Development and Use of a Validated Outcome Measure for Chronic Prostatitis

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Prostatitis is frequently diagnosed by urologists and primary care physicians. Nearly 2 million cases of prostatitis were diagnosed annually by urologists and primary care physicians between 1990 and 1994 [1]. Over this period, 8% of urology office visits and 1% of primary care visits were related to prostatitis. Prostatitis is the most common urologic diagnosis in men younger than 50 years of age and the third most common urologic diagnosis in men older than 50 years.

Despite its frequency, prostatitis has been ill defined and poorly understood until recently. An important step in improving the diagnosis and treatment of prostatitis was taken in 1998 with the establishment of the National Institutes of Health (NIH) consensus classification of prostatitis syndromes (Table 1). This system includes 4 categories of prostatitis based on symptoms, chronicity, infection, and inflammation [2]. Of these categories, chronic abacterial prostatitis (category III) is the most common, accounting for more than 90% of cases of prostatitis. Chronic prostatitis is characterized by a symptom complex of pelvic pain and lower urinary tract and sexual symptoms. These symptoms, rather than objective clinical measures, are the cause of morbidity in chronic prostatitis and are the reason men seek medical care. A standardized instrument that measures chronic prostatitis symptoms and their impact on daily life is an important clinical tool for physicians assessing and following patients with chronic prostatitis. This paper briefly reviews the NIH categories of prostatitis, describes the development of a valid instrument for measuring symptoms and quality of life (QOL) in patients with chronic prostatitis, and discusses the instrument’s potential applications.

Classification of Prostatitis

The prostatitis syndromes are defined by bacterial and leukocyte localization to prostate-specific specimens and a reasonably consistent symptom complex. Category I, or acute bacterial prostatitis, is characterized by a febrile illness caused by an acute generalized infection of the prostate gland. Physicians have little trouble diagnosing patients presenting with acute bacterial prostatitis, and treatment with antibiotics (duration of 2 to 3 weeks) is generally successful. Category II, or chronic bacterial prostatitis, is characterized by either constant or intermittent genitourinary pain and irritative voiding symptoms associated with the localization of uropathogenic bacteria (gram-negative Enterobacteriaceae and enterococci) to prostate-specific specimens (ie, expressed prostatic secretion and post-prostatic-massage urine, and/or semen). Patients with chronic bacterial prostatitis frequently have recurrent lower urinary tract infections. Treatment involves long courses of antibiotics (4 to 12 weeks), usually trimethoprim-sulfamethoxazole or fluoroquinolones because these achieve adequate concentrations in prostate tissues and ducts. Acute and chronic bacterial prostatitis are the least common types of prostatitis, with less than 5% of patients diagnosed with a prostatitis syndrome having a definite bacterial etiology.

Category III, chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), is characterized by genitourinary pain symptoms that are present for at least 3 months and are not associated with either recurrent urinary tract infections or uropathogenic bacteria detected by standard methodology. CP/CPPS is divided into an inflammatory subtype (category IIIA, or chronic nonbacterial prostatitis) and a noninflammatory subtype (category IIIB, or prostatodynia) based on the presence or absence of leukocytes in prostate-specific specimens. Patients with CP/CPPS have genitourinary and/or pelvic pain, frequently have irritative and obstructive voiding symptoms, and occasionally have sexual dysfunction. The etiology of CP/CPPS is unclear but may involve a microbiologic, anatomic, physiologic, immunologic, or neurogenic trigger or event that eventually results in a symptom complex involving localized pain and voiding symptoms, with or without demonstrable inflammation. The majority of patients diagnosed with prostatitis present with CP/CPPS. Few evidence-based treatment strategies are available for patients presenting...
with this condition. Frustrated physicians tend to prescribe antibiotics despite negative cultures, with variable anecdotal success rates. Other modalities of therapy specific for pain, inflammation, or voiding disturbances are also employed, and anecdotal experience, case reports, clinical series, and a number of small controlled studies reported in the literature provide some support for each of these therapies [3]. The most commonly used therapies for CP/CPPS are listed in Table 2. Category IV, asymptomatic inflammatory prostatitis, defines a group of asymptomatic patients who are noted to have either bacteria or inflammation incidentally detected in prostate specimens (expressed prostatic secretion, post–prostatic-massage urine specimen, semen, or histologic tissue preparations). This category is most commonly diagnosed in patients being investigated for infertility, benign prostatic hyperplasia (BPH), or prostate cancer. The etiology and significance of prostate inflammation and/or infection in asymptomatic patients is unknown.

### Objective Outcome Measures in Prostatitis

The objective outcome measure for patients with acute bacterial prostatitis is the resolution of fever and eradication of bacteria in the urine. This outcome is almost universally achieved in properly diagnosed and treated patients. In chronic bacterial prostatitis, the goal of antibiotic therapy is eradication of bacteria in prostate-specific specimens, which is achieved in 30% to 80% of patients treated with long courses of antibiotics. Unfortunately, improvement in this parameter is not always associated clinically with improvement in the symptom complex; however, this association has not been well studied because researchers have employed the microbiology outcome measure only.

Because uropathogenic bacteria are not detected in patients with CP/CPPS, a microbiologic parameter is unhelpful. In addition, the differentiation of patients into inflammatory and noninflammatory subtypes with similar clinical presentations has not been validated, and the presence, concentration, or change in number of leukocytes in these particular specimens has not been correlated with either the presenting or changing prostatitis-related symptoms. Therefore, although the presence, absence, or total number of leukocytes in prostate-specific specimens is a reasonable objective outcome measure, the clinical relevance of this parameter remains unknown.

### Symptom Assessment in CP/ CPPS

The morbidity of CP/CPPS results from the symptom complex of pain and urinary and sexual symptoms. It is this constellation of symptoms, rather than any objective clinical parameter, that leads men to seek medical care. Urologists have become familiar with the importance of using instruments that measure health-related QOL and symptoms in patients presenting with other symptom-oriented urologic conditions. Validated instruments commonly employed by urologists include the International Prostate Symptom Severity Index (IPSS, also known as the American Urological Association symptom severity index) for BPH [4], the BPH impact index and the symptom problem index [5], the sexual function symptom index [6], and the interstitial cystitis symptom and problem indices [7].

A number of prostatitis indices have been developed independently by various international research groups [8–12], and 3 of these symptom indices have proven particularly useful in clinical research in prostatitis. Neal and Moon [8] developed a

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**Table 1. National Institutes of Health Classification of the Prostatitis Syndromes**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Presentation</th>
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<tbody>
<tr>
<td>Category I</td>
<td>Acute infection of the prostate gland</td>
<td>Acute febrile illness associated with perineal and suprapubic pain, dysuria, and obstructive voiding symptoms</td>
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<tr>
<td>Category II</td>
<td>Chronic infection of the prostate gland</td>
<td>Recurrent urinary tract infections with pain and voiding disturbances</td>
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<tr>
<td>Category III</td>
<td>Chronic genitourinary pain in the absence of uropathogenic bacteria localized to the prostate gland employing standard methodology</td>
<td>Chronic perineal, suprapubic, testicular, penile, or ejaculatory pain associated with variable dysuria and obstructive and irritative voiding symptoms</td>
</tr>
<tr>
<td>Category IIIA</td>
<td>Significant number of white blood cells in expressed prostatic secretions, post-prostatic-massage urine sediment, or semen</td>
<td>See above (category III)</td>
</tr>
<tr>
<td>Category IIIB</td>
<td>Insignificant number of white blood cells in expressed prostatic secretions, post-prostatic-massage urine sediment, or semen</td>
<td>See above (category III)</td>
</tr>
<tr>
<td>Category IV</td>
<td>White blood cells (and/or bacteria) in expressed prostatic secretions, post-prostatic-massage urine sediment, semen, or histological specimens of prostate gland</td>
<td>Asymptomatic</td>
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4-question instrument for use in an open-label study of alpha blockade for treatment of chronic prostatitis. This first attempt at a symptom score was validated during an uncontrolled therapeutic trial, and although the validation methodology was not ideal and was much too biased, this was the first published symptom score in prostatitis and the 4 questions covered important domains of this condition. Kreiger and colleagues developed a 21-item instrument to assess pain, sexual dysfunction, and voiding symptoms in a standardized fashion [9]. The clinical validation process included control patients with BPH and sexual dysfunction, and the authors did discover that pain (various locations and types) was the predominant symptom; however, the psychometric properties of the instrument and the validation process were not presented. This index has not been used in clinical trials but has proven important in providing an inventory of pain and voiding and sexual dysfunction symptoms experienced by patients with chronic prostatitis. Nickel and Sorensen [10] developed the 10-item symptom frequency questionnaire and a 10-item symptom severity index for use in a Canadian randomized double-blind sham-controlled trial of transurethral microwave thermal therapy for chronic prostatitis. These symptom indices were developed with a control group of asymptomatic volunteers. Although the sample size was small, the investigators employed and described an appropriate validation process. These 2 symptom indices have proven useful in ongoing multicenter clinical research studies.

Quality of Life in CP/CPPS

The symptom complex associated with chronic prostatitis significantly affects patients’ ability to function and their general QOL. Survey studies and QOL evaluations have improved our understanding of the chronic prostatitis experience. De la Rosette and colleagues [13] surveyed Dutch urologists and general practitioners on their diagnosis and treatment of prostatitis syndromes. Moon [14] similarly surveyed Wisconsin urologists and general practitioners, while Nickel and colleagues [15] surveyed Canadian urologists on the diagnosis and treatment of chronic prostatitis. Alexander and Trissel [16] employed a 54-item questionnaire to survey men on the Internet at prostateitis support groups. Wenninger and colleagues [17] used the symptom-impacts profile of a generic health measure in 39 patients with chronic prostatitis and noted that the QOL of patients with chronic prostatitis was similar to that of patients with unstable angina, acute myocardial infarction, or active Crohn’s disease. McNaughton Collins and colleagues [18] employed health-related QOL measures in 218 men diagnosed with CP/CPPS. The QOL for these patients was worse than that for the most severely ill subgroups of patients with diabetes and congestive heart failure.

Development of the NIH Chronic Prostatitis Symptom Index

In 1997, the National Institute of Diabetes and Digestive and Kidney Diseases funded the Chronic Prostatitis Collaborative Research Network (CPCRN). This research network is a multi-institutional, collaborative group whose purpose is to establish the definition of prostatitis and its etiology, describe its natural history, develop validated outcome measures, and determine improved treatment strategies. The institutions involved in the research network are Brigham and Women’s Hospital/Massachusetts General Hospital, Boston, MA; Queen’s University, Kingston, ON, Canada; Northwestern Memorial Hospital, Chicago, IL; Temple University Hospital, Philadelphia, PA; University of California, Los Angeles, CA; University of Maryland Medical System, Baltimore, MD; and University of Pennsylvania, Philadelphia, PA.

Investigators from each of these 6 institutions collaborated on the development and validation of the NIH Chronic Prostatitis Symptom Index (NIH-CPSI). The goal in developing a chronic prostatitis symptom index was to create a short, practical, self-administered, clinically sensible tool with excellent psychometric properties to capture the frequency and severity of symptoms related to chronic prostatitis as it is diagnosed and treated in the course of usual care among urologists and primary care physicians. The index was also designed to capture how the condition affects various domains of patients’ lives. The initial step in developing the instrument was the generation of statements (items)
The most immediately relevant areas of the chronic prostatitis group were compared with analysis of variance. Regression analysis was used to determine the best scoring algorithm [19]. The primary component of the chronic prostatitis index includes pain, urinary symptoms, sexual symptoms, and overall QOL impact. The 21-question instrument underwent formal validation testing along with the 7-item IPSS and 4 demographic items on age, ethnicity, highest level of education, and year of diagnosis of chronic prostatitis. At each site, the principle investigator identified patients with symptoms suggestive of prostatitis and 2 control groups: men with BPH and men without any urologic symptoms. Test-retest reliability was assessed by sending an identical questionnaire to patients in the chronic prostatitis group 2 weeks after they had completed the first questionnaire. Survey responses were coded and analyzed with descriptive statistics, cross tabulations, and univariate analysis. The distribution of answers and means of cross groups was compared using chi-square statistics for categorical variables and t test for continuous variables. Item associations and test-retest reliabilities were calculated using Pearson’s product-moment correlations. Internal consistency for the index and its domains was calculated with Cronbach’s alpha-coefficient. Responders and nonresponders to the retest questionnaire were compared with analysis of variance. Regression analysis was used to determine the best scoring algorithm [19].

Based on the validation testing, the draft was revised into its final format containing the 9 items that performed best in the samples, discriminated among the groups, and captured the most immediately relevant aspects of the prostatitis experience (Figure) [19]. The primary component of the index is pain, which was captured in 4 questions that focused on anatomic areas, frequency, and severity of pain symptoms. Urinary function was captured in 2 questions, 1 irritative and 1 obstructive. The impact of symptoms on QOL was captured in 2 questions, while general QOL was adequately described by a single question.

The 9 questions have high test-retest reliability (r = 0.83–0.93) and internal consistency (alpha = 0.86–0.91). All but the urinary symptoms discriminated well between men with chronic prostatitis and men without chronic prostatitis.

The scores were determined by weighting the items in a regression analysis that maximized the explained variance and symptom impact (0.76) and overall QOL (0.73). Scores for pain location (0–6), pain frequency (0–5), and pain severity (0–10) yield a pain domain score ranging from 0 to 21. The 2-item measure of urinary symptoms yields a score from 0 to 10, mirroring the scoring algorithm of the IPSS. The 3 items that measure symptom impact and overall QOL were summed to create the third domain, which ranges from 0 to 12. The total score of the symptom index is the sum of the pain, urinary symptoms, and QOL impact (range, 0–43). Higher scores in both the total score and in all 3 domains indicate worse outcomes. Efforts are presently underway to develop a validated translation of the index in other languages, including Spanish, Korean, French, German, and Finnish.

The Index as an Outcome Parameter in Clinical Studies

Natural History Studies
The NIH has funded the CPCRN to recruit a cohort of more than 400 patients with abacterial chronic prostatitis (category III) and to follow the natural history of these patients over a 3-year period. In addition to studying and evaluating multiple epidemiologic parameters, socioeconomic measures, and other health-related outcome indices, the CPCRN is employing the NIH-CPSI as a measure of symptom progression over time. The symptom index has been administered at baseline, 3 months, and 6 months, and will be administered every 6 months for a total of 3 years. To date, more than 350 patients have been enrolled. The index has been reflective of the patients’ symptom progression over time and has correlated well with other health care parameters and indices (treatment, global assessments, and QOL). To better define the condition of CP/CPPS, an age-matched cohort of asymptomatic patients with no history of prostatitis is being recruited. These patients will be subjected to similar clinical evaluation, including the symptom index, as the patients enrolled in the natural history cohort study. These studies are ongoing, and although results are unavailable, the instrument appears to be highly appropriate for measuring symptom severity and evolution of symptoms over time. Data are now available from these studies to analyze the scoring algorithms further, to define clinically significant change, and to stratify scores as mild, moderate, or severe. This analysis will soon be available and will improve the utility of this outcome measure.

Treatment Studies
At this early stage, less is known about the responsiveness of the NIH-CPSI in response to treatment. Shoskes et al [20] was one of the first to employ this symptom outcome measure to evaluate the efficacy of a bioflavonoid (quercetin).
PROSTATITIS SYMPTOM INDEX

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?
   - Area between rectum and testicles (perineum) [Yes | No]
   - Testicles [Yes | No]
   - Tip of the penis (not related to urination) [Yes | No]
   - Below your waist, in your pubic or bladder area [Yes | No]

2. In the last week, have you experienced:
   - Pain or burning during urination? [Yes | No]
   - Pain or discomfort during or after sexual climax (ejaculation)? [Yes | No]

3. How often have you had pain or discomfort in any of these areas over the last week?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Usually
   - Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?
   - Pain Scale: 10 Points: NO PAIN = 0, PAIN AS BAD AS YOU CAN IMAGINE = 10

Uibration

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?
   - Not at all
   - Less than 1 time in 5
   - Less than half the time
   - About half the time
   - More than half the time
   - Almost always

6. How often have you had to urinate again less than 2 hours after you finished urinating, over the last week?
   - Not at all
   - Less than 1 time in 5
   - Less than half the time
   - About half the time
   - More than half the time
   - 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?
   - None
   - Only a little
   - Some
   - A lot

8. How much did you think about your symptoms, over the last week?
   - None
   - Only a little
   - Some
   - 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?
   - Delighted
   - Pleased
   - Mostly satisfied
   - Mixed (about equally satisfied and dissatisfied)
   - Mostly dissatisfied
   - Unhappy
   - 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

compared to placebo in a small randomized controlled trial. He compared 15 patients treated with 4 weeks of quercetin with 13 patients treated with placebo and noted an average decrease in total index scores from 21.0 at baseline to 13.1 at 4 weeks for the treatment group and from 20.2 to 18.8 in the placebo group. Sixty-seven percent of patients in the treatment group had at least a 25% decrease in symptom score compared with 20% in the placebo group. This study was small and of short duration, and while the significance of a 25% decrease in total score is uncertain, the symptom index did appear to be responsive to treatment effect.

In an uncontrolled trial, Nickel et al [21] employed a NIH-CPSI pain score (range, 0 to 21) derived from similarly worded (and scored) questions from the older symptom severity index and symptom frequency questionnaire [10] to assess the efficacy of pentosan polysulfate in category IIIA CP/CPPS. This pain score decreased from 14.5 at baseline to 9.2 at 6 months (54% had a ≥25% decrease in score), and its magnitude of decrease correlated with the decrease in the symptom frequency questionnaire and symptom severity index as well as QOL and global patient assessments.

The quasi-NIH-CPSI pain score also appeared to be responsive in a multicenter Canadian study [22] evaluating the effect of 12 weeks of antibiotic therapy on the symptoms of patients presenting with category II, IIIA, and IIIB chronic prostatitis. In the various prostatitis categories, the pain scores decreased from 12 to 14 (various categories of chronic prostatitis) at baseline to 6 to 8 at 24 weeks; 57% of patients across all categories had a decrease in score of at least this amount. Again, the magnitude of decrease in the NIH-CPSI pain score correlated with that seen in the symptom frequency questionnaire, symptom severity Index, QOL assessment, and patient global assessments.

The largest randomized placebo-controlled trial in prostatitis recently compared 2 doses of rofecoxib (a COX-2 inhibitor) to placebo. This study employed the NIH-CPSI as an outcome measure (manuscript in preparation). In this study of more than 150 patients, the change in the symptom index correlated with QOL and patient global assessment changes. However, patients’ global assessments appeared to be more responsive to therapy than did the index scores.

The NIH-CPCRN begins its first randomized placebo controlled trial in CP/CPPS in the first quarter of 2001. This trial will evaluate the 2 most commonly used therapies for the treatment of this condition (antibiotics and alpha blockers), alone or in combination compared to placebo. The primary outcome measure will be the symptom index.

Epidemiology Studies
The index was developed to be more evaluative than discriminative, although it does have robust discriminative ability among chronic prostatitis, BPH, and healthy controls. One must be cautious in using the index as a screening or diagnostic tool since some of the symptoms captured by the index will certainly be due to conditions other than chronic prostatitis. However, the index does characterize the experience of patients with chronic prostatitis, and it can be used to identify “prostatitis-like” symptoms. To date, our epidemiologic knowledge of prostatitis has relied on studies employing diagnostic coding, data banks, physician diagnosis, and physician surveys. These epidemiologic studies are limited by the unreliability of physician diagnosis and coding of prostatitis and by physicians’ short- and long-term recollection.

Nickel et al [23] employed the NIH-CPSI in a population-based study to determine the prevalence of prostatitis-like symptoms in the general population of men. Since the pain items seem to be the most discriminatory symptoms, the pain domain (0 to 21) was employed to determine the prevalence of prostatitis-like symptoms. In the NIH-CPSI validation studies, perineal pain/discomfort or pain/discomfort during or after ejaculation appeared to be the most common symptoms and were not only clearly specific to prostatitis but were the most discriminatory symptoms between prostatitis patients and BPH patients/normal controls [19]. In the Nickel study, 9.7% of male respondents aged 20 to 74 years reported pain/discomfort in the perineum and/or pain/discomfort with ejaculation plus a total pain score ≥4 (possible, 0 to 21). This location and level of pain symptoms would be sufficient to lead most physicians to make a diagnosis of chronic prostatitis. In addition, 6.6% of men in this age group reported similar symptoms over the previous week and a pain score ≥8, which would place them in the moderate or severe category based on the NIH chronic prostatitis cohort study [19].

Value of the Index in Clinical Practice
The symptom index was not designed to be employed as a diagnostic tool in clinical practice and should not be used for this purpose. The diagnosis of CP/CPPS in the office setting remains a clinical diagnosis based on careful evaluation of the traditional history and physical examination. The lower urinary tract should be evaluated for uropathogenic bacteria, and leukocytosis in prostate-specific specimens should be sought using either the traditional Meares-Stamey 4-glass test [24] or a similar 2-glass pre- and post-massage screening test [25]. The questions developed for the NIH-CPSI can be used to explore the patients’ experience during the traditional history taking. Once the clinical diagnosis is made, formal employment of the questionnaire will allow the physician to quickly cover the important domains of the prostatitis experience in a quantitative manner. This will help the physician to determine the severity of the patients’ pain and voiding symptoms and the impact they are having on the patients’ QOL. Once specific treatment is initiated, the
physician can employ the instrument to follow the patients’ progress and determine clinical treatment effect over time. At this time, the clinical reality is that patients with CP/CPPS are rarely cured with therapeutic intervention initiated by physicians. The goal of therapy is amelioration of symptoms, and the use of the index will allow both the physician and the patient to monitor whether an improvement in symptoms actually occurs. Such an approach will result in less physician and patient frustration in managing this disease. It also will allow the physician to continue therapy that appears to be improving symptoms while abandoning those therapeutic interventions that do not result in amelioration of symptoms.

Summary

The NIH-CPSI is a brief but reliable, valid, and comprehensive measure that quantifies the qualitative experience of men with CP/CPPS. It can be self-administered in less than 5 minutes and is well understood by patients. For men identified as having CP/CPPS, the index appears highly appropriate for measuring the severity and evolution of symptoms and QOL over time. Thus, the symptom index is helpful in natural history studies and in standard clinical practice. Within its limitations, the questionnaire appears to be a useful epidemiologic tool. If continuing studies show that it is responsive to improvement and deterioration in symptoms, it will be a valuable tool in clinical treatment studies. The International Prostatitis Collaborative Network has recommended that the index be employed for at least 1 outcome measure in all future clinical trials in CP/CPPS [26]. A uniformly adopted outcome measure will allow comparative analysis of clinical studies in CP/CPPS. The ultimate value of the symptom index will be determined as more researchers and clinicians employ this outcome measure in their research and clinical practice.

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