Fibromyalgia and Overlapping Disorders: The Unifying Concept of Central Sensitivity Syndromes

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Objectives: To discuss fibromyalgia syndrome (FMS) and overlapping conditions, eg, irritable bowel syndrome, headaches, and chronic fatigue syndrome, within the concept of central sensitivity syndromes (CSS).

Methods: A critical overview of the literature and incorporation of the author's own views.

Results: The concept of CSS seems viable. It is based on mutual associations among the CSS conditions as well as the evidence for central sensitization (CS) among several CSS members. However, such evidence is weak or not available in other members at this time, requiring further studies. The biology of CSS is based on neuroendocrine aberrations, including CS, that interact with psychosocial factors to cause a number of symptoms.

Conclusions: CSS is an important new concept that embraces the biopsychosocial model of disease. Further critical studies are warranted to fully test this concept. However, it seems to have important significance for new directions for research and patient care involving physician and patient education. Each patient, irrespective of diagnosis, should be treated as an individual considering *both* the biological and psychosocial contributions to his or her symptoms and suffering.

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Central sensitivity syndromes (CSS) comprise an overlapping and similar group of syndromes without structural pathology and are bound by the common mechanism of central sensitization (CS) that involves hyperexcitement of the central neurons through various synaptic and neurotransmitter/neurochemical activities (1,2). CS is manifested as hypersensitivity to various noxious (eg, pressure and heat) as well as nonnoxious (eg, touch) stimuli. Fibromyalgia syndrome (FMS) and similar conditions have been called "functional" (3), "functional somatic syndromes" (4), and medically unexplained symptoms (5), among others. None of these nomenclatures, however, clearly states 2 essential criteria of CSS, ie, an overlapping relationship between these syndromes and an appropriate pathophysiological mechanism (eg, CS) that is common to them. I have proposed CSS as a class terminology for these conditions (1,2) that seems rational and may explain several symptoms.

Besides a lack of structural pathology, the CSS diseases have several similar features in common, eg, pain, fatigue, poor sleep, sensitivity to noxious and nonnoxious stimuli, mutual associations, and the presence of psychosocial difficulties in a subgroup of patients. Many but not all patients with a CSS condition have psychological distress, so that CSS cannot be viewed as purely psychological or psychiatric in nature. For this essay, I shall use the terms disease and illness synonymously.

Current members of the CSS group are shown in Fig. 1. Interstitial cystitis (IC) has been included because of its close clinical similarity to female urethral syndrome (FUS), nonspecific bladder histology, presence of CS, and its association with other CSS members.

Other conditions not listed above, eg, premenstrual tension syndrome and vulvodynia, may also belong to the CSS spectrum on clinical grounds, but at this time they do not satisfy the 2 criteria mentioned above. Gulf war syndrome (GWS) has not been listed as a separate entity. It seems to be a mixture of several CSS conditions: FMS (6), chronic fatigue syndrome (CFS) (7), multiple chemical sensitivity syndrome (MCS) (7), posttraumatic stress disorder (PTSD) (8), and irritable bowel syndrome (IBS)

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Abbreviations	
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate
CEP	cerebral-evoked potential
CFS	chronic fatigue syndrome
CNS	central nervous system
CRPS	complex regional pain syndrome
COMT	catechol-$_O$-methyltransferase
CRH	corticotrophin-releasing hormone
CS	central sensitization
CSS	central sensitivity syndromes
D	dopamine
DNIC	diffuse noxious inhibitory control
EEG	electroencephalogram
FD	functional dyspepsia
f-MRI	functional magnetic resonance imaging
FMS	fibromyalgia syndrome
FUS	female urethral syndrome
GABA	γ-amino-butyric acid
GWS	Gulf war syndrome
HLA	human leukocyte antigens
HPA	hypothalamic-pituitary-adrenal
IBS	irritable bowel syndrome
IC	interstitial cystitis
MCS	multiple chemical sensitivity
mGlu	metabotropic glutamate
MPS	myofascial pain syndrome
NFR	nociceptive flexion reflex
NGF	nerve growth factor
NK1	neurokinin-1
NMDA	*N*-methyl-D-aspartate
PD	primary dysmenorrheal
PET	positron-emission tomography
PLMS	periodic limb movement in sleep
PMID	PubMed identification
PTSD	posttraumatic stress disorder
QST	quantitative sensory testing
RA	rheumatoid arthritis
REM	rapid eye movement
RLS	restless legs syndrome
RSTPS	regional soft-tissue pain syndrome
SLE	systemic lupus erythematosus
SP	substance P
TP	tender point(s)
TDS	time-dependent sensitization
TMD	temporomandibular disorders
Trk-B	tyrosine kinase B
TTH	tension-type headache
WDR	wide dynamic range

(8). Interestingly, visceral and cutaneous hypersensitivity were demonstrated in a subgroup of GWS patients with chronic gastrointestinal symptoms (9).

CS has been demonstrated in functional dyspepsia (FD) by gastric distension (10), and in vulvodynia (both locally and at distant sites) by pressure stimulus (11). FD is associated with IBS (12). Thus, FD is part of generalized gut sensitivity that also includes IBS, rather than being a separate CSS entity.

METHODS

This discourse is based on a critical overview of the literature (as of March, 2006) and an incorporation of the author's own ideas, insights, and opinions.

RESULTS

The Concept of Central Sensitivity Syndromes

To qualify for CSS membership, my conceptual paradigm includes (a) mutual associations between the CSS members; and (b) demonstration of CS to various stimuli among them (1,2).

Mechanisms of Central Sensitization

This section will provide only a general view of the CS mechanisms. For greater details the readers are referred to several reviews (13-15). CS is manifested by an abnormal and intense enhancement of pain by central nervous system (CNS) mechanisms.

Pain signaling involves activation of a variety of nociceptors at the periphery, in both somatic and visceral tissues. Such activation normally follows inflammation or trauma, even minor irritation (15) that releases inflammatory mediators, eg, bradykinin, serotonin, histamine, prostaglandin, and substance P (SP), among others. The peripheral nociceptive impulses travel through A-delta and C fibers to both nociceptive and wide dynamic range (WDR) neurons in the dorsal horn of the spinal cord. A-beta fibers carry nonnoxious impulses and both noxious and nonnoxious fibers converge in the WDR second-order neurons. Following a noxious stimulus, A-delta fibers carry sharp and well-localized pain known as first pain, whereas transmission of pain by C fibers is dull, diffuse, and burning, known as second pain. C fibers are involved in chronic pain.

WDR neurons respond to a range of stimulus intensities, from nonpainful (eg, gentle touch) to most painful. Thus, the WDR cells integrate input from converging nonnoxious A-beta, as well as noxious A-delta and C fibers. A-beta fibers, with proximity to noxious neurons in the area of WDR neurons, now become noxious in function, so that a normally nonpainful stimulus, such as touch or gentle pressure, is now perceived to be painful, a phenomenon known as allodynia. The postsynaptic fibers in the spinal cord then ascend to the thalamus, hypothalamus, the limbic system, and finally, the somatosensory cortex; these supraspinal structures are variously involved in the processing of different dimensions of pain, eg, sensory, evaluative, and affective (13-15).

The activated C-nociceptors express various neurotransmitters/neuromodulators at the afferent nerve terminals in the dorsal horn (Table 1). Following peripheral stimulation, these chemicals send a barrage of impulses and hyperexcite the postsynaptic neurons in the dorsal horn (mostly lamina I and II) where the afferent neurons terminate. Postsynaptic neurons bear certain receptors or

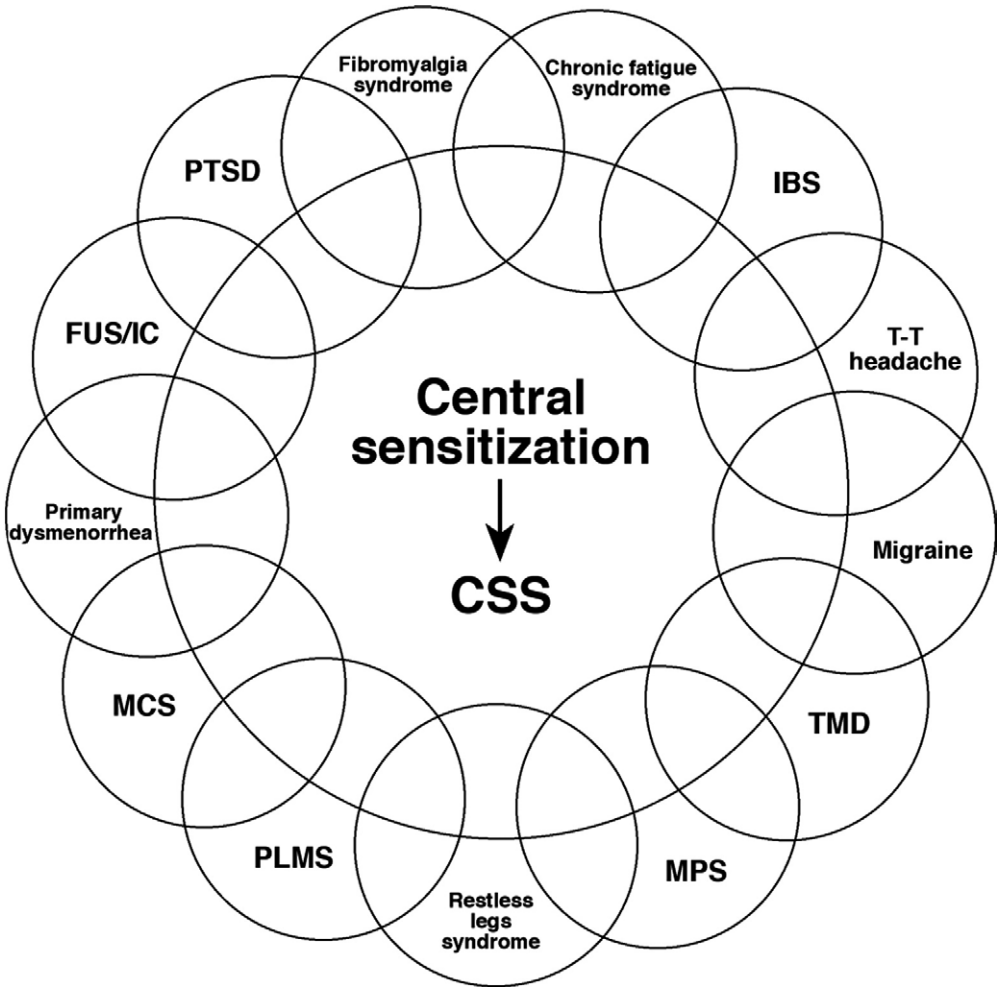

Figure 1 Currently proposed members of the CSS family with overlapping relationships and a common pathophysiological link of CS. IBS, irritable bowel syndrome; T-T headache, tension-type headache; TMD, temporomandibular disorders; MPS, myofascial pain syndrome; RSTPS, regional soft-tissue pain syndrome; PLMS, periodic limb movements in sleep; MCS, multiple chemical sensitivity; FUS, female urethral syndrome; IC, interstitial cystitis; PTSD, posttraumatic stress disorder. Depression may also be a member (see text). Modified from reference 198.

neuroeffector targets (Table 1). Neurokinin (NK)1 receptors are activated by SP; *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA), and metabotropic glutamine (mGlu) receptors by glutamate; and tyrosine kinase B (Trk-B) receptors by nerve growth factor (NGF).

Opioid receptors are found in the copresence of SP receptors in the spinal cord, in both pre- and postsynaptic sites and other CNS sites (16). Thus opioid receptors seem important in attenuation of neurotransmission by SP. Opioids can also modulate NMDA receptor activity (16).

SP has an important role in pain transmission and its amplification, causing CS. It unmasks the silent receptors in the synapses that contribute to augmentation of second-order neuron excitability. Moreover, it can diffuse some distance to excite other neurons beyond its origin, contributing to an anatomical expansion of the pain area (ie, increased receptive field), which is characteristic of CS (14,15). The release of SP and other neurochemicals, eg, NGF and glutamate, into the synapse causes synaptic hyperexcitability, which in turn removes the magnesium block of the NMDA receptor channel, allowing glutamate to activate the NMDA receptors on the postsynaptic neuron. Nitric oxide (NO) is also involved in NMDA receptor activation, which is vital to neurotransmission (14). Activation of the NMDA receptor is followed by an increased entry of intracellular calcium, membrane changes and activation of protein kinase, phospholipases, and nitric oxide synthetase (producing NO), as well as expression of c-fos, all of which contribute to a remarkable degree of CS (13-15). NMDA receptors seem mostly responsible for escalation of hyperexcitability of the second-order neurons. These phenomenal functional changes cause neuroplasticity, leading to excessive amplification of a peripheral stimulus, so that even an innocuous stimulus like touch is now perceived as painful.

Dopamine (D) also plays a role in CS. It has been shown that D_1-like receptors (that include D_1 and D_5) increase nociceptive neuronal excitability (15,17),

Table 1 Neurochemicals and Neuroreceptors Involved in Central Sensitization

Neuromodulators/Neurotransmitters Released by Activated C-nociceptors Presynaptically	
Substance P (SP)	Somatostatin
Calcitonin-gene-related peptide (CGRP)	Galanin
	Never growth factor
	Glutamate
Vasoactive intestinal peptide (VIP)	Aspartate
Post Synaptic Neuroreceptors/ Neuroeffector Targets	
Neurokinin 1 (NK1)	Metabotropic glutamate (mGlu)
N-methyl-D-aspartate (NMDA)	Tyrosine kinase B (Trk-B)
Alpha-amino-3-hydroxy-5-methyl 4-isoxazoleproprionate (AMPA)	Protein kinase gamma (PKC-gamma)
	Vanilloid subfamily (TRPV-1, TRPVL-1)

whereas D_2-like receptors (that include D_2, D_3, and D_4) inhibit it (15,18). In support of this, pramipexole, a D_3 agonist, has been shown to be effective in fibromyalgia in a randomized double-blind controlled study (19). Studies have demonstrated a role for ion channels (13,14) and cytokines released from microglia and astrocytes in the nervous system in generation of pain following an inflammatory or traumatic stimulus (14).

Windup is a progressive increase in pain perception with second-order neuronal response to repetitive stimulation (more often than every 3 seconds) of peripheral C fibers. This phenomenon, known as temporal summation (or summation) in humans, occurs in parallel to CS (14). Temporal summation involves the production of second pain, which is described as dull or burning, and leaves an after-stimulus unpleasant sensation. It is generally agreed that NMDA receptors mediate summation, and it can be inhibited by NMDA receptor antagonists, eg, ketamine (20), which may be relevant in treating chronic pain.

CS is clinically and physiologically characterized by hyperalgesia (excessive sensitivity to a normally painful stimulus), allodynia, expansion of receptive field (that is likely to explain widespread pain), a prolonged electrophysiological discharge (that may explain the chronic nature of pain), and an after-stimulus unpleasant pain (eg, burning, throbbing, and paresthesia) that lasts longer than that observed in normal controls following a noxious stimulus (13-15). Because of the remarkable overall hyperexcitement of the central neurons, CS may explain the hypersensitivity to many environmental (eg, noise, weather, stress) and chemical (eg, pesticides and medications) stimuli. CS becomes self-sustained without further stimuli, even minor, because of long-term CNS neuroplasticity, and is probably accentuated with chronicity in human diseases.

CS is dampened by the body's intrinsic mechanism of pain inhibition. Several descending pathways from the cortico-reticular system, locus ceruleus, hypothalamus, brain stem, and local spinal cord interneurons utilize neurotransmitters that include serotonin, norepinephrine, γ-amino-butyric acid (GABA), enkephalins, and adenosine (13-15). Evidence suggests that 5-HT_3 subtype has a facilitatory function, whereas 5-HT_{1A} receptor is inhibitory (15). Inhibition of the inhibitory function of 5-HT_{1A} augments CS in the dorsal horn, resulting in hyperalgesia and allodynia (15,18). The ascending and descending pathways do not have dichotomous functions, rather they are interactive and their functions are bidirectional; both pathways have the property of both facilitating and inhibiting pain, depending on the site of action and subtypes of a neurotransmitter.

The affective dimension of pain, eg, unpleasantness and emotional reaction, is mediated by spinal pathways to limbic structures and medial thalamic nuclei, and by anterior insular cortex, anterior cingulate cortex, and the somatosensory cortical areas (21).

Mutual Associations Among CSS Conditions

The initial report of an association between FMS, IBS, tension-type headache, and migraine using normal controls (22) has subsequently been confirmed by a large number of studies in the past 25 years using both normal and chronic pain (with structural pathology) controls (2,23-62), as reviewed by Aaron and Buchwald (23), and more recently by Yunus (2). Variations in the prevalence of several CSS members are most likely due to different methodology, including different criteria used, but these prevalences, irrespective of use of controls, seem much higher than those found in available population studies. A few studies were not referenced in the Reference section because of page limitation, small N, or otherwise unsatisfactory methods, but most of these are referred by their PubMed identification (PMID) numbers at the footnote of Table 2.

Evidence for Central Sensitization Among CSS Members

CS by peripheral stimuli has been documented in a majority of patients with a CSS condition as compared with normal controls (Table 3). Selected references will be provided here, and others will be indicated by their PMID numbers in the footnote of Table 3.

Fibromyalgia Syndrome

All patients with FMS have generalized exaggerated pain response by digital pressure (CS). Nondigital pressure, eg, by dolorimeter or palpometer, has also been applied to demonstrate hyperalgesia (63-72). Most of these studies have tested multiple modalities of stimuli besides pressure, eg, heat, cold, and electric, by quantitative sensory testing (QST).

Table 2 Mutual Associations Among Central Sensitivity Syndromes (CSS) members: Significantly Greater Prevalence of a CSS Member Among Other CSS Conditions*

CSS Condition Studied	Mean Prevalence (%) of Another CSS Member Among the Conditions Studied [range]	Total # of Studies (# with a control group)†	Total N of Patients from all Studies	References‡
FMS	CFS 39 [22–74]	6 (3)	214	24–29
	IBS 45 [32–70]	17 (13)	1,776	22,25,27 30–40
	TTH 42 [22–60]	6 (4)	889	22,27,33 39–41
	Migraine 38 [22–48]	3 (1)	183	22,25,41
	UHA 50 [35–56]	5 (2)	558	30,31,34
	TMD 50 [24–75]	2 (1)	82	27
	RLS 31	1 (1)	135	42
	PLMS 38	1 (1)	16	43
	MCS 36 [18–55]	3 (1)	104	27,29,44
	PD 48 [45–50]	2 (2)	103	33,40
	FUS 15 [12–18]	2 (2)	262	45,46
	IC 8	1 (1)	22	27
	PTSD 57	1 (0)	77	47
CFS	FMS 48 [16–80]	2 (2)	57	27,29
	IBS 36	1 (1)	25	27
	UHA 87	1 (0)	236	48
	TMD 28	1 (0)	25	27
IBS	FMS 36 [28–65]	5 (4)	179	25,38,49
	CFS 14	1 (0)	200	50
	UHA 42 [31–50]	3 (3)	297	51–54
	PD 68	1 (0)	100	51
Migraine	CFS 51	1 (0)	63	54
	RLS 34	1 (0)	50	55
TMD	FMS 13 [9–18]	3 (2)	104	27,56
	IBS 16	1 (1)	25	27
	TTH 23	1 (1)	25	27
	IC 17	1 (1)	25	27
MCS	FMS 49	1 (0)	100	57
	CFS 59 [30–88]	2 (0)	130	26,57
	UHA 63	1 (0)	30	26
IC	FMS 15 [12–17]	2 (1)	2,435	58,59
	IBS 50	2 (1)	2,445	58,60
PTSD	FMS 20 [19–21]	2 (2)	295	61,62
	IBS 37	1 (1)	266	61

*CFS-chronic fatigue syndrome; FMS-fibromyalgia syndrome; FUS-female urethral syndrome; HA-headache; IC-interstitial cystitis; MCS-multiple chemical sensitivity; PD-primary dysmenorrheal; PLMS-periodic limb movements in sleep; PTSD-post-traumatic stress disorder; RLS-restless legs syndrome; TMD-temporomandibular disorder; TTH-tension-type headache; UHA-unspecified headache.

†The prevalence of a CSS condition in uncontrolled studies were higher or much higher than that reported in general population.

‡Studies with first author (PMID#) that were not referenced in the table, but counted in the total N are: (1) FMS/IBS—Campbell SR (6347207); Veale D (2049586); Yunus MB (3171051) (2) FMS/UHA—Okifuji A (10593628); Yunus MB (3171051) (3) IBS/FMS—Veale D (2049586); Lubrano E (11515679) (4) TMD/FMS—Plesh O (8923373). Please note that space limitations do not allow listing of all the references in Table 2 and under References.

Fibromyalgia patients are hypersensitive to heat (64-66,68,72-77), cold (64-66,68,75,76), cutaneous electric (66,69,78), intramuscular electric (69,70), sural nerve electric (to assess nociceptive spinal reflex) (64,79), ischemic (65), and intramuscular hypertonic saline (69,70). Further, allodynia to warmth (68,73), cold (66,68), and pressure (73) has been documented. Temporal summation has been demonstrated by using heat (73,76), cold (74), and intramuscular electric (69) stimuli. Sensitivity to noise, as often complained by FMS patients, has been demonstrated in a human pain laboratory by using a noise generator (67).

Augmented pain sensitivity has been reported in FMS by objective functional magnetic resonance imaging (fMRI) findings in response to peripheral stimuli by pressure (80) and both noxious and innocuous heat (81). A recent study showed a lack of inhibitory control in the brain to nonpainful repetitive somatosensory stimuli (by examining event-related potentials recorded by electroencephalogram (EEG) (82)), suggesting CS.

Table 3 Evidence for Central Sensitization by Controlled Studies in Selected Members of the CSS group in Response to Various Peripheral (Somatic) or Rectal (Visceral) Stimuli*

Stimulus	FMS	CFS	IBS	TTH	Migraine	TMD	MPS/RSTPS	PD
	# of studies (N of patients)†							
Pressure (somatic)‡	15 (580)			4 (178)	3 (117)	2 (42)	9 (462)	1 (20)
Pressure (rectal)§			26 (822)					
Heat (somatic)	12 (480)		2 (21)	1 (50)	3 (117)	3 (76)	3 (137)	2 (42)
Heat (rectal)			1 (46)					
Cold (somatic)	8 (255)		1 (33)		1 (41)		2 (184)	
Electric (cutaneous)	4 (61)		1 (12)				2 (36)	
Electric (intra-muscular)	2 (41)	1 (23)					2 (36)	1 (10)
Electric (spinal Reflex)	2 (107)		1 (14)	1 (40)			1 (27)	
Electric (rectal)			2 (21)					
Ischemic	1 (60)					2 (72)		
Hypertonic saline	2 (41)					1 (22)	1 (11)	
Auditory stimulus	1 (20)		1 (15)		1 (65)			

*See text for other evidence of CS (e.g. allodynia and temporal summation) in a CSS member, as well as evidence for CS in other CSS members. MPS/RSTPS-myofascial pain syndrome/regional soft tissue pain syndrome. See Table 2 for other abbreviations.

†Studies in all CSS conditions with first author (PMID#) that were not referenced in the text but counted for N in Table 3 are: (1) FMS/somatic pressure—Kosek E (9106808); Bendtsen L (9008605); Marques AP (1566761); Mikkelsson M (1514890); Staud R (15890634) (2) FMS/somatic heat—Kosek E (9106808); Berglund B (11932073) (3) FMS/Cold—Kosek E (9106808); Berglund B (11932073) (4) FMS/cutaneous electric—Arroyo JF (7848390) (5) IBS/rectal pressure—Greenwood B (8907258); Bernstein CN (8880836); Drewes AM (11495078); Fukodo S (12572883); Kwan CL (15621377); Chun A (1008061); Caldarella (15667496) (6) Migraine/pressure and heat—Kitaj MB (16109112) (7) MPS/somatic pressure—Giesbrecht RJ (16180957). Please note that space limitations do not allow listing of all references in the text and under References.

‡By non-digital pressure.

§By balloon.

The issues of dependence on patients' verbal response to a noxious stimulus (hence subjective in nature) as well as response bias are often raised, particularly in the legal setting. A local spinal reflex, called nociceptive flexion reflex (NFR), can be demonstrated by electrically stimulating the sural nerve directly and measuring the electromyographic response of the biceps femoris. It is a valuable objective test of CS since it bypasses the peripheral nociceptors and does not require a subject's oral response to a stimulus, and is mediated by central neurons. An accentuated NFR has been demonstrated in FMS (64). Using heat and pressure stimuli in both ascending and random paradigms, it has been shown that response bias (eg, expectancy and hypervigilance) does not play a major role in the report of pain by QST by fibromyalgia patients (72).

Chronic Fatigue Syndrome

One controlled study of 21 patients with CFS, of whom 48% had myalgia, demonstrated hypersensitivity to electric stimulus in widely distributed muscles, but not in the overlying skin or subcutaneous locations, irrespective of the presence or absence of myalgia (83). Several brain imaging studies in CFS have shown decreased blood flow in different regions of the brain, eg, frontal, parietal, temporal, subcortical, and periventricular (84). The significance of these findings is unknown but the regions involved may play a role in modulating fatigue and pain in CFS.

Irritable Bowel Syndrome

Evidence of CS to somatic (skin) and visceral (rectal) stimuli in selected studies of IBS is shown in Table 3. With most stimuli there was diffuse spread of pain beyond the rectal area to lower abdomen and lower back with persistent unpleasantness, 2 markers of CS. Most studies have used rectal balloon pressure as a stimulus (10,85-102). CS was demonstrated using other rectal stimuli as well, eg, heat (95) and electric (90,99). Both rectal (88) and cutaneous (91) allodynia has been demonstrated in IBS. Similar to generalized hyperalgesia and allodynia in the somatic peripheral tissues in FMS, there is a global gut hypersensitivity in IBS that involves the stomach (10,100) and the esophagus (101). Patients with functional dyspepsia demonstrated both esophageal and rectal hypersensitivity (10). Initially it was thought that cutaneous hyperalgesia is absent in IBS (99). However, subsequent studies have established excessive sensitivity of the skin to heat (191,103), cold (100), and electric (99) stimuli, mostly in conjunction with rectal hyperexcitability, even in the absence of concomitant FMS (103). Such visceral as well as somatic sensitization in the same patient is supportive of the concept that CSS may represent both somatic and visceral hypersensitivity. Interestingly, there is enhanced sensitivity of hand–forearm veins to distension produced by injection of hypertonic saline into the antecubital vein of migraine sufferers, representing another example of visceral hypersensitivity (104).

Hypersensitivity to noise, tested in human pain labo-

ratory (105), and the objective test of CS by facilitated spinal NFR (102) have been demonstrated in IBS similar to FMS. By applying sensory decision theory (that allows discrimination between sensory experience and response bias), it was shown that there was no response bias among the IBS patients (98). Brain imaging studies by fMRI and ^{15}O-water positron-emission tomography (PET) following rectal or cutaneous stimulation have been reported (106) in support of CS/central pain in IBS.

Tension-type Headache

CS in tension-type headache (TTH) has been demonstrated in both cranial and extracranial sites in response to peripheral pressure (107-110), and heat (108) stimuli and by a facilitated spinal NFR (111). CS was also shown by qualitatively altered nociception (112), greater response to cerebral-evoked potential (CEP) (113), and a deficient pain inhibitory response by diffuse noxious inhibitory control mechanism (DNIC) (114) also demonstrated CS. However, a lack of CS has also been reported by cutaneous heat (113) and cutaneous electric stimuli (115).

Migraine

Enhanced sensitivity in migraine has been demonstrated in both cranial and extracranial (eg, hands) sites in response to mechanical (116,117), heat (116,117), cold (116), and CO_2 laser (118) stimuli. Hypersensitivity to sound (119) and light (120) has also been shown in the human pain laboratory. Other evidence for CS in migraine includes cutaneous allodynia in periorbital as well as forearm areas (116), summation to mechanical stimulus (117), and increased amplitude of cortical response to CO_2 stimulus (118). There is also venous hypersensitivity in migraine in the hand–forearm veins (a location away from the head) (104) as stated earlier. These observations of both somatic and visceral sensitivity in the same CSS condition (eg, migraine and IBS) raise an interesting possibility that CSS may represent a "pantissue sensitization."

Temporomandibular Disorders

Temporomandibular disorders (TMD) represent a heterogeneous group of disorders in patients with or without structural pathology. Only the myofascial variety by Research Diagnostic Criteria (RDC) (121) is included here as a member of CSS. Hyperresponsiveness to pressure (122,123), heat (124-126), ischemia (124,127), and hypertonic saline (123) has been recorded in both facial and extracranial sites, along with summation to thermal stimulus (125,126). One study failed to show hypersensitivity to heat (123). Most interesting is the description of a patient who demonstrated many features of CS in response to nonnoxious vibrotactile stimulus in the arm and face, eg, unpleasantness of evoked pain that lasted 30 minutes, temporal summation, and allodynia; allodynic pain decreased following administration of the NMDA receptor antagonist dextromethorphan using the vehicle as a control (126).

Myofascial Pain Syndrome/ Regional Soft-Tissue Pain Syndrome

We (128) and others (129) have questioned the current construct of chronic myofascial pain syndrome (MPS). Here I shall use the terms chronic "regional soft-tissue pain syndrome" (RSTPS) and MPS synonymously to include a regional chronic pain condition with TPs in the absence of structural pathology.

To qualify for CS in RSTPS/MPS, hypersensitivity to a stimulus needs to be demonstrated at both symptomatic and distant sites. Such an exaggerated response has been demonstrated to pressure (63,78,130-135), heat (131-133), cold (131,134), electric (78,132,135), and vibration (131). An accentuated spinal NFR (ie, a decreased threshold to electric stimulus) (135) and allodynia (131) have also been documented. One study, however, showed increased pain threshold to thermal stimulus (132). By fMRI, Giesecke and coworkers showed extensive cortical activation suggestive of augmented central pain processing in RSTPS (136), similar to FMS (80).

Restless Legs Syndrome

In the restless legs syndrome (RLS), punctate mechanical stimulation by pin prick showed a significant generalized hyperalgesia in both upper and lower extremities (137), and electric stimulation of the medial plantar nerve demonstrated increased excitability of the spinal NFR with spatial spread (138). Two transcranial magnetic stimulation studies exhibited decreased inhibition (and increased facilitation) of the central motor pathways (139,140).

Multiple Chemical Sensitivity

It has been theorized that MCS is based on a time-dependent sensitization (TDS) model that involves sensitization of the CNS (141). Repeated environmental exposures to a low-level chemical (or a large single exposure) produces CS to that chemical, particularly involving the limbic system, in susceptible individuals. A progressive amplification of the sensitivity to that chemical then occurs with repeated exposure, reminiscent of summation. Eventually the sensitization becomes self-sustained, so that re-exposure even to a minute amount of the chemical manifests the symptoms of severe sensitization. Evidence of CS to sensory stimuli by QST and other methods is lacking, except that greater noise sensitivity has been demonstrated (141). Studies of CS similar to other CSS members are strongly suggested in MCS.

Primary Dysmenorrhea

Several QST studies have been performed in patients with dysmenorrhea, presumably of the primary type. These

studies have compared pain sensibility to various stimuli across different phases of the menstrual cycle comparing dysmenorrheic and nondysmenorrheic patients. Dysmenorrheic patients showed decreased pain threshold to pressure (142), heat (142,143), and electricity (144) in the abdomen, back, and extremities, in a given menstrual phase, suggesting the CS threshold to cold pressure stimulus was increased (145), but tactile sensation was normal (142). One study showed increased amplitude by CO_2 laser-evoked cerebral potential (143).

Interstitial Cystitis

Greater sensitivity to somatic pressure in muscles, bladder distension by normal saline, as well as ischemic stimulus (by ischemic forearm test) was demonstrated in 1 study involving 13 patients and 13 healthy controls (146).

Posttraumatic Stress Disorder

It has been hypothesized that the underlying mechanism of sensitization in PTSD is similar to TDS, except that it is the emotional stress (instead of chemical) that causes sensitization by a single severe exposure or repeated ones to various stresses, eg, war, torture, childhood abuse, rape, natural disasters, and terrorist attacks (147). Startle reflex (by a loud auditory tone or noise and manifested by eye blinking and increased heart rate) is exaggerated in PTSD (148). The startle response may reflect a progressive CNS neuronal sensitization following stress (148). Cerebral blood flow studies by PET have shown increased activation of the amygdala with fear acquisition and lack of activation of the cingulate cortex (149). Studies of CS by QST and other relevant methods are greatly needed in PTSD.

Depression and Central Sensitization: Is Depression a Member of the CSS Spectrum?

The association between chronic pain disorders (including the CSS diseases) and depression is so well established that providing a large list of references would be superfluous. Prospective studies suggest that the relationship is bidirectional: chronic pain predicts depression (150) and major depression predicts chronic pain (151). A majority of patients with depression also complained of chronic pain (152). Intriguingly, patients with depression had *higher* pain thresholds than controls despite much pain. The number of TPs in depression was significantly *lower* than that in fibromyalgia (153). In the human pain laboratory, pain perception and threshold were mostly *increased* in patients with depression by most stimulus modalities, as critically reviewed by Dickens and coworkers (154). Decreased pain sensitivity has been demonstrated to several modes of stimuli, eg, pressure (155,156), heat (155,156), and cutaneous electric (156). On the other hand, ischemic stimulus produces decreased pain tolerance or threshold (157,158). All patients studied had major depression except minor depression in 1 study (157).

Besides the stimulation types, laterality seems to play a major role in sensitization in major depression. The left side of the body is more reactive to pain stimuli in depression (156,159). This would support the theory that negative affect activates the right cerebral hemisphere that, in turn, potentiates further adverse stimuli, including pain, thus integrating depression and pain in depressed patients (160). A cerebral blood flow study showed asymmetry in the anterior cingulate and prefrontal regions with lower activity in the left hemisphere in depression (160), indirectly supporting an active role for the right hemisphere in depression, as also noted by others (156).

In summary, the relationship between pain and depression is complex that is influenced by many factors, eg, mode of stimuli, laterality, gender, type of depression (eg, unipolar versus bipolar, acute versus chronic), emotional status, and status of medications at the time of the study (156).

I think the pain–affect relationship in depression is mediated by CS that is different from other CSS members. Thus, activation of certain right hemispheric regions may produce sensitization for negative affect ("negative sensitization") and negative effects, eg, pain, causing greater pain sensitivity on the left side. Negative emotional stimuli (eg, stress associated with childhood adverse experiences) may activate the right hemisphere and cause comorbid depressive illness and pain. Moreover, it is possible that the right hemispheric activation/sensitization may preexist because of genetic susceptibility.

Can depression be classified as a CSS member? Depression is associated with all the CSS diseases. There is evidence of CS in depression, although CS is limited to ischemic stimulus (157,158), and unlike other CSS members, there is *decreased* sensitivity to pressure, heat, and cutaneous electric stimuli. There is significant coaggregation of major depression with several CSS conditions among the first-degree relatives of patients with major depressive disorder (161), and there is similar coaggregation of depression among the first-degree relatives of patients with fibromyalgia (162). Thus, it would seem that depression may belong to the CSS groups of diseases, but further studies will be needed.

It must be cautioned that depression and CSS disorders are not the same disease (overlap does not mean total overlap). Several studies have shown that the biology of depression is different from that in fibromyalgia. As examples, sleep EEG typically shows rapid eye movement (REM) abnormalities in depression (163) as opposed to non-REM sleep abnormalities in fibromyalgia (164). The dexamethasone test shows nonsuppression in major depression (165) as compared with mostly normal suppression in fibromyalgia (166). The hypothalamic-pituitary-adrenal (HPA) axis is hyperactive with hypercortisolemia in depression (167) as opposed to relative hypocortisolemia in fibromyalgia (166,168). Findings similar to fibro-

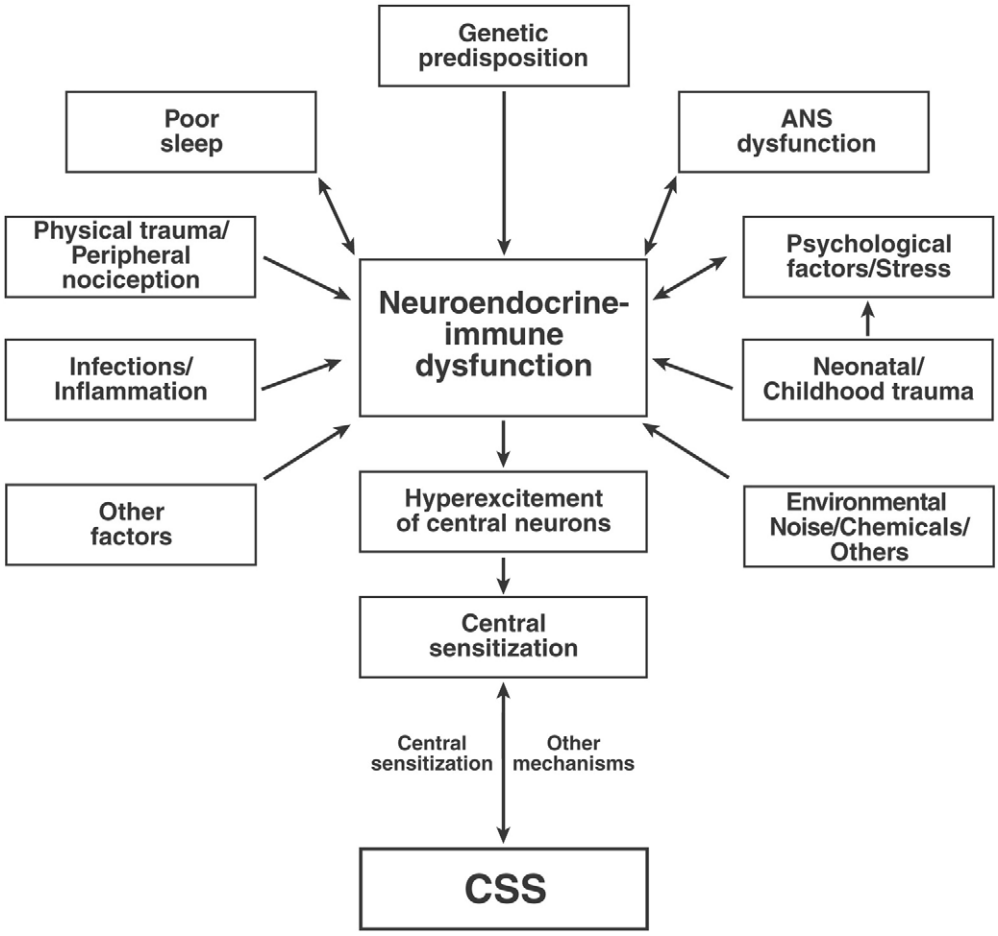

Figure 2 Simplified suggested biopsychosocial mechanisms for CS and CSS with interacting factors. ANS, autonomic nervous system. The relationship between central sensitization and CSS may be bidirectional; chronicity of CSS may accentuate central sensitization.

myalgia and different from depression have been observed in other members of CSS as well, including alpha-delta sleep (169) and enhanced cortisol suppression by the dexamethasone test (170) in CFS, and normal dexamethasone test results and blunted cortisol response to corticotrophin-releasing hormone (CRH) in IBS (171).

Studies on anxiety are limited. In panic disorder, 2 studies showed normal responses, 1 to pressure, cold, and heat stimuli (155), and the other to electric stimulus (172). Whether psychiatric disorders should be included in the CSS spectrum is quite unresolved at this time, and further studies will be needed to answer this question.

Factors That May Contribute to, or Trigger, Central Sensitization

A suggested simplified schema of various factors that may contribute to CS and CSS is shown in Fig. 2.

Genetic Contribution

Pain in general is known to be modulated by genetics (173). In FMS, reduced pressure pain threshold aggregate in first-degree relatives of FMS patients, even among those without symptoms (162,174).

Genetic factors in CSS are present in virtually all its members as demonstrated by twin, family, and molecular genetic studies. CSS diseases are polygenetic and are importantly influenced by environmental factors. Genetic markers related to serotonin, dopamine, catechol-*O*-methyltransferase (COMT), and human leukocyte antigens (HLA) have been found in FMS, as reviewed by Buskila and coworkers (175). T102C polymorphism (of the 5-HT2A receptor) was associated with FMS (176), IBS (177), TMD (178,179), and migraine (179). The COMT gene predicted TMD (180). The T/T genotype showed an association with severity of pain in FMS (176). Serotonin transporter gene polymorphism was reported in FMS (175), IBS (181), TTH (182), migraine (179), CFS (183), and depression (184). CFS was associated with HLA class II alleles (185) and PTSD with dopamine transporter gene (186). Linkage with HLA (187,188) and 5-HT2A receptor (188) genes in FMS, and with 12q and 15q loci 9 (189) in RLS has been demonstrated.

Autonomic Nervous System

Sympathetic overactivity (often associated with sympathetic hypoactivity in response to stressors) or parasympathetic underactivity, mostly measured by spectral analysis of heart rate variability, has been reported by several studies in FMS (190), IBS (191), CFS (192), and RLS (193). Increased sympathetic activity may be related to CS, as exemplified by complex regional pain syndrome (CRPS) (194), which is characterized by severe chronic pain and allodynia symptoms. There is CS in CRPS, with hyperalgesia and summation (195). Martinez-Lavin (196) suggests that sympathetic overactivity may not only cause diffuse pain, but also contribute to other symptoms of CSS, eg, poor sleep (due to sustained nocturnal sympathetic activity) and fatigue (due to deranged sympathetic response to stress).

Neuroendocrine Dysfunction

HPA axis dysfunction with mild or relative hypocortisolism is common to many CSS members, eg, fibromyalgia, CFS, chronic headaches, and PTSD (197). Based on animal and human data, Heim and coworkers suggest that a state of hypocortisolism and perturbed HPA axis resulting from early childhood and other stresses increases the vulnerability for developing CSS in the future, and that it is not due to the effect of chronic pain (197). The relationship between low cortisol and CS is currently uncertain, but it is possible that there is an interaction between them involving the stress mechanism.

Psychological Factors

Most studies show that anxiety, stress, depression, and other psychological problems are significantly more common in CSS conditions than controls in a subgroup of patients (48,198-203), with a bidirectional relationship (150,151,197). Stress plays an important role in the CSS disorders (197). However, data are sparse regarding the contribution of psychological distress to CS.

In healthy individuals, anxiety predicted temporal summation by heat stimulus (204). A correlation exists between anxiety and pain symptoms in population studies, but none by electric stimuli (205). CS evaluated by manual tender point (TP) examination correlated with psychological distress including anxiety, depression, and ill-health behavior in FMS (206,207). However, such a correlation was absent in other studies (208,209).

In FMS, catastrophizing was related to decreased pain threshold and tolerance to heat stimulus (73) and to increased activity in brain areas related to anticipation, attention, and the emotional aspects of pain, as shown by fMRI in response to pressure stimulus delivered by a rubber probe (210). Thus, psychological factors may play an important role in pain perception and pain processing in FMS. However, in IBS, pain sensitivity by rectosigmoid distension was not correlated with psychological distress (86). An association has been shown between childhood abuse and CSS conditions, eg, FMS and CFS (211), IBS (212), and headaches (213). Childhood adverse experiences may promote long-lasting neuronal plasticity that causes both physical and psychological symptoms, as well as CS among the adults.

Only a few studies assessed a relationship between childhood abuse and CS. Among healthy individuals, there is a decrease in pain sensitivity to heat and ischemic stimuli despite much pain complaints and negative affect (214). A history of adverse childhood experiences was associated with high TP counts in FMS in a population study (207), and low pain threshold in IBS by digital pressure at the periphery (212). However, there was an increased pain threshold to balloon pressure in IBS (215) and an increased pain tolerance to ischemic pain in TMD (216). The paradox between increased pain symptoms and decreased pain sensitivity in the laboratory setting among the abused patients may be explained by a psychological barrier to sharply painful stimuli in an experimental laboratory setting that may trigger a painful memory (215).

Infection, Inflammation, Trauma, Sleep, and Environmental Factors

General viral (48,217) or local (218) infections, as well as trauma (133,135), are reported to trigger many CSS conditions, probably through the action of inflammatory mediators that activate nociceptive fibers with resultant CS. However, there is no ongoing peripheral inflammation in FMS (219). The role of afferent neurons in CSS needs further study. A review article concluded that trauma from motor vehicle accidents (MVA) may trigger FMS in the presence of preexisting psychological vulnerabilities, and that there is a causal relationship between FMS and MVA (220), but another study failed to find an association between MVA and FMS (221). This latter article, however, has certain drawbacks, eg, a majority (60%) of the patients were male and no psychological factors were measured (221).

CS has been demonstrated in osteoarthritis (222), and several systemic diseases, eg, rheumatoid arthritis (RA) (223) and systemic lupus erythematosus (SLE) (224,225), are associated with FMS. It is possible that arthritis (222-225) or colonic inflammation (226) activates local nociceptors that initiate or sustain CS, particularly in susceptible individuals. However, other unknown shared neuroendocrine and genetic mechanisms may be involved.

Nonrestorative sleep may cause CS. Healthy individuals subjected to disturbed sleep in a sleep EEG laboratory demonstrate multiple TP that were absent at baseline before sleep deprivation (164). Moreover, CS by algometry and other nociceptive stimuli (71,76,227) is correlated with poor sleep. Environmental stimuli, eg, noise, may

also induce CS in the experimental pain laboratory (67,99,148).

DISCUSSION

Historically, the concept that several CSS disorders are interconnected was first published in 1984 (228) based on the previous demonstration of associations of several CSS members with FMS (22). Fifteen years ago, attention was drawn to the fact that the pathophysiology of FMS involves aberrant central pain mechanisms (229). Now it seems likely that a major component of the central pain mechanism is CS, and it is a major binder for the CSS conditions. At this time, evidence for CS is not present in all patients of the CSS family (similar to other diseases, eg, the HLA marker in spondyloarthropathies). Based on good and converging data, there is evidence for CS in FMS, IBS, MPS/RSTPS, and migraine, while modest evidence is present in TMD, RLS, and primary dysmenorrheal (PD) that require further study. Data are limited or not published for other members, eg, MCS, TTH, PTSD, CFS, and IC. However, restating a cliché, absence of proof does not mean absence; rather, proper studies addressing an array of methodological issues (see below) have not yet been performed.

The literature shows that the demonstration of CS will depend on numerous factors, many of which have not been addressed in currently available studies. A large number of elements that may affect CS include host factors (age, gender, genetics, interindividual variation in pain response), uniformity of disease classification, subgroups (eg, those with psychological distress), measurement of pain perception, threshold or tolerance, stimulus types (digital palpation, algometer, heat, electricity, ischemic, phasic versus tonic, ascending versus random, etc), sites tested, technique, and methods used (including QST, CEP, and brain imaging), types of tissues stimulated (eg, skin, subcutis, muscle, viscera), and treatment status among others. Thus, some patients not showing CS may do so if the above variables are taken into consideration. Response variability based on types of stimuli and types of tissue tested is well documented (65,66,68,69,117,123). Heat stimulator excites surface receptors, whereas cold pressor test affects deeper tissues (65). Pressure pain threshold was decreased but threshold to cutaneous electric stimulation was normal in FMS (69). Also in FMS, heat perception was normal, but heat threshold was decreased (64). These variabilities may also influence a correlation between CS and clinical or psychological symptoms.

CS is correlated with several symptoms, eg, pain (64,96,130,133,206,230), poor sleep (71,206,230), fatigue (206,207,230), and associated psychological factors (206,207,230). However, some studies failed to show a significant correlation between CS and spontaneous pain (65,66,102). This is hardly surprising considering the numerous complex factors that determine CS, as mentioned earlier, as well as the momentary nature of pain elicited in the laboratory as contrasted with chronic pain for months or years. The correlation between FMS symptoms and CS is stronger when CS is measured by TP examination, as compared with dolorimetry (65,206). TP assessed by digital pressure also shows greater correlation with psychosocial factors in comparison with dolorimetric pressure (206). It would seem that different biopsychopathology is involved in different modalities of stimuli and they do not clinically measure the same thing. At this time, there are only limited, and often contradictory, data on the relationship between CS and psychosocial factors as well as psychiatric diseases, as stated above. Given the complex and multiple facets of both CS and psychosocial factors, further studies are warranted.

CS is probably a preexisting phenomenon that may be present in asymptomatic individuals before developing symptoms and is likely to play a causative role in CSS, probably with other risk factors, eg, genetics. This view is suggested by the following: (a) the greater likelihood of asymptomatic subjects with genetically determined hypersensitivity to thermal and ischemic stimuli to develop TMD on follow-up than those without enhanced sensitivity (180); (b) the increasing degree of CS (as measured by number of TP) exists as a continuum among asymptomatic subjects, those with regional pain, and patients with widespread pain (63,65,206,207,230); (c) the presence of CS in asymptomatic first-degree relatives who are highly likely to develop a CSS condition in the future (162,174); and (d) the attenuation of CS by drugs (70,231-234) that also ameliorate symptoms during the study period (70,231-233). Thus, CS may be the cause rather than the effect of CSS diseases.

Given a correlation between CS and symptom duration (63), the relationship between CS and CSS may be bidirectional, ie, CS causes CSS, and the chronicity of CSS disease may further accentuate CS. A schematic representation of probable contributory factors of CS that may lead to CSS is shown in Fig. 2. Since psychosocial factors contribute to CS, consideration of these factors is very important in the management of CSS disorders that should involve a person-centered approach (235).

CS may not be the only mechanism causing symptoms in CSS disorders. Genetics, poor sleep, trauma, endocrine dysfunction, sympathetic overactivity, viral infection, environmental elements, psychosocial distress, and other unrecognized factors may all be independently involved through different mechanisms besides their possible or probable contributions to CS. It is possible that psychosocial distress interacts with biological factors to cause symptoms.

Should all CSS disorders be lumped together or split? There are many more similarities among them than differences, supporting the concept of group classification, as advocated by most investigators. However it is important to recognize that they are not the same diseases, and their biopathological mechanisms may vary in some aspects. In

FMS, for example, there is hyperactivity of the CRH neurons, whereas hypofunction of these neurons has been reported in CFS (168). Overlap among members of any group classification in medicine (eg, the vasculitides) does not mean *total* overlap, and this is also true of CSS disorders. The advantage of "lumping" of CSS is further described under "Significance of CSS" below.

In summary, the CSS paradigm seems an important new concept with considerable significance that deserves further exploration.

Significance of CSS

1. CSS diseases are based on both biological and psychological factors, with implications for patient and physician education and proper patient care. Thus questioning the veracity of a patient with CSS is unwarranted (236).
2. The concept of CSS will foster further research involving the CNS.
3. The recognition of mutual associations among the CSS diseases is helpful in their diagnosis and in avoiding costly and unnecessary investigations as well as surgery.
4. Since the CSS members have similar (but not the same) pathophysiological mechanisms, elucidation of a certain mechanism or treatment efficacy in 1 may apply to the others.
5. The existence of CS in an asymptomatic individual may predict symptomatic development of a CSS disease in the future.
6. The presence of CS in a disease with structural pathology, eg, RA, osteoarthritis, and SLE, would alert a physician to evaluate for a concomitant CSS condition (eg, FMS) by history and a simple TP examination (this examination would evaluate CS).
7. The copresence of a CSS condition with a disease having structural pathology would need a different management approach to avoid unnecessary and harmful medications and for successful holistic patient management.
8. The CSS as a group is probably the most common medical problem for which patients consult a physician, so that greater physician interest, academic research, and adequate funding for research are imperative.
9. The presence of multiple CSS disorders in the same patient is likely to increase CS and the burden of distress (28). So, a physician should focus and help to manage not only on the presenting symptoms, in a FMS patient as an example, but also on other associated CSS conditions, eg, IBS and RLS.
10. The effect of various drugs on CS and patient symptoms can be evaluated in the human pain laboratory by testing for CS and grading the symptoms at baseline and after clinical trials of a short duration (70,231-233) followed by longer trials. The same may also be true of nonpharmacologic therapy, eg, sleep hygiene, exercise, cognitive behavioral therapy, and meditation.

The drugs that are known to attenuate CS are the NMDA receptor antagonists, ie, ketamine (70,231,232) and amitriptyline (233), and gabapentin (234), among others. More effective and safer drugs are likely to be developed in the future. Functional brain imaging may also be used to visualize the changes related to CS following drug and non-drug therapy (106,234). Noting that buprenorphine, an opioid, not only has an analgesic, but also an antihyperalgesic effect to electrically evoked pain, Simonet remarked that drugs that inhibit CS may be a new and beneficial way to manage chronic pain (237). Much future work is necessary to explore various aspects of CS and its relevance to CSS and other diseases.

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