimate intensity of the symptoms. They also measured global HRQOL with a single item that has been used to estimate quality-of-life impact among men with BPH. This questionnaire was written by the investigators during a study of transurethral microwave therapy for CPPS. It appears to have germane content, but it was not developed with direct patient input, nor was it pilot tested, nor were reliability or validity statistics reported.

More recently, Brahler *et al.*[17] proposed the Giessen Index, an 18-item symptom checklist tested in 95 men with clinical prostatitis and in a control group. The checklist included various types of pelvic pain, itching, orchialgia, and voiding complaints. Patients rated the intensity of each symptom in a range from 0 to 4, yielding total scores of 0 to 72. The investigators reported internal consistency values of 0.81 to 0.84 in the 2 groups and found that median scores differed significantly between the 2 groups (10.6 vs 2.3, $p < 0.001$). The low mean score among men with prostatitis raises concerns that this proposed instrument may have a significant "floor effect," in which interpretation of scores is hampered by a severely skewed distribution. Validity and test-retest reliability were not reported in this abstract.

In summary, the previous literature in symptom assessment and HRQOL among men with CPPS primarily comprised studies that simply listed common symptoms. Only in occasional studies have investigators made an effort to define a set of disease-targeted items that might be combined into a rough symptom index. General HRQOL instruments applied to this population reveal that both the physical and psychosocial domains of general HRQOL appear to be impacted. No significant effort has been made to determine which existing general HRQOL instrument might be most appropriate for this population. Nonetheless, these works provided valuable insights into patients' perceptions of their symptoms and established a starting point on which we based our formal development and validation study for a reliable and valid symptom index and HRQOL impact index.

Research and clinical efforts to provide help for men with CPPS have been hampered by the absence of a widely accepted, reliable, and valid instrument to measure symptoms and quality-of-life impact. Investigators from the NIH-funded Chronic Prostatitis Collaborative Research Network (CPCRN) sought to remedy this problem by developing a psychometrically valid index of symptoms and quality of life impact in men with chronic prostatitis.[18] This instrument, now validated in English, Spanish, German, and Korean, is known as the NIH Chronic Prostatitis Symptom Index (NIH-CPSI). Its development is briefly reviewed below and is described in more detail in Reference 18.

After completing a structured literature review (see above), which provided a foundation for the new instrument, the CPCRN investigators conducted a series of focus groups with chronic prostatitis patients at 4 centers in North America; this identified the most important symptoms and impacts of the condition. Results of the focus groups were used to create the initial draft of 55 questions. This draft underwent formal cognitive testing with chronic prostatitis patients in the same centers. After expert panel review, a revised 21-item draft then underwent formal validation testing in a diverse group of men with chronic prostatitis and in 2 control groups—patients with BPH and healthy control subjects. Based on this validation study, the NIH-CPSI was finalized (Figure 1).

The analysis yielded an index of 9 items that address 3 different aspects of the chronic prostatitis experience. The primary component is pain, which is captured in 4 items that focus on location, severity, and frequency. Urinary function, another important component of patients' symptoms, is captured in 2 items: irritative and obstructive. Quality-of-life impact is captured with 3 additional items that ask about the effect of symptoms on daily activities. The 9 items have high test-retest reliability ($r = 0.83$ to 0.93) and internal consistency ($\alpha = 0.86$ to 0.91). All but the urinary items discriminate well between men with and without chronic prostatitis.

In summary, the NIH-CPSI provides a valid outcome measure for men with chronic prostatitis. It is psychometrically robust, easily self-administered, and highly discriminative. Since its publication, it has been useful as a primary endpoint in clinical trials as well as in clinical practice.

The study had several limitations. Patients in the validation study were predominantly white, edu-

NIH-Chronic Prostatitis Symptom Index (NIH-CPSI)

Pain or Discomfort

1. In the last week, have you experienced any pain or discomfort in the following areas?

	Yes	No
a. Area between rectum and testicles (perineum)	❑1	❑0
b. Testicles	❑1	❑0
c. Tip of the penis (not related to urination)	❑1	❑0
d. Below your waist, in your pubic or bladder area	❑1	❑0

2. In the last week, have you experienced:

	Yes	No
a. Pain or burning during urination?	❑1	❑0
b. Pain or discomfort during or after sexual climax (ejaculation)?	❑1	❑0

3. How often have you had pain or discomfort in any of these areas over the last week?

❑0 Never
❑1 Rarely
❑2 Sometimes
❑3 Often
❑4 Usually
❑5 Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?

❑ 0 NO PAIN ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8 ❑ 9 ❑ 10 PAIN AS BAD AS YOU CAN IMAGINE

Urination

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?

❑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

6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?

❑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

Impact of Symptoms

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

❑0 None
❑1 Only a little
❑2 Some
❑3 A lot

8. How much did you think about your symptoms, over the last week?

❑0 None
❑1 Only a little
❑2 Some
❑3 A lot

Quality of Life

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

❑0 Delighted
❑1 Pleased
❑2 Mostly satisfied
❑3 Mixed (about equally satisfied and dissatisfied)
❑4 Mostly dissatisfied
❑5 Unhappy
❑6 Terrible

Scoring the NIH-Chronic Prostatitis Symptom Index Domains

Pain: Total of items 1a, 1b, 1c,1d, 2a, 2b, 3, and 4 = _____

Urinary Symptoms: Total of items 5 and 6 = _____

Quality of Life Impact: Total of items 7, 8, and 9 = _____

FIGURE 1. *The National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI).*

cated, and sought care in academic referral centers, potentially making the NIH-CPSI less generalizable to the general population of men with chronic prostatitis. As the NIH-CPSI is used in a variety of settings, data should be collected to determine whether it performs as well in minority popula-

tions, men seeking care in nonreferral centers, and other diverse populations. Moreover, although the CPCRN investigators worked to develop the best possible index of symptoms and impact for CPPS, further refinements may be necessary. As in all newly validated instruments, these issues will be resolved with greater experience in using the NIH-CPSI in populations of color, less affluence or education, and in those with low literacy.

The NIH-CPSI is likely to function best if adopted widely as a standard instrument in the evaluation of men with chronic prostatitis. With a uniformly accepted outcome measure, patients, clinicians, and researchers can begin speaking the same language when assessing the natural history of this disease and its response to various treatments.

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DISCUSSION FOLLOWING DR. LITWIN'S PRESENTATION

Anthony J. Schaeffer, MD (Chicago, Illinois): Is it axiomatic that a good index can be used to judge response to therapy or is that not a given?

Mark S. Litwin, MD, MPH (Los Angeles, California): I would say it is axiomatic that a good index should be able to judge response to therapy. If the disease under study is primarily manifested by symptoms, then in fact, symptoms ought to be the primary outcome measure, provided those symptoms are reliably and validly measured by the instrument.

J. Curtis Nickel, MD (Kingston, Ontario, Canada): We have now used this index in clinical trials in 540 patients outside the first Chronic Prostatitis Collaborative Research Network (CPCRN) trial. We have all of this raw data, and we are finding that this instrument may not be as responsive as we would like it to be. Patients tell us that they have significant improvement on a subjective global assessment, but the scores of these same patients decrease only a couple of points on the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), which statistically is not meaningful. If you use the impact on quality of life as a measure, the change with treatment can be phenomenal. When you compare it with the total score or pain score, the improvement seems really minimal. As new information becomes available from ongoing clinical trials, we will want to look at this responsiveness issue again and see how the NIH-CPSI scores correlate with the patients' own perception of global improvement.

Dr. Litwin: When we started, we did not yet have data on the responsiveness to change of the CPSI. When you do a study, you have to pick a primary outcome. I would disagree that we can just change the primary outcome at this point. The CPCRN study was powered to use total score, 0 to 43, adding all the domains, pain, urination, and quality of life together.