Prostatitis: overview and assessment of pain outcomes and implications for inclusion criteria

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NIDDK Classification of Prostatitis[1]

- Type I: Acute Bacterial Prostatitis
- Type II: Chronic Bacterial Prostatitis
- Type III: Chronic Pelvic Pain Syndrome
  - IIIA: WBC in semen, EPS or VB3
  - IIIB: no WBC's present in fluids
- Type IV: Asymptomatic inflammatory Prostatitis

1. Krieger JN et al JAMA 282: 236, 1999

NIDDK Classification of Prostatitis

- Type III: combines prior diagnoses of chronic non bacterial prostatitis and prostatodynia in prior classification-Drach et al J Urol 120:266, 1978
- Raises ? of significance of inflammation
- “Chronic pelvic pain syndrome” instead of “prostatitis” recognizes pain may not be from prostate

Clinical Definition: Category III

- Key symptom: pelvic pain
- NIH Definition
  - GU/pelvic pain for $\geq$ 3 months
  - +/- voiding symptoms
  - Absence of uropathogen bacteria
  - Absence of other causes of pain such as malignancy

Sites of pain in CP/CPPS

- Penis
- Testes (not unilateral orchalgia)
- Suprapubic/bladder
- Perineum
- Pain with urination/dysuria
- Pain during or after ejaculation

Epidemiology of Prostatitis

- Urologic Diseases in America [1]
  - annualized visit rate for prostatitis of 1,798/100,000 population
- International Consultation on Male LUTS 2012 [2]

-Used 24 studies (N=336,846)

-Prevalence: 7.1% (2.2% to 16%); median 6.7%

-Continent: North America 6.9% to 12.2% in Africa

-Incidence: 3.3 per 1000 men per year (267,000 cases per year in US)

1. Pontari M et al J Urol 177: 2050, 2007
2. Chapple C and Abrams P eds, SIU, Montreal CA, 2013

NIH sponsored Chronic Prostatitis Collaborative Research Network (CPCRN)

- 488 males with CP seen at tertiary referral centers 1998-2002
- Mean age 42; range 4.3% < 25 and 13% > 55 years old
- Studied symptoms, bacterial studies, developed symptoms score and conducted 3 clinical trials

Symptom assessment: NIH-CPSI [1]

- Validated, self administered index to measure symptoms in prostatitis
- Symptoms compared in CPPS, BPH and asymptomatic controls
- 3 sections
  - pain
  - urinary symptoms
  - quality of life

1. Litwin MS et al J Urology 162: 369, 1999

Development of NIH CPSI

- Review of prior literature for inventory of symptoms
- Focus groups of 6-8 patients in 4 sites
- Initial draft of 55 questions covering pain, urinary sx, sexual sx, QOL and economic impact
- Cognitive testing of revised draft at 5 centers with 2 patients each-trimmed to 21 items

Development of NIH CPSI

- Validation: 21 items from draft, AUA sx score (7 items) and 4 demographic questions
- 2 control groups: BPH and asymptomatic men
- Pain: significant difference
  - BPH had < 10% pelvic pain, lower in other controls
  - Top 4 pain locations became items 1a through d
  - Frequency became item 3
  - Intensity item 4 as a 10 point scale
  - Ejaculatory pain added due to its prevalence in 2/3

Development of NIH CPSI

- Urinary symptoms
  - Dysuria discriminated well between CPPS and other groups, added to ques 2
  - AUA sx index high in both CPPS and BPH, near identical distribution
  - Obstructive voiding sx and frequency together correlated with the total AUA score-ques 5 and 6
- Quality of Life
  - 8 ques over 2 domains of psychological distress and physical limitations-picked one from each
  - Overall QOL item 9

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	1	2	3	4	5	6	7	8	9	10
NO PAIN										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 = _____

Responsiveness of NIH-CPSI
Propert KJ et al QOL Res 15:299, 2006

- Responsiveness to change over time in 174 men in CPCRN clinical trial-Total and 3 sub scores vs GRA (7 items, 3 on either side of no change)
- In patients who improved, total, pain and QOL were highly responsive, more from slight to marked improvement
- Urine only responsive in markedly improved
- Small response in any scale for all who became worse
- 4 point perceptible change, 6 point clinically significant

Responsiveness of NIH CPSI
Turner JA et al J Urol 169: 580, 2003

- Primary and secondary care, not tertiary sites
- Compared NIH CPSI to Graded chronic pain scale
- Pain and QOL moderately assoc with GCPS
- Urinary low correlation with GCPS
- Total, pain and QOL scores responsive to change, urinary scale was not
- Recc: can use NIH CPSI but add another validated pain measure

Alexander RB et al. Ciprofloxacin or tamsulosin in men with chronic prostatitis/chronic pelvic pain syndrome: a randomized, double-blind trial. Annals of Internal Medicine. 141(8):581-9, 2004 Oct 19.

Table 4. **Secondary End Points: Changes from Baseline to 6 Weeks, Main Effects***

Symptom Score	Ciprofloxacin			Tamsulosin		
	No	Yes	*P* Value	No	Yes	*P* Value
Patients, *n*	98	98		98	98	
Responders, *n* (%)†	23 (24)	16 (16)	>0.2	22 (23)	17 (17)	>0.2
Patients with complete data at 6 weeks, *n* (%)‡	90 (92)	84 (86)		87 (89)	87 (89)	
NIH-CPSI§						
Total score	−3.9 ± 5.7	−5.2 ± 6.8	0.15	−4.7 ± 6.4	−4.3 ± 6.1	>0.2
Pain score	−1.9 ± 3.3	−2.4 ± 4.2	>0.2	−2.3 ± 3.8	−2.0 ± 3.7	>0.2
Urinary score	−0.7 ± 2.0	−1.2 ± 2.0	0.10	−0.9 ± 2.1	−1.0 ± 1.9	>0.2
Quality-of-life score	−1.2 ± 1.8	−1.6 ± 2.2	0.20	−1.5 ± 2.0	−1.3 ± 2.0	>0.2
Medical Outcomes Study 12-Item Short-Form Survey						
Mental composite score	1.2 ± 10.1	−0.9 ± 8.9	0.19	0.8 ± 9.7	−0.5 ± 9.5	>0.2
Physical composite score	2.7 ± 7.2	2.6 ± 7.6	>0.2	2.0 ± 7.3	3.3 ± 7.4	0.17

* Values presented with a plus/minus sign are means ± SD. NIH-CPSI= National Institutes of Health Chronic Prostatitis Symptom Index.

† Patients who withdrew before 6 weeks were considered nonresponders and were included in the denominator for the calculation of response rates in an intention-to-treat analysis.

‡ Means ± SDs for symptom and quality-of-life end points include only the 174 patients who had complete data at both baseline and 6 weeks. Thus, this analysis excludes the 17 patients who withdrew from study before 6 weeks as well as 5 patients who continued in the study but missed the clinic visit at 6 weeks for various reasons. *P* values are derived from the longitudinal regression models that included all available data on all patients. These results do not represent an intention-to-treat analysis and should be interpreted cautiously because of the potential bias related to patient withdrawal from the study.

§ The ranges of possible scores on the 3 NIH-CPSI domains are as follows: pain, 0–21; urinary, 0–10; quality of life, 0–12. Total possible score ranges from 0 to 43 points. A negative change indicates improvement. The 3 domain scores may not sum to the total score because of rounding.

Changes at 12 Weeks in Scores for Measures of Secondary Outcomes According to Study Group.

Comparison of Alfuzosin to placebo in Men with sx < 2 yrs and alpha blocker Naïve

Endpoint: 4 point reduction in NIH CPSI

Placebo: 49.3% response
Alfuzosin: 49.3% response

Table 3. Changes at 12 Weeks in Scores for Measures of Secondary Outcomes According to Study Group.*

Measure	Placebo Group (N=134)	Alfuzosin Group (N=138)	Absolute Difference between Groups (95% CI)	P Value
NIH-CPSI				
No. evaluated	117	116		
Total score (0–43)	−6.5±8.5	−7.1±9.0	−0.6 (−2.7 to 1.5)	0.70
Pain score (0–21)	−3.0±4.4	−3.3±4.5	−0.3 (−1.4 to 0.8)	0.64
Urinary score (0–10)	−1.0±2.6	−1.2±2.6	−0.2 (−0.8 to 0.4)	0.62
Quality-of-life score (0–12)	−1.2±1.5	−1.2±1.5	0 (−0.4 to 0.4)	0.99
McGill Pain Questionnaire				
No. evaluated	116	112		
Total score (0–45)	−3.1±6.5	−3.4±6.4	−0.3 (−1.8 to 1.2)	0.45
Sensory score (0–33)	−2.3±4.9	−2.5±5.0	−0.2 (−1.4 to 1.0)	0.47
Affective score (0–12)	−0.9±2.3	−1.0±2.1	−0.1 (−0.6 to 0.4)	0.89
SF-12				
No. evaluated	113	115		
Physical component summary (0–100)	3.5±8.1	3.0±7.4	−0.5 (−2.3 to 1.3)	0.60
Mental-component summary (0–100)	1.9±10.6	4.0±10.5	2.1 (−0.4 to 4.6)	0.16
Hospital Anxiety and Depression Scale				
No. evaluated	117	115		
Total score	−1.5±5.5	−2.6±5.7	−1.1 (−2.4 to 0.2)	0.08
International Index of Erectile Function				
No. evaluated	109	110		
Total score	−0.2±14.7	0.5±12.7	0.7 (−2.6 to 4.0)	0.94
Male Sexual Health Questionnaire				
No. evaluated	111	107		
Total score (0–40)	0.6±6.8	1.7±4.5	1.1 (−0.3 to 2.5)	0.06

* Plus–minus values are means ±SD. For the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), higher scores indicate more severe symptoms (for the quality-of-life score, higher scores indicate a more negative effect). Score ranges are as follows: total score, 0 to 43; pain score, 0 to 21; urinary score, 0 to 10, quality-of-life score, 0 to 12; and average pain and urgency scores, 0 to 10. For the McGill Pain Questionnaire, higher scores indicate greater pain. Score ranges are as follows: total score, 0 to 45; sensory score, 0 to 33; affective score, 0 to 12. For the Medical Outcomes Study Short Form Health Survey 12 (SF-12), higher scores indicate better quality of life. Score range for both the physical and mental component summaries is 0 to 100. For the Hospital Anxiety and Depression Scale, higher scores indicate greater anxiety and depression; range, 0 to 42. For the International Index of Erectile Function, higher scores indicate better sexual function; range, 0 to 75. For the Male Sexual Health Questionnaire, higher scores indicate better function with respect to erection and ejaculation and greater satisfaction with sexual life; range, 0 to 40.

Nickel JC et al. N Engl J Med 2008;359:2663-2673.

The NEW ENGLAND JOURNAL of MEDICINE

Pregabalin Trial for CPPS
Arch Int Med 170: 1586, 2010

- Dose Escalation of Pregabalin from 150 to 600 per day
- Primary outcome 6 point drop in NIH-CPSI
- Primary outcome: p=0.7
- Secondary outcomes all significantly improved

Table 4. Primary and Secondary Outcome Measures at Baseline and 6 Weeks and Differences in Change Across Time by Treatment Arm

Outcome Measure	Baseline		6 wk		Differences in Change, Pregabalin–Placebo, No. (95% CI)[a]	*P* Value
	Pregabalin Arm	Placebo Arm	Pregabalin Arm	Placebo Arm		
Primary outcome						
NIH-CPSI responder rate (≥6-point decline), No./total No. (%)	NA	NA	103/218 (47.2)	38/106 (35.8)	10.9 (–0.0 to 21.8)	.07
Secondary outcomes[b]						
GRA responder rate, No./total No. (%)	NA	NA	68/218 (31.2)	20/106 (18.9)	12.0 (2.6 to 21.5)	.02
NIH-CPSI score, mean (SD)						
Total	26.2 (5.6)	25.9 (6.1)	19.7 (8.5)	21.6 (8.9)	–2.4 (–4.1 to –0.6)	.01
Pain domain	12.3 (3.0)	12.4 (3.1)	9.1 (4.6)	10.1 (4.7)	–1.0 (–2.0 to –0.04)	.04
Urinary symptoms domain	4.9 (2.7)	4.7 (2.7)	3.7 (2.6)	4.0 (2.7)	–0.7 (–1.2 to –0.2)	.01
QOL domain	8.9 (2.0)	8.9 (2.0)	6.9 (2.9)	7.4 (3.1)	–0.7 (–1.2 to –0.1)	.02
HADS score, mean (SD)	14.8 (7.5)	14.1 (7.3)	12.4 (7.8)	12.2 (7.8)	–0.7 (–2.0 to 0.7)	.36
IIEF-SHIM score, mean (SD)	16.9 (7.9)	17.4 (7.1)	16.4 (8.4)	17.2 (7.8)	–0.6 (–2.1 to 0.9)	.40
McGill Pain Questionnaire score, mean (SD)	13.8 (8.7)	14.1 (8.5)	9.6 (8.8)	12.4 (9.1)	–2.3 (–4.0 to –0.7)	.01
MOS SF-12 score, mean (SD)						
PCS	44.9 (10.1)	43.9 (10.3)	46.9 (10.1)	44.3 (10.6)	1.3 (–0.5 to 3.2)	.34
MCS	41.8 (10.6)	42.8 (10.6)	45.0 (11.2)	44.6 (10.6)	1.4 (–0.9 to 3.8)	.22

Abbreviations: CI, confidence interval; GRA, Global Response Assessment; HADS, Hospital Anxiety and Depression Scale; IIEF-SHIM, International Index of Erectile Function Sexual Health Inventory for Men; MCS, Mental Component Summary; MOS SF-12, Medical Outcomes Study 12-Item Short Form Health Survey; NA, not applicable; NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; PCS, Physical Component Summary; QOL, quality of life.

[a] The pooled rate difference and the 95% CI for this rate difference in response rates across clinical centers were calculated using the "metan" routine in STATA version 10 (StataCorp LP, College Station, Texas) to implement a Mantel-Haenszel estimator for the pooled rate difference across clinical centers.[25]

[b] Sample sizes for secondary outcomes ranged from 201 to 210 for the pregabalin arm and from 98 to 103 for the placebo arm.

Pontari et al Arch Int Med 170: 1586, 2010

Male Genitourinary Pain Index

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

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

2. In the last week, have you experienced:

a. Pain or burning during urination?	❑1 Yes	❑0 No
b. Pain or discomfort during or after sexual climax (ejaculation)?	❑1 Yes	❑0 No
c. Pain or discomfort as your bladder fills?	❑1 Yes	❑0 No
d. Pain or discomfort relieved by voiding?	❑1 Yes	❑0 No

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 you had it, over the last week?

❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

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

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

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

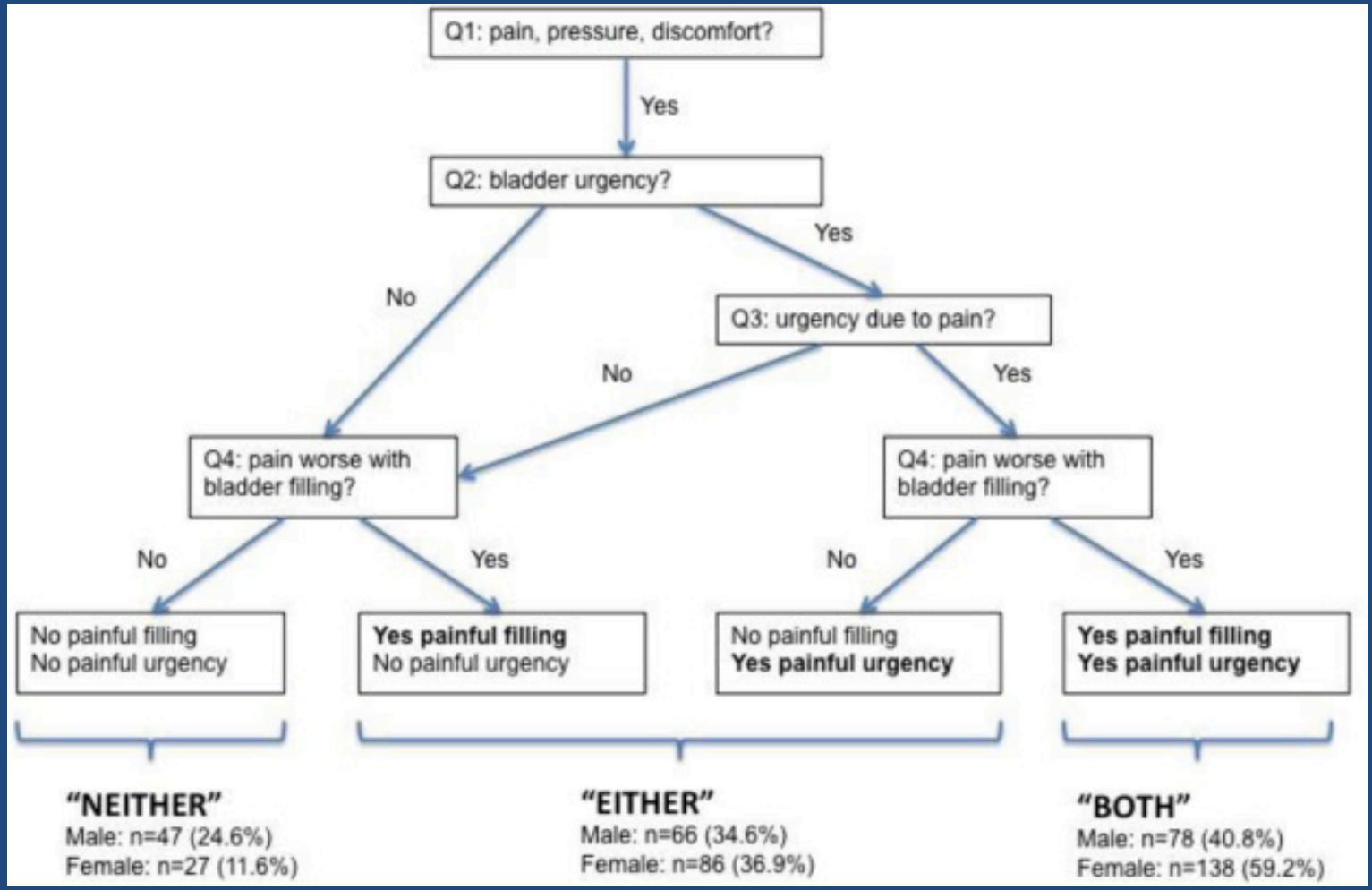
Validation of a Modified NIH CPSI to Assess Genitourinary Pain in Both Men and Women

Clemens JQ et al
Urology 74: 983, 2009

The “GUPI”

-adds questions 2c and 2d to NIH CPSI

MAPP study Bladder sx: Lai et al J Urology 194: 1634, 2015



- Going from "Both" to "Either" to "Neither" : see gradient of more severe pain, frequency, urgency, somatic symptom burden, depression and worse QOL
- Men: 75% of men have bladder sx c/w dx of IC/PBS

Pain and Urinary symptoms should not be combined into single score
Griffith JW et al J Urology 195: 949, 2015

- "Questionnaires differ in their assumptions about how symptoms cluster together"
- Exploratory factor analysis on MAPP patients
- GUPI, ICPI/ICSI, HADS and Sym Q
- 2 factors: pain and urinary sx
- Pain correlates c depression, urinary does not
- "Total scores that combine pain and urinary sx into 1 score may be limited for clinical and research purposes"

MAPP entrance criteria
BMC Urology. 14:58, 2014

1) a diagnosis of IC/BPS or CP/CPPS, with urologic symptoms present a majority of the time during any 3 of the past 6 months (CP/CPPS) or the most recent 3 months (IC/BPS)

2) at least 18 years old

3) reporting a non-zero score for bladder/prostate and/or pelvic region pain, pressure or discomfort during the past 2 weeks

4) consented to provide a blood or cheek swab sample to test DNA for genes related to the main study goals.

MAPP Exclusion criteria: BMC Urology. 14:58, 2014

- symptomatic urethral stricture,
- on-going neurological conditions affecting the bladder or bowel,
- active autoimmune or infectious disorders
- history of cystitis caused by tuberculosis or radiation or chemotherapies
- history of non-dermatologic cancer
- current major psychiatric disorders, or severe cardiac, pulmonary, renal, or hepatic disease.

- males diagnosed with unilateral orchalgia without pelvic symptoms
- males with a history of microwave thermotherapy, trans-urethral or needle ablation or other specified prostate procedures

CPCRN deferral criteria: Schaeffer AJ et al J. Urology168:593, 2002

Deferral criteria
1) Patient has been treated with antimicrobial agents in the last 3 months.
2) Patient has had a urinary tract infection with a urine culture value of greater than 100,000 colony-forming units per ml. within the last 3 months.
3) Patient has had any of the following sexually transmitted diseases in the last 3 months: gonorrhea, chlamydia, mycoplasma, or trichomonas but not including HIV/AIDS.
4) Patient has undergone prostate biopsy in the last 3 months.
5) Patient has experienced symptoms of acute or chronic epididymitis within the last 3 months.
6) Patient has been diagnosed with or treated for symptomatic genital herpes in the last 12 months.

Conclusions

- Main symptom of CP/CPPS is pain
- 75% of men with CP/CPPS also have bladder pain- implications for treatments
- Pain and Urinary symptoms may not respond together
- NIH/CPSI and GUPI total scores likely not useful in clinical trial
- Minimal controversy in entrance criteria for CP/CPPS