Central Sensitivity Syndromes: A New Paradigm and Group Nosology for Fibromyalgia and Overlapping Conditions, and the Related Issue of Disease versus Illness

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Objectives: To discuss the current terminologies used for fibromyalgia syndrome (FMS) and related overlapping conditions, to examine if central sensitivity syndromes (CSS) is the appropriate nosology for these disorders, and to explore the issue of disease versus illness.

Methods: A literature search was performed through PubMed, Web of Science, and ScienceDirect using a number of keywords, eg, functional somatic syndromes, somatoform disorders, medically unexplained symptoms, organic and nonorganic, and diseases and illness. Relevant articles were then reviewed and representative ones cited.

Results: Terminologies currently used for CSS conditions predominantly represent a psychosocial construct and are inappropriate. On the other hand, CSS seems to be the logical nosology based on a biopsychosocial model. Such terms as "medically unexplained symptoms," "somatization," "somatization disorder," and "functional somatic syndromes" in the context of CSS should be abandoned. Given current scientific knowledge, the concept of disease–illness dualism has no rational basis and impedes proper patient–physician communication, resulting in poor patient care. The concept of CSS is likely to promote research, education, and proper patient management.

Conclusion: CSS seems to be a useful paradigm and an appropriate terminology for FMS and related conditions. The disease–illness, as well as organic/non-organic dichotomy, should be rejected.

 Semin Arthritis Rheum 37:339-352

Keywords: *central sensitivity syndromes, fibromyalgia, overlapping syndromes, functional somatic syndromes, medically unexplained symptoms, somatization, disease versus illness*

It is now known that fibromyalgia syndrome (FMS) overlaps, and is associated with, several other similar syndromes that include chronic fatigue syndrome (CFS), irritable bowel syndrome (IBS), and tension type headaches (TTH) among others (Fig. 1). Collectively, I have called them central sensitivity syndromes (CSS) (1-3). Several names have been used in the literature for these conditions as a group. In this article, I discuss these terminologies and argue that CSS is a preferred nosology. I shall also discuss the related issue of diseases versus illness.

METHODS

Literature search was performed through PubMed, Web of Science, and ScienceDirect using a number of keywords that included "functional syndromes," "functional somatic syndromes," "medically unexplained symptoms," "somatoform disorders," "somatization disorder," "somatization," "psychosomatic syndromes," "psychosomatic pain," "organic and nonorganic," and "disease and illness." Articles were also obtained by clicking Related Articles on a pertinent citation shown in PubMed, and by the bibliography provided by the author(s). Relevant articles were

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The author has no conflict of interest to disclose.

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0049-0172/08/$-see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.semarthrit.2007.09.003

Abbreviations	
CFS	Chronic fatigue syndrome
CNS	Central nervous system
CRPS	Complex regional pain syndrome
CS	Central sensitization
CSS	Central sensitivity syndrome
DSM	Diagnostic and statistical manual of mental disorders
FMS	Fibromyalgia syndrome
HPA	Hypothalamic-pituitary-adrenal
IBS	Irritable bowel syndrome
IC	Interstitial cystitis
MPS	Myofascial pain syndrome
MUS	Medically unexplained symptoms
NEI	Neuroendocrine-immune
NFR	Nociceptive flexion reflex
NGF	Nerve growth factor
NMDA	N-methyl-D-aspartate
PMS	Premenstrual syndrome
RA	Rheumatoid arthritis
RSTPS	Regional soft-tissue pain syndrome
SP	Substance P
TP(s)	Tender point(s)
TMD	Temporomandibular disorders
TTH	Tension-type headaches
VVS	Vulvar vestibulitis syndrome
WSP	Widespread pain

reviewed and selected representative ones cited. Finally, the author's own views were incorporated.

RESULTS

Nosology Used in the Literature for CSS Conditions

Nosology is not simply about names, but names that should meaningfully and ideally depict the essence of a disease or a disorder, although such "meaning" may change over time. A misleading name may result in misleading concepts and treatment that may be harmful. Not too long ago, some patients labeled as "fibrositis" were treated with corticosteroids (4), since it was considered an inflammatory disease.

Several terms have been used for CSS conditions, including "functional" (5), "functional somatic syndromes" (6,7), "fashionable diagnoses" (8), "nondisease" (8), "somatization disorders" (8), "polysymptomatic somatizers" (9), "somatization spectrum conditions" (10), "psychosomatic syndromes" (11,12), "medically unexplained symptoms" (13-15), and "idiopathic pain disorders" (16), among several others. However, these terms are irrelevant to the CSS concept that is based on mutual associations among the members with overlapping clinical features and are bound by a common pathophysiological glue of central sensitization (CS). A number of authors wrongly state that the CSS symptoms are not medically explicable and are psychiatric, psychological, or psychosocial in nature (6-14,17-20), with which I disagree.

Manu states that there is "absence of proven pathophysiological mechanisms" (6). Barsky and Borus' description of "functional somatic syndromes" disorders as psychosocial constructs (7) was widely criticized for ignoring the biophysiological basis of these syndromes (21,22). The term "idiopathic pain disorder" (16) in describing CSS is also inaccurate, since recent research has advanced a fairly good understanding of the CSS disorders. They are no more "idiopathic" than some pain disorders with structural pathology, eg, complex regional pain syndrome (CRPS). To tell a patient with CSS (wrongly) that "we do not know the cause of your pain" would only accelerate her or his anxiety.

Of all the terms, "fashionable diagnoses" (8) is most reckless and disparaging, since it is dismissive of the very existence of the CSS disorders and the true suffering of the patients with these diseases. For this article, I use "disease" and "illness" synonymously, as will be discussed later.

Functional/Functional Somatic Syndromes

The term "functional" (as in "functional disorder" and "functional somatic syndromes") is intriguing, considering that there is dysfunction of the neuroendocrine system as well as dysfunction of normal daily activities in these

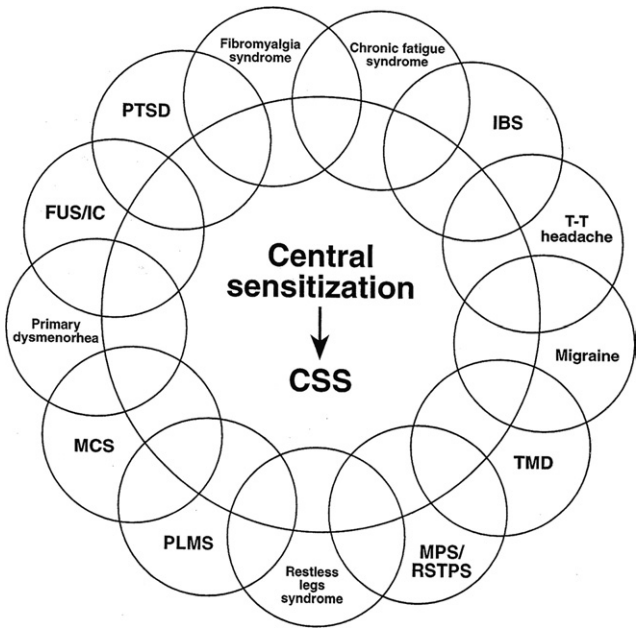

Figure 1 Currently proposed members of the CSS family. The common binding glue of pathophysiology among them is central sensitization.
IBS, irritable bowel syndrome; T-T headache, tension-type headache; TMD, temporomandibular disorders; MPS, myofascial pain syndrome; PLMS, periodic limb movements in sleep; MCS, multiple chemical syndrome; FUS, female urethral syndrome; IC, interstitial cystitis; PTSD, posttraumatic stress syndrome.
Modified from Yunus (120). Premenstrual syndrome and vulvodynia/vulvar vestibulitis syndrome also belong to the CSS spectrum (see text).

disorders. If the word "functional" is supposed to mean a derangement of function, should it not be applied also to all "organic" diseases that result in an impairment of function? "Functional somatic syndromes" have been inappropriately explained by psychological or psychosocial mechanisms (6,7), and the term "functional" has a negative connotation among patients (10).

Do CSS Disorders Represent Somatization?

Despite widespread use of the Diagnostic and Statistical Manual of Mental disorders (DSM), the DSM-IV-TR (Text Revision) criteria for somatization disorder (23) are fallacious and confusing (24-29). The current status of somatoform disorders is best characterized by stating that they are in a disorderly state of flux in search of meaningful and rational conceptual stability. Nearly 80% of patients with somatoform disorders have overlapping depression and anxiety by DSM-IV criteria (28), thus raising the issue of the specificity of these disorders. Martin talks of "dubious logic and the inconsistencies that underlie linking of the various diagnoses under the Somatiform Disorder rubric" (26). Mayou and colleagues suggest its abolition for future DSM-V (25). They instead describe them as "medically compatible" functional somatic syndromes, with greater integration of psychiatric factors on various axes. However, such terminology would be equally confusing and misleading. What is important, however, is not to include any CSS condition under the label of somatoform disorders.

The term somatization has been defined as representing physical expression of psychologic distress (8). Somatization disorder (a subcategory of somatoform disorders) is a psychiatric condition that is often interpreted by some physicians and their patients as being "all in the mind" (10). Historically this condition has been referred to as hysteria or Briquet's syndrome (23). Patients resent being labeled a somatizer, which implies self-culpability, and it creates patient–physician hostility (24). Physician researchers, who also care for CSS patients, have stated that CSS cannot be regarded a somatization or a somatoform disorder (30,31).

Let us examine if the CSS conditions represent somatization disorder. By DSM-IV-TR criteria it essentially consists of multiple symptoms (at least 8 symptoms among many) that "cannot be fully explained by a known medical condition" (23). Multiple symptoms in a CSS condition are due to its association with multiple other CSS members affecting different systems, most of which can be explained by the CS mechanism (3). Without the recognition of CSS disorders as medical conditions, they are likely to satisfy the criteria for somatization disorder. However, what is and what is not a medical condition needs a fresh appraisal. I argue that CSS are medical conditions.

In somatization disorder, "physical examination is remarkable for the absence of objective findings," and laboratory tests "are remarkable for the absence of findings to support the subjective symptoms" (23). None of these 2 statements are true of CSS diseases. CSS disorders, particularly FMS, have consistently demonstrated a greater number of tender points (TPs) than controls on physical examination (31). It has been stated that TPs are not true physical findings, since they depend on patient response to pressure, and are therefore subjective (8). This is also true, however, of tenderness elicited in a body part in many diseases with structural pathology (the so-called organic diseases), eg, the joint in rheumatoid arthritis (RA) and abdomen in Crohn's disease. Also, TPs are generally stable and reproducible on follow-up (32), and there is a good interrater reliability in TP examination (33,34). Importantly, the underlying hyperalgesia and allodynia represented by TPs can be demonstrated by objective neurophysiologic tests (35-39).

TPs Represent CS (1-3)

The nonsubjective test for CS in the human pain laboratory is an enhanced nociceptive (spinal) flexion reflex (NFR), that is obtained by directly stimulating the sural nerve electrically, and measuring the electromyographic response of the biceps femoris (35). NFR bypasses the peripheral nociceptors as well as the oral response of pain by the subjects. Oral response, however, is used to keep stimulus intensity within the tolerance level of a subject. Thus, it directly excites the nociceptive pathway and is regarded a specific and objective physiologic correlate of pain sensation (35). NFR is mediated by central mechanisms at the spinal cord level. An accentuated NFR (or decreased stimulus threshold) is indicative of CS and has been demonstrated in several CSS members, eg, FMS (35), IBS (38), TTH (39), and myofascial pain syndrome (MPS)/regional soft tissue pain syndrome (RSTPS) (36). The issue of response bias (eg, expectancy and hypervigilence) to different peripheral stimuli (eg, pressure, heat, and electric) has been raised. However, use of these stimuli in ascending and random paradigms in FMS has demonstrated an absence of such bias (40). With the ascending method, a patient may report increased or decreased pain sensitivity because of anticipation of a painful stimulus of the same intensity (as is usually the case in TP examination). Such a response bias is obviated with random stimuli of varying intensity (40).

The most consistent laboratory finding in CSS is the presence of CS that can be tested in the human pain laboratory. Other objective testing besides NFR includes functional magnetic resonance imaging and cerebral evoked potential recorded by electroencephalography (2,3). CS is mediated by a number of neurotransmitters or neuromodulators that are measurable (3,41). Additionally, a number of neuroendocrine tests are abnormal in FMS and CFS (42). Several laboratory findings are also abnormal in IBS (43). The current laboratory tests in CSS are not specific, but this is also true of many diseases with

structural pathology. For example, a positive rheumatoid factor or an antinuclear antibody is not specific for any particular disease.

Among other features, somatization disorder *must* (emphasis is mine) include symptom onset before age 30 years, and common associated features include *loss* (my emphasis) of touch and pain sensation, inconsistency in history, and antisocial behavior (23). Fibromyalgia symptoms in most patients begin after the age 30 years; 1 study of elderly fibromyalgia patients showed that 45% of the patients had their symptom onset at or after the age of 60 years (44). In follow-up visits, patients with FMS and other CSS conditions give a remarkably consistent history, along with consistent presence of TPs in FMS. CSS patients are not known for their antisocial behavior, and importantly, these patients show global *hyper*sensitivity to touch (causing pain), pressure, and other stimuli, rather than a *loss* of these sensations (1-3).

Somatization has been defined as an illness behavior in which an individual communicates psychological distress through unexplained physical symptoms (8,45). Given the above definition, the term "somatization" continues to be used improperly as a psychological variable in the context of widespread pain (WSP) (an essential component of FMS) (46-48). The Somatic Symptom Checklist used to evaluate somatization (46) consists of 7 symptoms, of which memory loss is associated with CFS and FMS (49); pain in fingers and toes are well known to be present in FMS and CFS as part of generalized pain; menstrual cramps are manifestations of dysmenorrhea (a member of the CSS family); and frequent vomiting is a symptom of functional dyspepsia (50). There is evidence for CS in all 4 of these conditions (2,3). Considering that CS has been clearly demonstrated in WSP (ie, reduced tourniquet tolerance, and decreased threshold to heat, cold pressure, and von Frey stimuli) (51), it is incorrect to state that somatization *as a psychological phenomenon* is a risk factor for WSP (46). I suggest that the term "somatization" is replaced with "multiple symptom reporting" in the context of CSS. From the above discussion, it is clear that CSS do not represent a somatoform disorder, including somatization disorder.

Medically Unexplained Symptoms (MUS)

Just why so many authors use the term MUS, that also includes CSS conditions (13-15), is unclear. MUS was probably first used by de Figueiredo in 1980 to describe a case of Briquet syndrome, a psychiatric disease (52). Since then, this term has been used to describe any condition that lacks structural pathology in the tissues (13-15). MUS is an inaccurate term for CSS, with false definition of organicity and pathology and no standardized criteria. Like many, Nettleton describes it as a pure psychosocial construct (13). Binder provides as many as 17 references in support of the statement that many experts regard MUS as "surrogates for psychological disorders" (14). Such "psychocentric" position may perhaps be partly explained by the fact that a good number of the authors come from a psychological or psychiatric background, understandably with greatest interest in their own specialties.

The literature is burdened with a large number of articles on MUS or similar tautological appellations, with little or no discussion of their biological aspects (6-14,17-20). Common to most of these publications is the repetitive claim of "no evidence for organic pathology" and "no explanation for symptoms." I think both these assertions are fallacious, as I shall discuss below.

Pathophysiology and Explaining the Symptoms of CSS

Definition of Pathology

Much of the problem is the outdated definition of pathology, born out of the curse of the Cartesian concept of mind–body dualism. The word "pathology" has come to mean structural pathology only. It has been defined as "the medical science, and specialty practice, concerned with all aspects of disease, but with special reference to the essential nature, causes and development of abnormal conditions, as well as the structural and functional changes that result from disease process" (53). Two important aspects of the above definition are "abnormal conditions" and "functional changes," that are true of the CSS. Since abnormality can be objectively and reproducibly demonstrated in the neuroendocrine-immune (NEI) systems in CSS diseases by current brain imaging techniques as well as neurophysiological testing in the human pain laboratory, the definition of pathology should include both structural and NEI changes. These changes in CSS conditions include CS (1-3,35-41,51,54-57) as well as neuroendocrine dysfunction (41,42). NEI pathology can be literally visualized by modern imaging techniques (3,37). With regards to NEI, the role of the immune system in pain physiology and CS (58) will be briefly described in the section below. An interaction between the nervous system, hormones, and immunity has been well described in the literature (59).

It is mysterious why only diseases with structural pathology are called "organic," as if the spinal cord and brain cease to be organs if they show NEI pathology! I think the word "organic" should be replaced with "diseases with structural pathology" (versus diseases with NEI pathology).

Central Sensitization

Common to the pathophysiological mechanisms of CSS diseases is CS as stated above. CS is clinically and physiologically characterized by hyperalgesia (excessive sensitivity to a normally painful stimulus, eg, pressure), allodynia (painful sensation to a normally nonpainful stimulus, eg, touch and massage), expansion of the recep-

tive field (pain beyond the area of peripheral nerve supply), prolonged electrophysiological discharge, and an after-stimulus unpleasant quality of the pain (eg, burning, throbbing, tingling or numbness) (3,54,55). CS is mediated by the central nervous system (CNS).

The physiology of CS (3,54,55) involves activation of the nociceptors of the A-delta and C fibers at the peripheral tissues by bradykinin, serotonin, prostaglandins, and substance P (SP) among others, following inflammation that may be caused by even minor trauma (3). C fibers are involved in chronic pain. The nociceptive impulses carried through these fibers travel to the wide dynamic range neurons in the spinal cord. These second-order neurons contain both nociceptive and nonnociceptive fibers, so that intense activation of the nociceptive fibers may also activate the surrounding nonnociceptive fibers. The activated C fibers express, at their nerve terminals, several neurotransmitters or neuromodulators eg, SP, nerve growth factor (NGF), calcitonin gene-related peptide, vasoactive intestinal peptide, glutamate, aspartate, and brain-derived neurotrophic factor. These chemicals cause a barrage of impulses at the synapse that now hyperexcite the postsynaptic receptors, eg, neurokinin 1, *N*-methyl-D-aspartate (NMDA), metabotropic glutamate, and protein kinase gamma. Activation of these receptors results in a remarkable physiologic change in the postsynaptic nerve cells, including membrane changes, intracellular influx of calcium, protein kinase activation, and expression of c-fos. These changes cause an escalation of hyperexcitability of the second-order neurons, giving rise to hypersensitivity to various peripheral stimuli along with other characteristics of CS as stated before.

Parallel to CS, temporal summation takes place in the second-order neurons. It is characterized by a progressive increase in electrical discharges (and corresponding increase in pain) in response to each repetitive stimulation (more often than every 3 seconds) of peripheral C fibers. Summation has the typical elements of CS. NMDA receptors mediate summation, and it can be inhibited by NMDA receptor antagonists, eg, ketamine and dextromethorphan (3,54). NMDA receptors are believed to play an essential role in human chronic pain and are in fact vital for nervous system functioning, so that they are widely present in both the peripheral and the CNS tissues.

Increasingly, immunological mechanisms in pain physiology are being recognized. Activation of immune-like glial cells in the CNS may release pro-inflammatory cytokines and enhance neuronal excitability, causing CS and pain (58).

It is important to remember that pain has an important psychological component, ie, the affective (unpleasant emotional feelings) dimension, as well as attentional and cognitive aspects, that is based on CNS mechanisms (3,37,60). Emotion and selective attention enhances pain perception. This form of CS is mediated by the forebrain with involvement of the descending pathways having a facilitatory effect on dorsal horn neurons (60).

CS is normally dampened by an inhibitory mechanism that involves descending as well spinal cord neurons. The neurotransmitters involved in such inhibition of pain include serotonin, norepinephrine, enkephalins, gamma-amino-butyric acid, and dopamine (3,41,54). It follows that CS may result from excess neurochemicals that transmit pain (eg, substance P and NGF) or from a decrease in neurotransmitters that inhibit pain, such as serotonin, norepinephrine, and dopamine.

Multiple Interacting Factors in CSS

CS may not be the only pathophysiological mechanism for CSS diseases. Other factors, which may or may not be related to CS, include genetics, sympathetic overactivity, endocrine dysfunctions (eg, relative hypofunction of the adrenal cortex and decreased growth hormone), viral infection, peripheral nociception generators (eg, arthritis), poor sleep, environmental stimuli (weather, noise, chemicals, adverse childhood experience), and psychosocial distress (3,47,48). CSS should perhaps be regarded not just as multifactorial but also as "factors multiplied," implying that the several factors in combination may amplify and sustain CS and/or cause symptoms through their interactive and synergistic actions. As examples, CS, in combination with genetic predisposition, predicts future temporomandibular disorders (TMD) among asymptomatic subjects (61); dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis in conjunction with psychological distress predicts future WSP (62); trauma from a motor vehicle collision in association with preexisting psychological factors causes FMS (63). Genetic factors have been documented in almost all CSS conditions (3).

The Concept of CSS

The Yunus criteria for CSS are based on (a) mutual associations (1-3,64) *and* (b) the presence of CS among the CSS members (1-3). Additionally, a CSS disorder should be based on NEI pathology; a concurrent disease with structural pathology is not an exclusion. Based on these criteria, studies have shown that premenstrual syndrome (PMS) and vulvodynia/vulvar vestibulitis syndrome (VVS) are also members of CSS, in addition to those shown in Figure 1. PMS is associated with FMS (65) and shows CS (66). VVS demonstrates association with FMS (67) as well as CS (68,69). CS has been demonstrated in various conditions by using different modalities of stimuli, eg, pressure (including pressure by balloon distension in the rectum of IBS patients), heat, cold, electric, ischemic, and laboratory-generated noise in a large number of studies (2,3). Just as a few examples, FMS patients showed hypersensitivity to pressure, cold, and electric stimuli (3,35,51,70); IBS patients to rectal pressure (71,72), rectal heat (71,72), and electric stimuli (38); TMD patients

showed hypersensitivity to thermal and ischemic stimuli (73); TTH patients to heat and pressure (74) as well as electric (39) stimuli; migraine patients to mechanical and heat stimuli (75); and MPS/RSTPS patients showed hypersensitivity to pressure (76) and electricity (36).

The concept of CSS embraces both biology and psychology. CS may be modulated by psychological distress, although data are limited at this time (3). Anxiety predicts CS in healthy individuals (77). Catastrophizing in FMS is associated with decreased pain threshold and tolerance (78). Moreover, pain catastrophizing is associated with increased activity in certain brain areas (79). Psychological factors in CSS will be discussed at the end of the next section.

Explaining the CSS Symptoms

Despite claims to the contrary (6-8,13,14,17-20), many symptoms of the CSS can be medically explained on the basis of current biological mechanisms that are likely to act, in a subgroup of patients, in concert with psychosocial factors. Such an interaction between biology and psychology is also true of all chronic diseases, irrespective of NEI or structural pathology. The most striking example in diseases with structural pathology is the consistent relationship between depression and coronary artery disease (80,81). The postulated mechanisms of this link are abnormal blood coagulation, inflammation, and autonomic nervous system dysfunction (81), as well as a common genetic predisposition (81).

CSS can be explained by NEI pathology, although further studies are needed. Similar to many diseases with structural pathology, such explanation is incomplete at this time. Pain, either as a spontaneous symptom or resulting from a stimulus, is generally explicable by CS. Pain symptoms correlate with CS in FMS (82-84), IBS (85), chronic low back pain (86), and MPS/RSTPS following whiplash injury (87).

Some studies failed to find a correlation between CSS symptoms and CS (38,51,65,88). The issue of correlations between CSS symptoms and CS is not straightforward, given that both chronic pain and CS are very complex phenomena. CS depends on a large number of factors, including genetics, measurement of pain perception versus threshold or tolerance, subgroups, intersubject variability of symptoms, types of tissues stimulated, psychosocial factors, and the types of stimuli used, eg, digital pressure, dolorimetry, heat, ischemia, or electricity (3). A better correlation may be found if all the above factors are addressed. Moreover, the nature of pain in the laboratory is transient as contrasted with chronicity of pain in CSS. Future research may show a cause–effect relationship between CS and several symptoms.

In general, it seems that CS, despite its enormous complexity, may explain several symptoms of the CSS, including pain and poor sleep (discussed below), as well as hypersensitivity to environmental stimuli, eg, sound, as tested by laboratory-generated noise in FMS (89) and IBS (90). Numbness, a symptom in FMS (31,44), may be explained by CS, since it is a manifestation of central pain (2,3,54). As part of CS, expansion of the receptive field may account for widespread pain, and prolonged postsynaptic discharge with lingering pain may explain chronicity.

Enhanced neurotransmission and decreased pain inhibition in CS (both resulting in amplified pain) are mediated by several neurotransmitters or neuromodulators that may explain clinical pain. Neurotransmission mediated by SP, calcitonin gene-related peptide, vasoactive intestinal peptide, and NGF are increased in CSS conditions (91-95). On the other hand, serotonin, norepinephrine, enkephalines, and dopamines are mediators of pain inhibition (3,54), and their decreased levels in CSS (96-102) would enhance pain. This is further evidenced by the efficacy of serotonergic/norepinephric (103-106) and dopaminergic (107) drugs in CSS conditions. It is clear that the central analgesic effects of serotonergic and norepinephric drugs in CSS conditions are different from their antidepressant effects (103,104), and they likely work by modulating pain processing in the spinal cord (104).

Since sleep difficulties may result from serotonin deficiency, as shown in CSS (96-98), it is not surprising that serotonergic drugs would help restorative sleep (103). Deprivation of sleep may cause enhanced nociception, as has been objectively demonstrated in the human sleep laboratory (108). This would suggest a causal relationship between sleep and CS. Sleep is correlated with CS assessed by algometry (109) and by TP examination (82,83). Sustained nocturnal sympathetic overactivity may also contribute to nonrestorative sleep in FMS (110), and such hyperactivity, as manifested in CRPS, demonstrates CS (111).

Fatigue in FMS cannot be satisfactorily explained by CS at this time. However, fatigue is correlated with CS (47,82,83). Fatigue is also related to poor sleep and psychological distress (31,112). Deficiency of serotonin, norepinephrine, and dopamine may partly explain fatigue, given that fatigue is significantly ameliorated by serotonergic/norepinephric (103,104) as well as dopaminergic (107) drugs.

Explanation of fatigue in CFS has been less convincing so far. A variety of abnormal neuroendocrine (56,113), immunological, and brain functions (112) have been demonstrated in CFS, but their causal relationship with fatigue remains to be determined. However, patients with CFS have demonstrated CS to electric stimuli irrespective of having musculoskeletal pain (114). Various aspects of NEI pathology, including CS, need further studies.

Psychological factors are associated with CS (47,79,82,83). Apart from an association of catastrophizing with low pain threshold and tolerance to pressure and heat stimuli in FMS (78), studies by functional magnetic resonance imaging in FMS have shown that pain catastrophization, independent of depression, is significantly

associated with pressure pain-induced activation ("sensitization") of several areas of the brain (eg, claustrum, medial frontal cortex, dorsal anterior cingulated cortex, and dorsolateral prefrontal cortex) that are related to emotional, anticipation, and attentional aspects of pain (79).

At this time the relationship between CS and the cognitive difficulties in CFS and FMS is not clear. Animal studies suggest that impairment of memory may be partly due to complex synaptic plasticity in the hippocampus that may result from stress (115).

Does CS cause CSS symptoms or does the chronicity of symptoms cause CS? The answer, actually, may be both. Several studies have demonstrated that CS antedates symptoms. CS measured by thermal and ischemic stimuli among asymptomatic individuals at baseline, in combination with 3 major haplotypes of the catechol-*o*-methyltransferase gene, predicts future TMD (116). An equally interesting observation is that dysfunction of the HPA axis antedates new onset of CWP even after controlling for depression and other psychological distress (62,117), although a relationship between the HPA axis and CS is not clearly understood. Moreover, in FMS, the presence of CS precedes symptoms, since there is an increasing gradient of TP numbers between asymptomatic normal subjects, regional pain, and WSP (76). Additionally, the asymptomatic first-degree relatives of FMS patients have multiple TPs, many of who are likely to develop FMS at a later time, given a high prevalence of FMS among these relatives (118).

A probable causal relationship between CS and symptoms of FMS is further suggested by the efficacy of several medications that decrease both symptoms (pain, poor sleep, fatigue) and CS (eg, number of TPs) in random controlled trials, as stated earlier. The known mechanisms of action of these drugs that inhibit descending pathways are compatible with their attenuation of CS (104). Taken together, it seems that an aberrant NEI function is the cause, rather than the effect, of the chronicity of CSS diseases. However, given an association between symptom duration and CS (76), it is possible that the chronicity of CSS may accentuate CS.

Psychosocial factors (eg, anxiety, stress, depression, and poor coping skills) are common in CSS (47,48,82,83,112,113,117,119,120), and their role in contributing to pain, fatigue, and poor sleep is well recognized (46,48,111,117,120,122). However, psychosocial risk factors may operate through an interacting biological mechanism (67,117).

Thus, based on the foregoing discussions, CSS should be regarded as medical conditions based on a biopsychosocial model, as is true of other chronic diseases based on structural pathology.

History of CSS

It is now well accepted that the members of the CSS family are interrelated. However, they were considered heterogeneous, even in recent publications (6), under a nebulous and nonspecific umbrella of psychological or psychosomatic conditions. Although the associations between the CSS are now accepted, the concept of their overlapping nature with mutual associations was not suggested until 1984 when Yunus first described the clinical overlap between FMS, IBS, TTH, and primary dysmenorrhea and clearly depicted their interrelationships in a Venn diagram (123) (Fig. 2). This concept was received with skepticism at that time. "What is the connection between the skeletal muscles of fibromyalgia and the smooth muscles of the bowel?" was a frequently asked question by medical residents as well as practicing physicians.

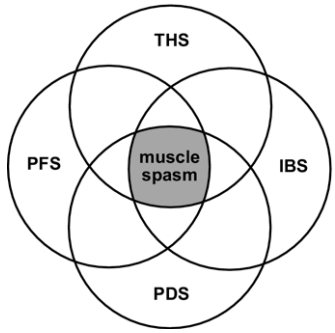

Figure 2 The first proposed concept of overlapping syndromes shown in a Venn diagram in 1984.
THS, tension-type headache; IBS, irritable bowel syndrome; PDS, primary dysmenorrhea syndrome; PFS, primary fibromyalgia syndrome.
Reproduced with permission from Yunus (123).

The first clue came in 1981 when fibromyalgia was shown to be associated with IBS, TTH, and migraine when compared with normal controls (121). The associations held even when an additional control group with chronic pain having structural pathology, eg, RA, was used (122). The hypothesized common binder of the FMS-associated conditions was thought to be muscle spasm, muscle being present in these 4 conditions (123). At that time, the idea of muscle spasm was popularized by the Mayo Clinics (124), and little was known about CS in clinical medicine. However, such muscle spasm could not be documented electrophysiologically at a later time (125).

Since 1984, only a few other terminologies have been suggested that incorporated the 2 elements of the CSS concept, ie, mutual associations and a hypothesized common physiologic binder. These are "stress-related syndromes" (126), "affective spectrum disorder" (127), "dysfunctional spectrum syndromes" (120), and CSS (1-3). Although psychosocial stress plays an important role in CSS (47,48,119,120), associated with elevated corticotrophin-releasing hormone (128), stress-related syndromes seems too general and vague, since stress may contribute to symptoms of many diseases with structural pathology as well. Affective spectrum disorder is generally inter-

Table 1 History of Central Sensitivity Syndromes (CSS)

Year	Description	Reference
1981	First data-based demonstration of associations among FMS and TTH, migraine, and IBS	121
1984	First conceptual depiction (by a Venn diagram) of an interrelationship among several CSS members with similar and overlapping features; muscle spasm is theorized to be the common pathophysiologic link	123
1985	Use of the terminology "stress-related syndromes"	126
1989	"Affective" mechanism is suggested for FMS and overlapping syndromes, including several medical ("functional") as well as psychiatric condition described as "affective spectrum disorder"	127
1994	The collective term "dysfunctional spectrum syndrome" is suggested implying the dysfunction of the neurohormonal system as the common binding mechanism among the CSS members	120
2000	The nosology "central sensitivity syndromes" is coined based on the evidence that FMS and overlapping members of the CSS family demonstrate CS to multiple stimuli. CS is proposed to be the common pathophysiological binder of the CSS diseases	1

preted as depression being the common link among the CSS disorders. This term is not appropriate, given the fact that a minority subgroup of patients with CSS is depressed, and, as will be discussed later, depression is biologically different from many CSS diseases. Depression alone does not explain CSS, and it is present in diseases with structural pathology as well. The term dysfunctional spectrum syndromes was suggested because of the underlying common link of dysfunction of the neuroendocrine systems, but this, too, is nonspecific.

The nosology "central sensitivity syndromes (CSS)" was first coined by Yunus in 2000 based on the observation that the common pathophysiological link among its members is CS that was shown to be present among several CSS members in a number of studies (1). In an earlier article, Bennett had reviewed the evidence of CS in FMS (55). Since then the evidence for CS among the CSS diseases has been mounting (2,3). The history of CSS is shown in Table 1.

Disease versus Illness

Related to the topic of nosology is the issue of currently defined disease (based on structural pathology) versus illness (absence of such pathology). Thus, CSS conditions are presently viewed as illnesses. Esterson defined illness as "an experience . . . It cannot be investigated by methods of bio-medicine because its study ultimately depends directly on phenomenological analysis of experienced suffering through individual self-reports and behavior" (129). Disease, on the other hand, "is demonstrable pathophysiology or pathochemistry, and is demonstrable by pathologic findings" (129). Since mental disorders as defined by American Psychiatric Association (130) are also referred to as mental illness (131), psychiatric disorders, eg, depression and anxiety, will be included in the illness category for discussion.

With currently available methodology, eg, experiments in the human pain laboratory and sophisticated brain imaging procedures, the pathophysiology and pathochemistry of the CSS disorders can now be objectively demonstrated, as I have already discussed. These conditions, therefore, would qualify as diseases. The symptoms of CSS are not just phenomenological or purely subjective experiences.

The word "disease" is derived from 'dis-ease' and simply means a lack or opposite of ease and has been defined as "an interruption, cessation, or disorder of bodily functions, systems, or organs" (132). CSS patients with dysfunction of the NEI system would fit into this definition, and they suffer as much as those with a structural pathology.

The boundary between currently defined disease and illness is nebulous and highly porous, and the dualism challenges logic. In fact, DSM-IV-TR states that "a compelling literature documents that there is much "physical" in "mental disorders" and much "mental" in "physical" disorders" (130). Virtually every chronic disease with structural pathology has a psychological or psychiatric element, and many with a currently defined illness also suffer from a disease with structural pathology. FMS, for example, is common among older patients with osteoarthritis, and both conditions may contribute to joint pain.

There is a much increased and significant prevalence of FMS in several connective tissue diseases (3), eg, RA (133) and systemic lupus erythematosus (134). Thus, the same patient may have diseases with both structural and NEI pathology. The presence of a psychological or psychiatric condition ("illness"), eg, anxiety, depression, stress, and other psychosocial factors, is common in coronary artery disease (80,81), diabetes mellitus, arthritis, and chronic pulmonary disease (135,136), RA (136), psoriatic arthritis (136), and systemic lupus erythematosus (137). In fact diseases having structural pathology with associated psychiatric conditions have increased morbidity (133,134,136,137), and mortality (80). Giving the example of both diabetes mellitus and

schizophrenia, Engel, in his originally proposed biopsychosocial model, states that ". . . inclusion of somatic and psychosocial factors is indispensable for *both*" (emphasis is mine) (138).

So, the question is: why should one separate out currently defined disease and illness when the same patients may have both, both are based on biopsychosocial mechanisms, and their coexistence can influence morbidity and mortality? Biology and psychology are intertwined. Symptoms contributed by psychological factors may be mediated or modulated by neuroendocrine factors, such as hypofunction of the HPA axis (67,117), as stated earlier. Stress is also mediated biologically, eg, corticotrophin-releasing hormone, locus ceruleus-norepinephrine, HPA axis, and the autonomic nervous systems (128,139). I think the distinction between diseases and illness is artificial and a sophistry.

It is important to recognize that both biology and psychology, including an individual's vulnerability to environmental stress, is determined by genes (2,3,116,140) and that behavioral modulation involving the threat of tissue damage utilizes the same forebrain, brainstem, and dorsal horn mechanisms as actual tissue damage (65,141). So, it is all biology anyway.

It is a mistake to treat every patient the same way. Subgroups, especially in chronic diseases, is a vital concept. All patients with a particular diagnosis are not alike. Subgroups in FMS have been recognized with variation in psychological distress (142,143), pain severity (144), and treatment outcome (143). Our subgroup analysis of FMS patients by factor analysis (145), similar to that by Giesecke et al (142), showed that only one-third of the patients have significant psychological distress. It is well documented that psychological factors are not essential for the expression of FMS symptoms (120,146,147). Other CSS diseases also show psychosocial difficulties only in a subgroup of patients (148).

Psychiatric disorders have overlapping NEI pathology with CSS, but they are not the same diseases. Depression is associated with CSS conditions, but most studies suggest that it is biologically different from FMS in several ways (3,31), eg, results of dexamethasone suppression test (149,150), function of the HPA axis (42,151), sleep electroencephalogram studies (108,152), and information processing (153). CS is mostly absent in depression despite associated pain symptoms, as discussed elsewhere (3). The relationship between CSS and psychiatric diseases needs further studies.

DISCUSSION

Is CSS the Appropriate Term?

As stated above, different terms used for the CSS conditions (5-16) are psychocentric and inappropriate. Unfortunately a good part of the psychology literature on these conditions is replete with eloquent writing of confusion that provides little new insight. However, Barsky deserves credit for conceptualizing amplification of bodily sensations based on clinical observation alone 29 years ago (154). Such amplification can now be objectively demonstrated in the human experimental pain laboratory by documentation of CS at a biophysiological level (1-3,35-41,51,54-57,70-76,78,79,84-90,109) in the CSS. Focusing on psychology alone and ignoring the well-documented biological contributions is misleading and a great mistake. If CSS were based on a pure psychosocial construct, decades of psychotherapy and similar approaches would have cured them. In fact, the long Holy Grail quest by psychocentric patient caregivers for a psychosocial solution for the suffering of patients with CSS has been a failure (9).

In the nosology of "central sensitivity syndromes," I prefer the term "sensitivity" rather than "sensitization." The latter term, at the first thought, connotes a neuropathophysiological phenomenon, although it is really a biopsychological construct as stated earlier. Sensitization also implies that it is an active process that results from various stimuli, eg, trauma. On the other hand, the term sensitivity is a clinical manifestation of sensitization, exemplified by sensitivity or amplification response to various nociceptive, nonnociceptive, and environmental stimuli (3). It is possible that some patients are genetically hypersensitive (3,155,156) and do not require further physical stimulation, eg, inflammation, to develop CS. In summary, sensitization is a process, and sensitivity is the result, ie, clinical manifestations, of that process.

Analogous to the term "fibromyalgia" that succinctly states the *clinical* characterization of the syndrome, "sensitivity" is a clinical description, but it also indirectly implies the underlying pathophysiology of CS. In coining a term, 1 is on a more solid ground in describing the clinical pithy of a disease that is generally unchanging, rather than the pathological process that may end in quicksand because of new research findings years later. As an example, the term "fibrositis," coined by Gowers in 1904 (157), was readily accepted by the medical community when Stockman described "inflammation" in "fibrositis" in the same year in an open study (158). It took another 8 decades to convincingly demonstrate in a controlled and blinded study that there was no inflammation in FMS (159).

Another important aspect of the CSS is that these conditions are frequently associated with diseases with structural pathology. Such an association may be related to CS in part. Chronic inflammation (eg, arthritis as a source of nociception) as well as NEI pathology in these diseases may lead to CS. This is of significance in clinical practice, since many "organic" focused physicians are unaware of these associations and fail to treat a coexistent CSS condition that requires a different management approach. For example, the inflammation of RA may be under control, but a patient having both RA and FMS continues to have much joint and muscle pain due to the FMS component. The physician, unaware of the presence of FMS,

continues to treat this patient as having active RA with unwanted toxic drugs, such as corticosteroids, methotrexate, or biologics.

So, what is in a name? The answer is: a lot! Quoting McWhinney and coworkers (24), ". . . language both expresses and influences how we think and act." I agree. Is it advantageous to use the term "central sensitivity syndromes (CSS)?" I would say "yes" for the following reasons:

1. CSS is a clinical term, but it also alludes to the underlying biopsychopathology.
2. It is a useful paradigm that encompasses the overlapping nature of its members with a common mechanistic link, rather than viewing them as discrete conditions.
3. It replaces such inaccurate, misleading, and even deleterious terms as "somatization disorder," "functional somatic syndromes," and "medically unexplained symptoms" that may lead to unsatisfactory patient care, since these terminologies are inaccurately described by many authors as psychosocial constructs (6-14,17-20), that is resented by patients (10,24).
4. This term, CSS, that incorporates both biological and psychosocial components, will foster research in appropriate areas and improve physician–patient communication for optimal care.
5. The significance of the terminology CSS is substantial and discussed below.

Significance of CSS

The significance of the CSS has been elaborated elsewhere (1-3). CSS diseases have implications for proper physician education and patient management. The first place to start such education is the medical school where appropriate and adequate teaching of CSS diseases must form a part of the curriculum both nationally and internationally, acknowledging that the CSS as a group are the most common conditions that a future physician will be asked to treat. Since the underlying pathophysiology of the CSS is similar (but not the same) (3), disease mechanisms and treatment elucidated in 1 CSS member may apply to the others. The CSS paradigm will direct attention to fruitful areas of research, ie, both biology and psychology. CSS conditions, eg, fibromyalgia, may coexist with other diseases with structural pathology (eg, RA, osteoarthritis, and systemic lupus erythematosus). Recognition of these associations is vital for appropriate management of a patient as a whole. Since CS can be objectively and reproducibly demonstrated in a CSS disease, the effect of a drug on CS can be tested in a laboratory or by brain imaging techniques (3,37).

Disease and Illness: Implication for Patient Care

Perhaps the single most destructive force in the practice of medicine today is the drumbeat dichotomization between disease and illness (160,161). Unfortunately, this fallacious dogma has gone mostly unchallenged. In the face of this unfortunate Cartesian curse, I join only a few who hold the view that it does not matter whether 1 has an illness or a disease in terms of patient care (5,162). The schism between "functional" versus "organic" or disease versus illness (vis-à-vis structural pathology versus NEI pathology) has resulted in a 2-class classification of patients: those with a structural pathology are the "real" patients who deserve real care, and those without (such as CSS patients) are second-class patients (analogous to second-class citizens) not worthy of serious physician attention.

There is little doubt that disease–illness dualism creates a negative attitude of many health care providers toward patients labeled as having an illness (or a diagnosis that implies illness). Such an attitude results in blaming the patients for their own suffering (8,13,18-20,24) and creates tension and hostility between a physician and his or her patients (24,163). At the same time psychosocial factors are often ignored in those having a currently defined disease (ie, those with structural pathology). With reference to somatoform disorders, Kroenke makes the appropriate observation that "the term itself has acquired a negative connotation, with the implication that the physical symptoms are 'all in the head'" (10). Similarly, the nosology "functional" (as in "functional somatic syndromes") is viewed by patients as derisive (10).

The deleterious physician attitude is first implanted among the medical students and then reinforced during residency training by attending physicians. I have addressed this vital issue in detail previously (163). The CSS paradigm embraces the important concept of person-centered patient care (164) that takes into account the varying degrees of both biology and psychosocial factors in a given patient.

It follows that, in the suggested new paradigm, illnesses are diseases as well. It must be emphasized that disease is not a reductionistic concept that embodies only pathology—structural or NEI. Description of a chronic disease in a textbook of medicine includes the importance of psychosocial and functional elements as well (165-166).

James Bryce, a British historian and politician at the beginning of the last century, said: "Medicine is the only profession that labors incessantly to destroy the reason for its existence" (163). Not much has changed since. The reason for the existence of our profession is service to humanity, as stated in the World Medical Association Oath: "I solemnly pledge to consecrate my life to the service of humanity . . . . I will maintain the utmost respect for human life." This or similar oaths taken by a physician nowhere states that service to humanity and showing respect to human life is limited only to those with structural pathology!

The suffering caused by both forms of pathology (structural and NEI) are considerable and comparable.

Disease paradigms with both forms of pathology need to embrace Engel's visionary concept of a biopsychosocial model (138).

Abolition of disease–illness dualism will encourage better communication between "psychocentric" and "biocentric" researchers and patient care providers and offers a bridge between them for the greater good of the suffering patients. It is important that health care providers who are involved in managing the CSS patients are equally knowledgeable in both the biological and the psychosocial components of the CSS diseases. Adopting a biopsychosocial approach with equal attention to biology and psychology in an individual patient, irrespective of the type of pathology, would help physicians to strengthen their commitment to the Oath and not abandon it.

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