



Published in final edited form as:

*J Urol.* 2013 January ; 189(1 Suppl): S66–S74. doi:10.1016/j.juro.2012.11.019.

## Evidence for Overlap Between Urological and Nonurological Unexplained Clinical Conditions

María Ángeles Bullones Rodríguez, Niloofar Afari, Dedra S. Buchwald\*, National Institute of Diabetes and Digestive and Kidney Diseases Working Group on Urological Chronic Pelvic Pain

Department of Psychology, University Rey Juan Carlos, Madrid, Spain (MABR), Department of Psychiatry, University of California, San Diego, La Jolla and Veterans Affairs San Diego Healthcare System and Veterans Affairs Center of Excellence for Stress and Mental Health, San Diego, California (NA), and Department of Medicine and Center for Clinical and Epidemiological Research, University of Washington, Seattle, Washington (DB)

### Abstract

**Purpose:** Unexplained clinical conditions share common features such as pain, fatigue, disability out of proportion to physical examination findings, inconsistent laboratory abnormalities, and an association with stress and psychosocial factors. We examined the extent of the overlap among urological and nonurological unexplained clinical conditions characterized by pain. We describe the limitations of previous research and suggest several possible explanatory models.

**Materials and Methods:** Using hallmark symptoms and syndromes as search terms a search of 12 databases identified a total of 1,037 full-length published articles in 8 languages from 1966 to April 2008. The search focused on the overlap of chronic pelvic pain, interstitial cystitis, painful bladder syndrome, chronic prostatitis/chronic pelvic pain syndrome or vulvodynia with fibromyalgia, chronic fatigue syndrome, temporomandibular joint and muscle disorders or irritable bowel syndrome. We abstracted information on authorship, type of case and control groups, eligibility criteria, case definitions, study methods and major findings.

**Results:** The literature suggests considerable comorbidity between urological and nonurological unexplained clinical conditions. The most robust evidence for overlap was for irritable bowel syndrome and urological unexplained syndromes with some estimates of up to 79% comorbidity between chronic pelvic pain and symptoms of irritable bowel syndrome. However, most studies were limited by methodological problems, such as varying case definitions and selection of controls.

**Conclusions:** The overlap between urological and selected nonurological unexplained clinical conditions is substantial. Future research should focus on using standardized definitions, and rigorously designed, well controlled studies to further assess comorbidity, clarify the magnitude of the association and examine common pathophysiological mechanisms.

\*Correspondence: Department of Medicine, 1730 Minor Ave., Suite 1760, Seattle, Washington 98101 (telephone: 206-543-2260; FAX: 206-543-3830; dedra@u.washington.edu).

Final review findings are endorsed by and represent the views of the authors, and the National Institute of Diabetes and Digestive and Kidney Diseases Working Group on Urological CPP.

## Keywords

urogenital system; fatigue syndrome; chronic; fibromyalgia; irritable bowel syndrome; temporomandibular joint disorders

Functional somatic syndromes, medically unexplained symptoms, somato-form disorders and unexplained clinical conditions are common names given to conditions characterized by a lack of clear physical or biological etiology, or an inconsistent demonstration of laboratory abnormalities.<sup>1</sup> These conditions are further characterized by symptoms such as pain, fatigue, sleep disturbances and disability. The literature suggests that many of these conditions also share demographic characteristics, clinical courses and psychosocial profiles.<sup>1</sup> The diagnosis given to a patient with 1 of these conditions often depends on the hallmark symptom and the expertise of the treating clinician rather than on the illness.<sup>1</sup> The frequency of co-diagnosis and the common features shared by unexplained clinical conditions have become topics of growing interest in the last few years.

Physicians are challenged to diagnose and appropriately treat patients with unexplained clinical conditions such as FM, CFS, TMD, IBS, CPP, IC, PBS, CP/CPPS and vulvodynia. A recent review found that patients with IC often have other unexplained conditions and symptoms.<sup>2</sup> Although a substantial body of literature describes the comorbidity of nonurological, unexplained clinical conditions such as FM, CFS and IBS,<sup>3</sup> the extent of the overlap between urological and nonurological unexplained clinical conditions, and the potential mechanisms of their co-occurrence remain largely unknown.

The recent emphasis by NIDDK on a multidisciplinary approach to the study of urological CPPSs further underscores the need to examine and understand the overlap between urological and nonurological unexplained clinical conditions (<http://www2.niddk.nih.gov/Research/ScientificAreas/Urology/MAPP>). Thus, we reviewed the literature on comorbidity between the most common urological pelvic pain syndromes, ie CPP, IC, PBS, CP/CPPS and vulvodynia, and the nonurological conditions of FM, CFS, TMD and IBS. We focused on overlap with these nonurological conditions for several reasons. 1) Our goal was to examine overlap among conditions with a significant pain component, which ruled out overlap with psychiatric conditions such as panic disorder that also have been shown to co-occur with urological pelvic pain syndromes. 2) Frequently comorbid pain conditions with a known physical or biological etiology were not included since they would not satisfy the definition of an unexplained clinical condition. 3) These 4 nonurological conditions were the focus of most data based articles in the existing literature and of particular interest to NIDDK. 4) These nonurological conditions differed in the pain site, which could influence the extent of overlap between urological and nonurological unexplained clinical conditions.

## MATERIALS AND METHODS

### Search Strategy

Articles were identified by a database search, including PubMed® (1966 to April 2008), CINAHL® (1981 to April 2008), The Cochrane Collaboration (Cochrane Reviews) (1993 to April 2008), Current Contents Connect® (2000 to April 2008), EBSCO Academic Search

Premier (1975 to April 2008), EMBASE® (1974 to April 2008), ISI Web of Science® (1980 to April 2008), PsycINFO® (1967 to April 2008), Science Citation Indexes (1996 to April 2008), and Scirus®, Scopus® and Google™ Scholar (April 2008).

Our initial search included certain search terms for the 5 urological unexplained clinical conditions, including chronic pelvic pain, interstitial cystitis, painful bladder syndrome, chronic prostatitis and vulvodynia, combined with 4 nonurological unexplained clinical conditions, that is chronic fatigue syndrome, fibromyalgia, temporomandibular disorder and irritable bowel syndrome. MeSH® terms were combined with truncated key words describing the symptoms of the various conditions. All possible combinations of the 2 search term sets were examined.

We then looked for all search terms individually and combined with the words overlapping, overlap, comorbidity and comorbid. Also, we combined the terms for the hallmark symptoms associated with each nonurological condition with the hallmark symptoms associated with each urological condition, eg chronic fatigue and painful bladder. The bibliography of relevant articles was examined to identify reports that may have been missed. Finally, members of the NIDDK Working Group on Urological CPP, a group of experts in urology, rheumatology, epidemiology and internal medicine, were contacted to review the list of relevant articles and locate other pertinent peer reviewed publications. Together these search strategies yielded 1,037 unique publications.

### Study Inclusion Criteria

Articles included in this review examined the comorbidity or overlap of at least 1 urological condition or hallmark symptom with at least 1 nonurological condition or hallmark symptom. We focused on articles in English, Hebrew, German, French, Spanish, Korean, Japanese and Russian because we or working group members could review them. No limits were placed on participant age but all relevant articles pertained to adults, of whom most were women.

We reviewed comparison and single condition studies. The first type compared 2 or more groups diagnosed with different unexplained clinical conditions, eg patients with IC vs patients with FM, to each other or compared 1 group diagnosed with a urological unexplained clinical condition to a healthy control group, eg patients with CP vs healthy volunteers. In single condition studies participants with a specific unexplained clinical condition or symptom were examined for the co-occurrence of other conditions, eg the frequency of vulvar pain in IBS cases or of IBS in vulvodynia cases. Comparison studies can more precisely estimate the extent of comorbidity or overlap than single condition studies and highlight potential similarities in pathophysiology across conditions.

Studies that were initially excluded because they did not meet the overlap criterion were reviewed again for possible incidental findings on the overlap of urological and nonurological conditions that may have been reported as part of the data analysis or in the context of other study findings.

## Study Exclusion Criteria

Of identified articles 90% were excluded from analysis because they did not examine the overlap between urological and nonurological conditions. Other articles were excluded because the main patient group did not have an unexplained clinical condition (eg migraine or panic), the article focused on an unexplained clinical condition or symptom not considered in our review or presented data on broad symptom categories, including conditions other than those considered (eg functional digestive disorders), despite mentioning overlap the article lacked relevant data or the main topic was not pertinent to our review (eg abuse or pharmacological treatment approaches). Articles that did not present primary data, such as reviews, were not included in our analysis or tables even when they supported our findings and conclusions.

## Data Extraction and Synthesis

Based on study inclusion and exclusion criteria 41 relevant publications were identified and reported (tables 1 and 2).<sup>1</sup> For each study we extracted information on study characteristics (eg name of first author and publication year), participant group type (eg patients or community participants), group sample size, diagnostic criteria, methods and major findings. Initial review findings were examined by a second reviewer who independently extracted information from the relevant publications. Working group members reviewed drafts of the findings for completeness of the literature review and contributed to the synthesis and interpretation of the findings.

## RESULTS

### Symptom and Syndrome Overlap in Comparison Studies

We found 25 publications on comparison studies that provided data on the comorbidity of urological and nonurological unexplained clinical conditions or symptoms (table 1). Although some studies were published in the early 1990s, 68% were published since 2005. Of these 25 studies 19 described patient populations and 6 described nonclinical samples derived from population surveys. The studies used diverse diagnostic approaches, including physician diagnosis, symptom based definitions and more rigorous, well established criteria, such as NIDDK criteria for IC diagnosis or American College of Rheumatology criteria for fibromyalgia. Study methods included self-report questionnaires on medical history, standardized surveys and interviews, physician and tender point examinations, and computerized reviews of ICD-9 codes.

A total of 16 groups reported data on the overlap between urological unexplained clinical conditions and musculoskeletal conditions, or symptoms such as FM or chronic widespread pain, joint pain, generalized pain or myalgia.<sup>4-19</sup> However, only 4 studies were specifically designed to examine the comorbidity of FM or chronic widespread pain with 1 of the urological conditions.<sup>5,8,14,15</sup> About 9% to 12% of patients with IC also experienced FM,<sup>5,14</sup> and 23% to 27% of patients with FM had symptoms consistent with IC.<sup>5</sup> An early study showed that 68% of men and 66% of women with FM also reported pelvic pain symptoms.<sup>4</sup> In a twin study that controlled for genetic and environmental confounding approximately 23% of twins with chronic widespread pain and 11% of their pain-free co-twins reported

urinary tract problems.<sup>9</sup> Although to our knowledge the overlap between CP/CPPS and FM has not been directly examined, 1 group noted that 21% of individuals with CP/CPPS symptoms reported a history of musculoskeletal, rheumatological or connective tissue diseases<sup>11</sup> and another observed a trend toward higher manual tender point examination scores in patients with CP/CPPS vs controls.<sup>16</sup> Vulvodynia was also described as co-occurring with FM.<sup>8,15</sup>

Only 3 studies, all in nonclinical populations, examined the overlap between urological unexplained clinical conditions and CFS. A study of twin pairs discordant for various definitions of chronic fatigue or CFS showed that fatigued twins were up to 20 times more likely to have IC and up to 6 times more likely to have CPP than their nonfatigued co-twins.<sup>20</sup> Conversely CFS was reported more than twice as often by individuals with CP/CPPS symptoms than by asymptomatic age matched controls.<sup>11</sup> Also, individuals with vulvodynia more often reported CFS than asymptomatic controls.<sup>15</sup> We did not find comparative studies of overlap between TMD and any urological unexplained clinical condition.

Finally, 15 of 25 comparison studies examined the overlap between urological unexplained clinical conditions and IBS. Using different methods several groups reported that 7% to 48% of patients with IC or symptoms of PBS also had IBS.<sup>10,14,21,22</sup> Others found that patients with IC were 11 times more likely to be diagnosed with IBS than controls.<sup>23</sup> Furthermore, 22% of men with CP/CPPS or its symptoms had IBS<sup>11,19,22</sup> and 37% of women with CPP met IBS criteria.<sup>24</sup> Conversely 1 group found that 35% of patients with IBS but only 14% with inflammatory bowel disease reported CPP symptoms.<sup>25</sup> In other studies IBS was associated with an increased probability of an IC diagnosis and increased urinary symptom scores.<sup>13,26,27</sup> Vulvodynia was also documented as comorbid with IBS.<sup>8,15,28</sup>

### Symptom and Syndrome Overlap in Single Condition Studies

We found 16 publications that assessed individuals with a single unexplained clinical condition for at least 1 additional syndrome or hallmark symptom (table 2). Despite methodological differences the results of these investigations are generally consistent with those listed in table 1. A study of patients with CPP symptoms showed that 19% also had FM symptoms and 8% had CFS symptoms.<sup>29</sup> These rates are similar to those in other publications of self-reported FM (17%) and CFS (9%) in individuals with IC<sup>30</sup> and vulvar pain.<sup>31</sup> Conversely a recent study using American College of Rheumatology criteria for FM showed that 11% of patients with IC met FM diagnostic criteria.<sup>32</sup> Also, 2 studies provided data on the overlap between TMD and at least 1 urological unexplained clinical condition. One group found that 13% of patients with TMD had a history of IC<sup>33</sup> and the other reported that almost 20% of women with vulvar pain reported TMD.<sup>31</sup>

Most single condition studies examined the comorbidity of urological unexplained clinical conditions and symptoms with IBS. They indicated that 30% to 75% of individuals with IC or IC symptoms had IBS or IBS symptoms,<sup>30,34,35</sup> and 26% to 56% of patients with IBS reported urinary problems.<sup>36,37</sup> Likewise 19% to 79% of patients with CPP had IBS or IBS symptoms.<sup>29,38–40</sup> Of women with vulvar pain 35% reported IBS.<sup>31</sup>

## DISCUSSION

### Evidence of Overlap

Our extensive review of the literature on urological and nonurological unexplained clinical conditions identified a small but growing body of published reports on the comorbidity of these conditions. The most robust evidence for overlap exists for IBS and unexplained urological conditions in terms of the number of publications and the relative consistency of results across studies. This overlap may reflect publication bias or the anatomical fact that urological CPP conditions and IBS develop in a similar region of the body and involve visceral pain sensations. In contrast, the few studies of FM, CFS and TMD suggest more modest comorbidity with urological unexplained clinical conditions. Nonetheless, our findings generally support previous assertions of overlap among some or all of the urological and nonurological unexplained clinical conditions.<sup>2,3,41</sup>

The common sociodemographic and clinical features shared by these conditions, the symptom overlap in many case definitions and the tendency to respond to the same therapies have led several investigators to suggest that all unexplained clinical conditions are different manifestations of the same underlying pathophysiological process.<sup>1,3</sup> Also, some experts argue that the comorbidity of FM, CFS, TMD and IBS could result from similarities in their case definitions.<sup>1</sup> Although this explanation may apply to the overlap between urological pelvic pain conditions and IBS,<sup>41</sup> urinary and pelvic pain symptoms are not part of the symptom criteria for FM, CFS or TMD. Thus, commonalities in symptom criteria cannot completely account for the overlap that we summarize. Nonetheless, the heterogeneity of these conditions, especially subgroups of patients with uncharacteristic symptoms, can in part account for the substantial overlap between these conditions.

### Proposed Explanations

Despite decades of research on unexplained clinical conditions their etiology and pathophysiology remain elusive. We identified 3 dominant perspectives on the mechanisms of these conditions, including 1) physiological processes, particularly neuroendocrine, immunological and neurotransmitter dysfunction in the central nervous system, 2) victimization, abuse and trauma, and 3) psychological distress, psychiatric disorders, stress tolerance and recovery from stress.<sup>3</sup> Although abnormalities have been demonstrated across several domains that are consistent with all of these perspectives, most groups have examined only single hypotheses. Also, many affected patients do not have neuroendocrine abnormalities, or depression or other psychiatric conditions and were not abused or victimized. Organ based approaches, ie examining the bladder, prostate or skeletal system, have similarly failed to provide useful insights into the etiology of or effective treatments for these conditions. Generally research on urological CPP conditions and similar disorders has not distinguished epiphenomena from underlying pathophysiology.

A multidimensional conceptual model seems better suited to guide research and understanding of these conditions and their co-occurrence.<sup>1</sup> A multidimensional model can encompass the range of predisposing (eg genetic and environmental influences, and physiological perturbations), precipitating (eg trauma and infection) and perpetuating (eg

central sensitization and perceptual amplification) factors as well as predictors of chronicity (eg psychological and sleep disturbances) that are necessary but not individually sufficient for 1 or more unexplained clinical conditions to develop (see figure). A strength of this conceptualization is that it incorporates the 2 most prominent overarching theories of pain to facilitate the understanding and treatment of unexplained clinical conditions. The diathesis-stress model considers predisposing biological and genetic factors as well as the environmental and life events that interact to trigger behaviors and disorders.<sup>42</sup> Alternately the gate control theory of pain and its more recent expansion emphasize the role of the brain and its interaction with cognitive and emotional factors in pain transmission and modulation.<sup>43</sup> The multidimensional model presented combines these overarching theories to offer multiple hypotheses that test similarities in vulnerability factors and stressors as well as the central affective, sensory, cognitive, motor, inhibitory and autonomic responses involved in pain processing. Elements of this model have spurred a small but growing body of literature, especially in pain sensitivity, and its enhanced perception and central sensitization of pain in FM and CFS cases,<sup>44,45</sup> and support basic similarities across these conditions. A more broadly based conceptual model can facilitate interdisciplinary linkages among basic, clinical and population sciences to investigate etiology, clinical manifestations, comorbidity and prognosis.

Conceptually driven investigations of the mechanisms that may predispose, precipitate, perpetuate and predict these conditions can improve our understanding of urological unexplained clinical conditions and their comorbidities. Given the prominence of pain across the syndromes of interest, examination of the central sensitization hypothesis is crucial to understanding their substantial comorbidity. Furthermore, twin and family studies can clarify the role of shared genetic and environmental factors in syndrome genesis and perpetuation.

### Limitations of Studies

We discovered several methodological shortcomings in the literature that undermine the strength of our conclusions and limit comparability across studies.

1. Study participants were drawn primarily from tertiary care clinics, hampering the generalizability of findings to primary care patients and to the general population. Clinical ascertainment and other biases associated with the study of treatment seeking populations are well-known<sup>46</sup> and can be an important source of spurious comorbidity. Anxiety, poor coping, stressful events and other psychological factors also may have a role in health care seeking in IBS and FM cases.<sup>47</sup> Thus, the comorbidity of urological and nonurological unexplained clinical conditions may be an artifact of health care use.
2. We found inconsistencies in assessment. Although research on unexplained clinical conditions may be hampered by a lack of diagnostic markers, these conditions have established case definitions designed to facilitate symptom based diagnosis and comparability across research studies. Nonetheless, many methods were used to assess the conditions of interest, ranging from established case definitions to self-reported physician diagnoses and review of computerized ICD-9 codes. Several investigations relied on medical history questionnaires

or self-reported diagnoses without independent confirmation by medical record reviews or clinical examinations. This reliance questions the accuracy of all rates of conditions based on self-report but especially those requiring physical examination findings (eg FM) or the exclusion of specific medical disorders (eg CFS). Also, studies based on physician diagnoses in medical records may underestimate comorbidity if a patient attends 1 clinic for primary symptoms but is discouraged from seeking specialty care for other symptoms, which may occur in health maintenance organizations. Studies also differed in inclusion and exclusion criteria. All of these factors affect the degree of overlap among urological and nonurological unexplained clinical conditions, and make comparisons across studies problematic.

3. Except CP/CPSS in men, most participants with unexplained clinical conditions were women. It has been debated whether certain urological unexplained clinical conditions, particularly IC/PBS and CP/CPSS in men, represent somewhat different manifestations of the same disorder and whether IC/PBS risk factors and manifestations differ in men and women.<sup>48</sup> Sex differences clearly exist in the epidemiology, symptomatology, physiology and psychological features of FM, CFS and IBS,<sup>49</sup> raising the possibility that the overlap between urological and nonurological unexplained clinical conditions is sex specific. Clearly there are too few studies in men to fully examine any sex differences in overlap that may exist. Studies in large samples of men are needed to examine the role of sex in the co-occurrence of these conditions. Likewise, more data are needed to examine the association of these conditions across different cultural, racial and ethnic groups.
4. In studies comparing 2 or more groups controls consisted variously of healthy individuals, those with another chronic illness or controls with unreported health status. Only 2 studies were controlled for genetic and common environmental effects using co-twin control methods.<sup>9,20</sup> Most groups did not use multivariate analytical techniques to adjust for demographic or other differences that could decrease the strength of the association between comorbid conditions.

## CONCLUSIONS

Our extensive review of the published literature on the overlap between urological and nonurological unexplained clinical conditions suggests that comorbidity is common. However, these studies have several methodological shortcomings that undermine the strength of our conclusions and limit comparability across studies. Future studies of the overlap should adhere to the established research diagnostic criteria for each condition. Large-scale, rigorously designed and well controlled studies in clinical and community populations can yield more definitive answers to questions of overlapping symptoms and syndromes. Also, longitudinal cohort designs are needed to examine risk factors, temporal onset and prognosis. A recent study published since this review was done showed significant associations between antecedent nonurological unexplained clinical conditions and incident cases of IC/PBS,<sup>50</sup> further underscoring the need for longitudinal studies. Other



studies of urological unexplained clinical conditions should focus on health and behavior related characteristics, for example quality of life, disability or health care use, that can estimate the added burden of co-occurring syndromes on meaningful outcomes such as functional status, employment and health care costs. Examining possible mediators for comorbidity, for example abuse, victimization or psychological distress, can elucidate the relationship between overlapping conditions and identify subgroups at risk for urological CPP syndromes and related conditions. Well controlled studies to assess comorbidity and pathophysiological mechanisms can advance our understanding and improve treatment for these conditions.

## ACKNOWLEDGMENTS

Dayron Rodriguez, Michael D. Smith, Jaeseop Lee and Michael O'Leary, Harvard Medical School; Almudena López, University Rey Juan Carlos, Madrid, Spain; and Debra Sprague, University of Washington assisted with the literature review and reviewed the manuscript. Drs. John Kusek, Leroy Nyberg and Christopher Mullins of the primary funding agency reviewed the manuscript.

Supported by NIDDK Grant U01 DK082325 (DSB, NA), and National Institute of Arthritis and Musculoskeletal and Skin Diseases Grants R21 AR053963 (DSB) and R01AR51524 (NA).

## APPENDIX

NIDDK Working Group on Urological CPP: Drs. Niloofar Afari, Dedra S. Buchwald, Daniel Clauw, Jordan Dimitrakov, John Kusek, Christopher Mullins, Leroy Nyberg, Christopher Payne, Cecilia Peñacoba, Michael Pezzone, Michel Pontari, Jeannette Potts, María Ángeles Bullones Rodríguez, and John Warren.

## Abbreviations and Acronyms

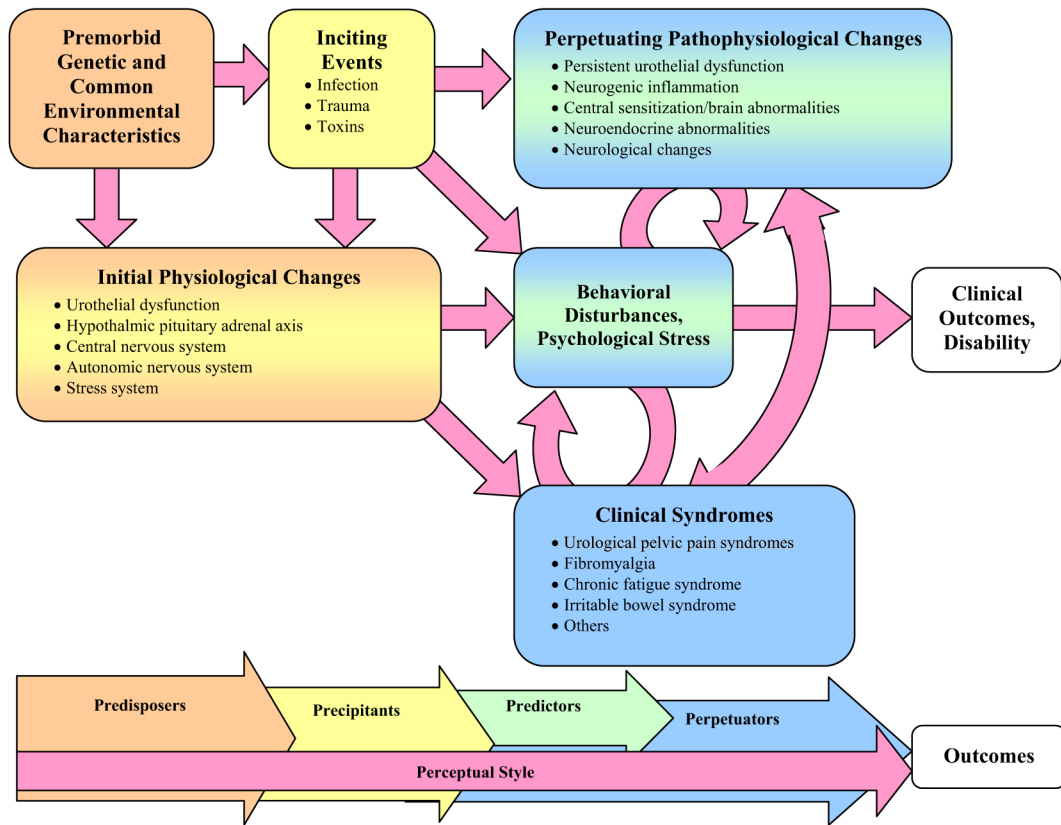
<b>CFS</b>	chronic fatigue syndrome
<b>CP</b>	chronic prostatitis
<b>CPP</b>	chronic pelvic pain
<b>CPPS</b>	CPP syndrome
<b>CWP</b>	chronic widespread pain
<b>FM</b>	fibromyalgia
<b>IBD</b>	inflammatory bowel disease
<b>IBS</b>	irritable bowel syndrome
<b>IC</b>	interstitial cystitis
<b>NIDDK</b>	National Institute of Diabetes and Digestive and Kidney Diseases
<b>PBS</b>	painful bladder syndrome
<b>TMD</b>	temporomandibular joint and muscle disorders

## REFERENCES

1. Wessely S, Nimnuan C and Sharpe M: Functional somatic syndromes: one or many? *Lancet* 1999; 354: 936. [PubMed: 10489969]
2. Buffington CA: Comorbidity of interstitial cystitis with other unexplained clinical conditions. *J Urol* 2004; 172: 1242. [PubMed: 15371816]
3. Aaron LA and Buchwald D: A review of the evidence for overlap among unexplained clinical conditions. *Ann Intern Med* 2001; 134: 868. [PubMed: 11346323]
4. Waylonis GW and Heck W: Fibromyalgia syndrome. New associations. *Am J Phys Med Rehabil* 1992; 71: 343. [PubMed: 1466872]
5. Clauw DJ, Schmidt M, Radulovic D et al. : The relationship between fibromyalgia and interstitial cystitis. *J Psychiatr Res* 1997; 31: 125. [PubMed: 9201654]
6. Ostensen M and Schei B: Sociodemographic characteristics and gynecological disease in 40–42 year old women reporting musculoskeletal disease. *Scand J Rheumatol* 1997; 26: 426. [PubMed: 9433402]
7. Erickson DR, Morgan KC, Ordille S et al. : Non-bladder related symptoms in patients with interstitial cystitis. *J Urol* 2001; 166: 557. [PubMed: 11458068]
8. Arnold LD, Bachmann GA, Rosen R et al. : Vulvodynia: characteristics and associations with comorbidities and quality of life. *Obstet Gynecol* 2006; 107: 617. [PubMed: 16507933]
9. Kato K, Sullivan PF, Evengard B et al. : Chronic widespread pain and its comorbidities: a population-based study. *Arch Intern Med* 2006; 166: 1649. [PubMed: 16908799]
10. Kennedy CM, Bradley CS, Galask RP et al. : Risk factors for painful bladder syndrome in women seeking gynecologic care. *Int Urogynecol J Pelvic Floor Dysfunct* 2006; 17: 73. [PubMed: 15995790]
11. Pontari MA: Chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis: are they related? *Curr Urol Rep* 2006; 7: 329. [PubMed: 16930505]
12. Shaver JL, Wilbur J, Robinson FP et al. : Women's health issues with fibromyalgia syndrome. *J Womens Health (Larchmt)* 2006; 15: 1035. [PubMed: 17125422]
13. Wu EQ, Birnbaum H, Kang YJ et al. : A retrospective claims database analysis to assess patterns of interstitial cystitis diagnosis. *Curr Med Res Opin* 2006; 22: 495. [PubMed: 16574033]
14. Wu EQ, Birnbaum H, Mareva M et al. : Interstitial cystitis: cost, treatment and co-morbidities in an employed population. *Pharmacoeconomics* 2006; 24: 55.
15. Arnold LD, Bachmann GA, Rosen R et al. : Assessment of vulvodynia symptoms in a sample of US women: a prevalence survey with a nested case control study. *Am J Obstet Gynecol* 2007; 196: 128. [PubMed: 17306651]
16. Berger RE, Ciol MA, Rothman I et al. : Pelvic tenderness is not limited to the prostate in chronic prostatitis/chronic pelvic pain syndrome (CPPS) type IIIA and IIIB: comparison of men with and without CP/CPPS. *BMC Urol* 2007; 7: 17. [PubMed: 17908331]
17. Araujo MP, Faria AC, Takano CC et al. : Urodynamic study and quality of life in patients with fibromyalgia and lower urinary tract symptoms. *Int Urogynecol J Pelvic Floor Dysfunct* 2008; 19: 1103. [PubMed: 18317663]
18. Clemens JQ, Meenan RT, O'Keeffe Rosetti MC et al. : Case-control study of medical comorbidities in women with interstitial cystitis. *J Urol* 2008; 179: 2222. [PubMed: 18423759]
19. Dimitrakov J, Joffe HV, Soldin SJ et al. : Adrenocortical hormone abnormalities in men with chronic prostatitis/chronic pelvic pain syndrome. *Urology* 2008; 71: 261. [PubMed: 18308097]
20. Aaron LA, Herrell R, Ashton S et al. : Comorbid clinical conditions in chronic fatigue: a co-twin control study. *J Gen Intern Med* 2001; 16: 24. [PubMed: 11251747]
21. Koziol JA: Epidemiology of interstitial cystitis. *Urol Clin North Am* 1994; 21: 7. [PubMed: 8284848]
22. Clemens JQ, Brown SO, Kozloff L et al. : Predictors of symptom severity in patients with chronic prostatitis and interstitial cystitis. *J Urol* 2006; 175: 963. [PubMed: 16469592]
23. Novi JM, Jeronis S, Srinivas S et al. : Risk of irritable bowel syndrome and depression in women with interstitial cystitis: a case-control study. *J Urol* 2005; 174: 937. [PubMed: 16093997]

24. Grace V and Zondervan K: Chronic pelvic pain in women in New Zealand: comparative well-being, comorbidity, and impact on work and other activities. *Health Care Women Int* 2006; 27: 585. [PubMed: 16844672]
25. Walker EA, Gelfand AN, Gelfand MD et al. : Chronic pelvic pain and gynecological symptoms in women with irritable bowel syndrome. *J Psychosom Obstet Gynaecol* 1996; 17: 39. [PubMed: 8860885]
26. Zimmerman J: Extraintestinal symptoms in irritable bowel syndrome and inflammatory bowel diseases: nature, severity, and relationship to gastrointestinal symptoms. *Dig Dis Sci* 2003; 48: 743. [PubMed: 12741465]
27. Whitehead WE, Palsson OS, Levy RR et al. : Comorbidity in irritable bowel syndrome. *Am J Gastroenterol* 2007; 102: 2767. [PubMed: 17900326]
28. Kennedy CM, Nygaard IE, Bradley CS et al. : Bladder and bowel symptoms among women with vulvar disease: are they universal? *J Reprod Med* 2007; 52: 1073. [PubMed: 18210896]
29. Nimnuan C, Rabe-Hesketh S, Wessely S et al. : How many functional somatic syndromes? *J Psychosom Res* 2001; 51: 549. [PubMed: 11595242]
30. Alagiri M, Chottiner S, Ratner V et al. : Interstitial cystitis: unexplained associations with other chronic disease and pain syndromes. *Urology* 1997; 49: 52. [PubMed: 9146002]
31. Gordon AS, Panahian-Jand M, McComb F et al. : Characteristics of women with vulvar pain disorders: responses to a Web-based survey. *J Sex Marital Ther, suppl.*, 2003; 29: 45. [PubMed: 12735088]
32. Yamada T, Funahashi M and Murayama T: Clinical evaluation of 30 patients with interstitial cystitis complicated by fibromyalgia. *Nippon Hinyokika Gakkai Zasshi* 2005; 96: 554. [PubMed: 16083033]
33. Korszun A, Papadopoulos E, Demitrack M et al. : The relationship between temporomandibular disorders and stress-associated syndromes. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; 86: 416. [PubMed: 9798224]
34. Giamberardino M: Sex-related and hormonal modulation of visceral pain. In: *Sex, Gender and Pain*. Edited by Fillingim R. Seattle: IASP Press 2000; vol 17, pp 135–162.
35. FitzGerald MP, Brensinger C, Brubaker L et al. : What is the pain of interstitial cystitis like? *Int Urogynecol J Pelvic Floor Dysfunct* 2006; 17: 69. [PubMed: 15995791]
36. Maxton DG, Morris JA and Whorwell PJ: Ranking of symptoms by patients with the irritable bowel syndrome. *BMJ* 1989; 299: 1138. [PubMed: 2513023]
37. Blanchard EB, Keefer L, Lackner JM et al. : The role of childhood abuse in Axis I and Axis II psychiatric disorders and medical disorders of unknown origin among irritable bowel syndrome patients. *J Psychosom Res* 2004; 56: 431. [PubMed: 15094028]
38. Walker EA, Katon WJ, Jemelka R et al. : The prevalence of chronic pelvic pain and irritable bowel syndrome in 2 university clinics. *J Psychosom Obstet Gynaecol, suppl.*, 1991; 12: 65.
39. Williams RE, Hartmann KE, Sandler RS et al. : Recognition and treatment of irritable bowel syndrome among women with chronic pelvic pain. *Am J Obstet Gynecol* 2005; 192: 761. [PubMed: 15746669]
40. Fenton BW, Durner C and Fanning J: Frequency and distribution of multiple diagnoses in chronic pelvic pain related to previous abuse or drug-seeking behavior. *Gynecol Obstet Invest* 2008; 65: 247. [PubMed: 18196907]
41. Riedl A, Schmidtman M, Stengel A et al. : Somatic comorbidities of irritable bowel syndrome: a systematic analysis. *J Psychosom Res* 2008; 64: 573. [PubMed: 18501257]
42. Turk DC: A diathesis-stress model of chronic pain and disability following traumatic injury. *Pain Res Manag* 2002; 7: 9. [PubMed: 16231063]
43. Melzack R: From the gate to the neuromatrix. *Pain, suppl.*, 1999; 6: S121. [PubMed: 10491980]
44. Gracely RH, Petzke F, Wolf JM et al. : Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum* 2002; 46: 1333. [PubMed: 12115241]
45. Ullrich PM, Afari N, Jacobsen C et al. : Cold pressor pain sensitivity in monozygotic twins discordant for chronic fatigue syndrome. *Pain Med* 2007; 8: 216. [PubMed: 17371408]

46. Bogenschutz MP and Nurnberg HG: Theoretical and methodological issues in psychiatric comorbidity. *Harv Rev Psychiatry* 2000; 8: 18. [PubMed: 10824294]
47. Ringstrom G, Abrahamsson H, Strid H et al. : Why do subjects with irritable bowel syndrome seek health care for their symptoms? *Scand J Gastroenterol* 2007; 42: 1194. [PubMed: 17852851]
48. Moldwin RM: Similarities between interstitial cystitis and male chronic pelvic pain syndrome. *Curr Urol Rep* 2002; 3: 313. [PubMed: 12149163]
49. Munce SE and Stewart DE: Gender differences in depression and chronic pain conditions in a national epidemiologic survey. *Psychosomatics* 2007; 48: 394. [PubMed: 17878497]
50. Warren JW, Howard FM, Cross RK et al. : Antecedent nonbladder syndromes in case-control study of interstitial cystitis/painful bladder syndrome. *Urology* 2009; 73: 52. [PubMed: 18995888]



Multidimensional conceptual model of unexplained clinical conditions

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1.

Symptoms and syndrome overlap among urological and nonurological unexplained clinical conditions in studies comparing at least 2 groups

References	Groups (No. pts)	Diagnostic Criteria	Study Methods	Major Findings
Waylonis and Heck <sup>4</sup>	FM (554), controls (169)	Physician diagnosis	Medical history questionnaire	Pelvic pain in 68.4% of males with FM vs 0% of male controls + in 65.8% of females with FM vs 33.3% of female controls
Kozioł <sup>21</sup>	IC (565), healthy controls (171), pts without IC	Physician diagnosis	Medical history questionnaire	IBS in 22.5% of pts with IC vs 6.7% of controls (p < 0.0001)
Walker et al <sup>25</sup>	IBS (60), IBD (26)	Physician diagnosis, symptom based	Structured psychiatric interview, self-reported interview, medical + psychiatric history questionnaire	CPP in 35% of pts with IBS vs 13.8% of those with IBD (p < 0.05)
Clauw et al <sup>5</sup>	FM (60), IC (30), controls (30)	American College of Rheumatology, National Institutes of Health IC criteria	Questionnaire on current + lifetime history of symptoms + syndromes, tender point examination	Of pts 12% with IC met FM criteria, 23% with FM vs 2% of controls had bladder fullness symptoms, 23% with FM vs 4% of controls had urinary urgency symptoms + 27% with FM vs 2% of controls had pelvic pain
Ostensen + Schei <sup>6</sup>	Musculoskeletal disorders (1,988), controls (2,046)	Symptom based	Health problem questionnaire, self-reported history of health problems + behaviors, health screening	Of women consulting for FM symptoms 4% had gynecological symptoms including CPP
Aaron et al <sup>20</sup>	Twins with chronic fatigue or CFS (127), control twins (127)	Symptom based	Questionnaires on demographics, habits, lifestyle, physical conditions + checklist of medical disorders, fatigue classified according to 3 levels of stringency	Twins with fatigue at the 3 levels were 2–20 times more likely to have IC + 3.5–6 times more likely to have CPP than co-twins without fatigue
Erickson et al <sup>7</sup>	IC (35), controls (35)	Physician diagnosis, NIDDK criteria	University of Wisconsin questionnaire	Pts with IC had higher scores than controls for other pelvic discomfort, backache, dizziness, chest pain, aches in joints, abdominal cramps + headache (p < 0.01)
Zimmerman <sup>26</sup>	IBS (53), IBD (55), controls (56)	Clinical criteria, Rome I IBS criteria	Standardized questionnaire	Pts with IBS had higher urinary symptom scores than those with IBD (p < 0.02) + controls (p < 0.001)
Novi et al <sup>23</sup>	IC (46), controls (46)	ICD-9	Standardized IC symptom questionnaire, Rome II standardized IBS questionnaire	Women with IC 11 times more likely to be diagnosed with IBS than controls (95% CI 2.7–52, p < 0.001)
Arnold et al <sup>8</sup>	Vulvodynia (208), controls (77)	Physician diagnosis	Questionnaire on health history, use of health system, quality of life + vulvodynia	Pts with vulvodynia 3.84 times more likely to report FM (95% CI 1.54–9.55) and 3.11 times more likely to report IBS (95% CI 1.60–6.05) than controls
Clemens et al <sup>22</sup>	CP/CPPS (174), IC (111, men excluded)	ICD-9	Questionnaires on medical history, lifestyle + reproductive history in females	IBS in 22.4% of pts with CP/CPPS + 40% of those with IC
Grace + Zondervan <sup>24</sup>	CPPS (286), dysmenorrhoea (286), dyspareunia (110), healthy controls (397)	Symptom based, Rome II criteria	Postal questionnaire on women's health and functioning	Of women with CPP symptoms 37.3% met IBS criteria
Kato et al <sup>9</sup>	Twins with CWP (1,776), control twins (41,562)	Symptom based, ACR criteria for CWP	Symptom questionnaire, standardized questionnaires, structured psychiatric interview	Urinary tract problems in 23.4% of twins with CWP vs 10.7% of control twins

References	Groups (No. pts)	Diagnostic Criteria	Study Methods	Major Findings
Kennedy et al <sup>10</sup>	PBS symptoms (190) bladder pain (55), gynecology pts without bladder symptoms (400)	Symptom based, Rome II criteria	Standardized questionnaires, medical history questionnaires	Of pts with vs without bladder pain 48% vs 14% had IBS (p <0.01) + 27% vs 7% had generalized pain (p <0.01)
Pontari <sup>11</sup>	CP/CPPS (463), control (121)	Symptom based	Medical history + sexual practice epidemiological questionnaires	IBS history in 12.8% of pts with CP/CPPS symptoms vs 2.5% of controls, musculoskeletal, rheumatological or connective tissue disease history in 21.2% vs 10.8% + CFS history in 2.2% vs 0.8%
Shaver et al <sup>12</sup>	FM (442), control (205)	Physician diagnosis	Medical diagnosis + lifestyle behavior telephone survey, standardized questionnaires	Bladder infection in 68.4% of pts with FM vs 47.2% of controls
Wu et al <sup>13</sup>	IC (992), control (9, 920)	Physician diagnosis	Database analysis	IC diagnosis probability in women vs men within 3 yrs after initial FM diagnosis 0.59% vs 0.08% if 1 IC episode + 0.77% vs 0.09% if multiple episodes, + within 3 yrs after initial IBS diagnosis 0.83% vs 0.08% if 1 IC episode + 1.14% vs 0.09% if multiple episodes
Wu et al <sup>14</sup>	IC (749), control (1,498)	Physician diagnosis	Database analysis	IBS in 7.21% of pts with IC vs 1.47% of controls + FM in 8.68% vs 3.34%
Arnold et al <sup>15</sup>	Vulvodynia (100), control (325)	Symptom based	Medical + pain history, + health care use telephone survey	Women with vulvodynia symptoms vs controls were 2.78 times more likely to report CFS (95% CI 1.33–6.19), 2.15 times more likely to report FM (95% CI 1.06–4.36) + 1.86 times more likely to have IBS (95% CI 1.07–3.23)
Berger et al <sup>16</sup>	CP/CPPS (62), control (98)	Physician diagnosis	Standardized questionnaires, manual tender point examination	Of pts with CP/CPPS 16.7% vs 11.8% of controls had high manual tender point examination scores (OR 2.64, 95% CI 0.93–7.51, p = 0.069)
Kennedy et al <sup>28</sup>	Primary vulvar disease (324), gynecology control (321)	Physician diagnosis, 1999 Rome II IBS criteria	Standardized questionnaires	Pts with dysplasia, vestibulitis, lichen sclerosus, lichen planus + lichen simplex were 3–26.7 times more likely to have IBS than controls
Whitehead et al <sup>27</sup>	IBS (3,153), IBD (571), control (3,153)	Physician diagnosis	ICD-9 code computer search	Pts with IBS vs controls were more likely to be diagnosed with cystitis (OR 3.6, 95% CI 1.94–6.69), pelvic pain (OR 2.76, 95% CI 2.13–3.58) + prostatitis (OR 2.65, 95% CI 1.70–4.10)
Araújo et al <sup>17</sup>	Lower urinary tract symptoms with (51) + without (50) FM	Physician diagnosis, symptom based	Urinary symptom + health function questionnaire, gynecologic examination, urodynamics, filling cystometry	Urge urinary incontinence in 64% vs 90.2% of pts with vs without FM (p = 0.004), increased urinary frequency in 8% vs 31.4% (p = 0.007) + detrusor overactivity in 28% vs 60.8% (p = 0.002)
Clemens et al <sup>18</sup>	IC/PBS (239), control (717)	Physician diagnosis	ICD-9 code computer search	Gastritis or duodenitis in 1.7% of pts with IC/PBS vs 0.7% of controls (OR 12.2, p = 0.004) + myalgia or myositis in 16.3% vs 6.1% (OR 3.0, p <0.00001)
Dimitrakov et al <sup>19</sup>	CP/CPPS (27), control (29)	NIDDK criteria	Standardized questionnaire, blood + urine tests	Ax 2.4 comorbid disorders in pts with CP/CPPS (CFS, FM or arthritis in 7 + IBS in 6)

**Table 2.** Symptom and syndrome overlap among urological and nonurological unexplained clinical conditions in studies of 1 group

References	Groups (No.)	Diagnostic Criteria	Study Methods	Major Findings
Maxton et al <sup>36</sup>	• IBS (100)	Physician diagnosis, symptom based	Interview assessing symptoms, standardized questionnaire	Urinary problems in 56% of pts
Walker et al <sup>38</sup>	• CPP (137)	Symptom based	Physician diagnosis, standardized questionnaires	IBS symptoms in 79% of pts
Alagiri et al <sup>30</sup>	IC (2,682)	Symptom based, patient registry	Symptoms + syndrome medical history questionnaire	IBS diagnosis in 30.2% of pts, IBS symptoms in 37.7%, FM diagnosis in 17.2%, FM symptoms in 28.6%, CFS diagnosis in 8.7% + CFS symptoms in 13.8%
Korszun et al <sup>33</sup>	• CFS +/-or FM (92, TMD in 42%)	1990 American College of Rheumatology FM criteria, 1988 Centers for Disease Control + Prevention CFS criteria	Prior psychosomatic illness, facial pain + TMD questionnaire	IC history in 19% of pts with CFS +/-or FM + 13% with TMD
Giamberardino <sup>34</sup>	• IC (2,405)	NIDDK, 1999 Rome II IBS criteria	Standardized questionnaires	IBS criteria met in 75% of pts
Nimnuan et al <sup>29</sup>	Gastroenterology, gynecology, neurology, rheumatology, respiratory medicine, cardiology + dentistry clinics (550)	Symptom based	Various syndrome questionnaire, severity, sleep + psychological complaint measures	Of pts with CPP symptoms, 19% had IBS symptoms, 19% had FM symptoms + 8% had CFS symptoms
Zondervan KT: Am J Obstet Gynecol 2001; <b>184</b> : 114	Oxfordshire Health Authority Register randomly selected women (3,916)	Symptom based	Women health issue questionnaire	IBS and CPP in 114 women
Gordon et al <sup>31</sup>	Internet savvy women on vulvar pain discussion lists (428)	Symptom based	Web based survey	IBS in 34.6%, FM in 20.6%, TMD in 18.5% + chronic fatigue in 11.2% of women
Blanchard et al <sup>37</sup>	IBS (196)	1999 Rome II IBS criteria, physician diagnosis	Standardized questionnaires	Urinary track disorders in 26% of 50 pts with IBS
Bernatsky S: Swiss med wkly 2005; <b>135</b> : 76	FM (180)	1990 American College of Rheumatology FM criteria, physician diagnosis	Clinical + psychosocial variable, health care use + standardized questionnaires	IBS in 36.1%, CFS in 2.2% + irritable bladder in 1% of pts
Williams et al <sup>39</sup>	CPP (987)	1988 Rome I IBS criteria	Standardized questionnaires	IBS criteria met in 35% of pts
Yamada et al <sup>32</sup>	IC (30)	NIDDK, 1990 American College of Rheumatology FM criteria, physician diagnosis	Standardized questionnaires	FM diagnostic criteria met in 11% of pts
FitzGerald et al <sup>35</sup>	Pain associated with urinary symptoms (589)	Symptom based	Questionnaires	IBS in 30%, CFS in 18% + FM in 9% of pts
Hughes L: Orthopaed Nurs 2006; <b>25</b> : 112	FM (107)	1990 American College of Rheumatology FM criteria	Standardized questionnaires, physical measures	Fatigue, pelvic pain + physical trauma explained 23% of sensory pain score variance, + activity level, depression + pelvic pain explained 23% of affective pain score variance



Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

References	Groups (No.)	Diagnostic Criteria	Study Methods	Major Findings
Temml C: Eur Urol 2007; 51: 803	IC symptoms (981)	Symptom based	Standardized questionnaires	Women with bowel disorders at 4.5-fold increased risk for moderate or severe IC symptoms (95% CI 1.3–15.1, p = 0.016)
Fenton et al <sup>40</sup>	CPP (175)	Physician diagnosis, 1999 Rome II IBS criteria	Questionnaires, physician examination	IC in 35%, IBS in 24% + myalgia in 45% of pts