

Overlapping Conditions Among Patients With Chronic Fatigue Syndrome, Fibromyalgia, and Temporomandibular Disorder

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Background: Patients with chronic fatigue syndrome (CFS), fibromyalgia (FM), and temporomandibular disorder (TMD) share many clinical illness features such as myalgia, fatigue, sleep disturbances, and impairment in ability to perform activities of daily living as a consequence of these symptoms. A growing literature suggests that a variety of comorbid illnesses also may commonly coexist in these patients, including irritable bowel syndrome, chronic tension-type headache, and interstitial cystitis.

Objective: To describe the frequency of 10 clinical conditions among patients with CFS, FM, and TMD compared with healthy controls with respect to past diagnoses, degree to which they manifested symptoms for each condition as determined by expert-based criteria, and published diagnostic criteria.

Methods: Patients diagnosed as having CFS, FM, and TMD by their physicians were recruited from hospital-based clinics. Healthy control subjects from a dermatology clinic were enrolled as a comparison group. All subjects completed a 138-item symptom checklist and underwent a brief physical examination performed by the project physicians.

Results: With little exception, patients reported few past

diagnoses of the 10 clinical conditions beyond their referring diagnosis of CFS, FM, or TMD. In contrast, patients were more likely than controls to meet lifetime symptom and diagnostic criteria for many of the conditions, including CFS, FM, irritable bowel syndrome, multiple chemical sensitivities, and headache. Lifetime rates of irritable bowel syndrome were particularly striking in the patient groups (CFS, 92%; FM, 77%; TMD, 64%) compared with controls (18%) ($P < .001$). Individual symptom analysis revealed that patients with CFS, FM, and TMD share common symptoms, including generalized pain sensitivity, sleep and concentration difficulties, bowel complaints, and headache. However, several symptoms also distinguished the patient groups.

Conclusions: This study provides preliminary evidence that patients with CFS, FM, and TMD share key symptoms. It also is apparent that other localized and systemic conditions may frequently co-occur with CFS, FM, and TMD. Future research that seeks to identify the temporal relationships and other pathophysiologic mechanism(s) linking CFS, FM, and TMD will likely advance our understanding and treatment of these chronic, recurrent conditions.

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OBSERVANT physicians over the years have described numerous clinical conditions that share features such as fatigue, pain and other symptoms in the absence of objective findings, disability out of proportion to physical findings, and an apparent association with “stress” and psychosocial factors. These include illnesses such as chronic fatigue syndrome (CFS), fibromyalgia (FM), and temporomandibular disorder (TMD), as well as irritable bowel syndrome (IBS), interstitial cystitis, multiple chemical sensitivities, chronic tension-type headaches, post-concussive syndrome, chronic pelvic pain, and chronic low back pain. Although often labeled “psychosomatic” or “functional” disorders, similarities in clinical manifestations among these conditions, such as increased pain sensitivity in patients with FM and interstitial

cystitis, suggest a possible common alteration in central processing mechanisms.¹

A small literature on relationships between CFS, FM, and TMD supports the contention that, despite a multiplicity of diagnostic labels, these syndromes may represent “overlapping” conditions. In this regard, it has been estimated that between 20% and 70% of patients with FM meet criteria for CFS and, conversely, 35% to 70% of those with CFS also have FM.²⁻⁵ Studies investigating the relationship between FM and TMD have demonstrated that 18% of patients with TMD meet FM criteria, and 75% of patients with FM satisfy the Research Diagnostic Criteria for TMD (myofascial type).^{6,7} Other data, though limited, suggest that patients with CFS, FM, and TMD commonly report symptoms that characterize other overlapping disorders. However, only recently have the similarities of CFS, FM, and

SUBJECTS AND METHODS

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The sample consisted of 25 patients with CFS, 22 patients with FM, 25 patients with TMD, and 22 healthy control subjects. All subjects were new or established patients recruited from hospital-based clinics affiliated with the University of Washington and Pacific Medical Center in Seattle between January 1993 and September 1994. Patients with CFS were attending the Chronic Fatigue Clinic, a tertiary care referral practice. Patients with FM and TMD were seeking care at an academic rheumatology and oral medicine clinic, respectively. Control subjects included individuals from 2 dermatology clinics who were being evaluated for conditions other than CFS, FM, or TMD. Control subjects were healthy (ie, without major, chronic medical problems) and were typically being seen for minor, nonsystemic, skin conditions (eg, warts).

In each of the clinics, a single, designated participating physician was asked to approach patients diagnosed as having CFS, FM, or TMD. In the case of the control subjects, the physician selected only patients who were healthy with the exception of their dermatologic condition. Treating physicians were well-versed in the application of published research criteria¹¹⁻¹³ for the 3 conditions under study. Patients with CFS were diagnosed using the 1988 Centers for Disease Control case definition¹¹ and a recommended modification that does not exclude those with specific psychiatric diagnoses.¹⁴ Patients with FM were classified according to the American College of Rheumatology criteria for FM.¹² The diagnosis of TMD was directed by the Research Diagnostic Criteria.¹³ This study was approved by the University of Washington Human Subjects Office and all subjects provided written, informed consent upon enrollment.

DATA COLLECTION

Subjects were approached to participate in the study during routine clinic visits or by mailed letters to patients deemed eligible by the designated clinic physician. Information was gathered from interested subjects at their convenience, either following a regularly scheduled appointment or during a separate study appointment scheduled at another time. Patients who were unable to complete the lengthy questionnaire at the time of the study evaluation were asked to complete it at home and mail it to the investigators. After describing the study and obtaining informed consent, all patients underwent a physical examination by a physician (M.M.B. or D.B.) and completed a 138-item symptom checklist. The physical examination included an assessment of pharyngeal inflammation; submandibular, anterior cervical, posterior cervical, and axillary lymphadenopathy; and manual palpation of the 18 tender point sites as described by the American College of Rheumatology.¹²

The symptom checklist included 138 items assessing demographic and clinical information (eg, age, education, sex, and duration of illness) as well as self-report of previous diagnoses and the presence of relevant symptoms of the following 10 overlapping conditions: CFS, TMD, FM,

chronic tension-type headache, IBS, interstitial cystitis, post-concussive syndrome, multiple chemical sensitivities, chronic pelvic pain, and chronic low back pain. For the self-reported overlapping conditions, subjects were asked "Have you ever been told by a health care provider that you have . . .". Symptoms for the 10 conditions of interest were derived from several sources. For CFS, FM, IBS, and chronic tension-type headache we used published criteria.^{12,15-17} For TMD, interstitial cystitis, post-concussive syndrome, multiple chemical sensitivities, chronic pelvic pain, and chronic low back pain, characteristic symptoms were derived from 2 additional sources: (1) consultations with university faculty who had established expertise in the diagnosis and treatment of a given disorder ("experts"), and (2) searches of the extant literature for characteristic symptoms. Thus, the final items compiled for each disorder in the symptom checklist included both criteria-based symptoms and well-recognized features used in clinical practice in the diagnosis of the study conditions. Prior to the administration to subjects, the questions contained in the checklist for each individual disorder were approved by the appropriate expert.

To score the symptom checklist, the total number of symptoms endorsed for each syndrome were summed to obtain a subject's score for the relevant clinical condition. This score was intended to approximate the degree to which subjects reported characteristics of a particular syndrome as determined by our experts. All reported diagnoses and symptoms represent lifetime occurrence rates.

Finally, we were interested in common and distinguishing symptoms among the patient groups. "Common symptoms" were those for which there was both a clinical (defined as >25% difference in frequency) and a statistically significant ($P \leq .01$) difference between the CFS, FM, TMD patient groups and controls. To be designated as a "distinguishing symptom," the symptom must have differentiated the specified group(s) of interest from the other(s) by these same criteria. For example, a distinguishing symptom of TMD was considered to differentiate patients with TMD from those with CFS, those with FM, and controls if a greater than 25% difference in frequency and $P \leq .01$ statistical difference existed between the TMD group and each of the other groups' mean scores on that symptom.

STATISTICAL ANALYSES

We used χ^2 analyses to compare the 4 groups (CFS, FM, TMD, controls) on all dichotomous variables. In the event of significant overall group differences, individual χ^2 analyses then assessed associations between patient status (CFS, FM, TMD) and controls on the dichotomous variable. Next, a series of 1-way analyses of covariance controlling for age and sex were performed for the summation of scores from each of the continuous ("expert-based") variables. When overall effects or trends were detected ($P \leq .05$), each patient group was compared with control subjects in follow-up univariate analyses (1-tailed). All P values are shown in the tables. However, to decrease the likelihood of a type I error, only P values of .01 or less are considered significant; values of $P \leq .05$ are described as trends.

Table 1. Self-reported Diagnoses by Group Status*

Diagnosis	No. (%) of Subjects				P
	CFS	FM	TMD	Controls	
CFS	25 (100)	4 (18)	0	0	<.001†‡
FM	20 (80)	22 (100)	2 (9)	0	<.001†§
TMD	7 (28)	5 (24)	21 (88)	3 (14)	<.001
IBS	9 (36)	13 (59)	4 (16)	0	<.001†§
Interstitial cystitis	2 (8)	2 (8)	4 (17)	0	.22
Post-concussive syndrome	2 (8)	0	0	0	.13
Multiple chemical sensitivities	1 (4)	4 (18)	0	0	.02‡
Chronic tension-type headache	1 (4)	5 (23)	9 (36)	0	.002‡
Chronic pelvic pain	2 (8)	4 (18)	2 (8)	0	.21
Chronic low back pain	8 (32)	14 (67)	4 (16)	4 (18)	<.001§

* Total number of subjects in each group may vary due to missing values. CFS indicates chronic fatigue syndrome; FM, fibromyalgia; TMD, temporomandibular disorder; and IBS, irritable bowel syndrome.

†CFS > controls, $P \leq .01$.

‡FM > controls, $P \leq .05$.

§FM > controls, $P \leq .01$.

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TMD with other clinical conditions such as IBS, chronic headache, interstitial cystitis, multiple chemical sensitivities, and others been systematically studied.^{1,2,8} For example, investigations using standardized criteria have reported 42% to 70% of patients with FM concurrently met criteria for IBS compared with only 10% to 16% of healthy control subjects.^{9,10}

No previous study has examined the co-occurrence of a comprehensive array of overlapping symptoms and conditions among patients diagnosed as having CFS, FM, or TMD. We hypothesized that, given the similarities between CFS, FM, and TMD, symptoms consistent with overlapping conditions such as IBS and interstitial cystitis and others would likewise be commonly observed. We therefore compared these 3 patient groups with a healthy control group with respect to these questions: (1) Do patients with CFS, FM, or TMD more often receive diagnoses of other overlapping conditions? (2) Do patients with CFS, FM, or TMD more frequently report the symptoms characteristic of 10 overlapping conditions than healthy persons? (3) Which symptoms do the CFS, FM, and TMD patient groups share and which distinguish the groups from each other? and (4) If published case definitions for CFS, FM, IBS, and chronic tension-type headache are applied, what proportion of CFS, FM, and TMD patients and healthy control subjects will meet diagnostic criteria?

RESULTS

Patients with FM were significantly older than those with TMD (48.5 vs 38.0 years; $P \leq .01$). The CFS, FM, TMD, and control groups did not differ with respect to sex (range, 73%-96% female; $P = .06$) or educational level (most having attended college, $P = .18$). Moreover, the patient groups were not different with respect to duration of illness (FM, 8.2 years; CFS, 4.3 years; and TMD, 8.1 years; $P = .15$).

Table 1 compares the percentage of subjects in each group who reported a prior diagnosis made by a health care

provider for the 10 clinical conditions. Compared with control subjects, patients with CFS received diagnoses of CFS, FM, and IBS significantly more often. Patients with FM were significantly more likely to report diagnoses of FM, IBS, and chronic low back pain. They also tended to report diagnoses of CFS, multiple chemical sensitivities, and chronic tension-type headache. Of interest is the variability in the pattern of overlapping diagnoses. For instance, although only 18% of patients with FM had been diagnosed with CFS, 80% of those with CFS had received a diagnosis of FM. Patients with TMD more frequently had a history of chronic tension-type headache compared with control subjects. Overall, relatively few patients had histories of interstitial cystitis, post-concussive syndrome, or chronic pelvic pain.

Table 2 shows the mean number of expert-based symptoms for each clinical condition by group status. All patients reported significantly more symptoms consistent with CFS, FM, IBS, and chronic tension-type headache compared with control subjects, even after controlling for the effects of age and sex. Interestingly, patients with CFS were no more likely than control subjects to endorse symptoms characteristic of TMD, although patients with FM tended to report a greater number of the features characteristic of TMD. In striking comparison with the infrequent physician diagnosis of multiple chemical sensitivity syndrome observed in Table 1, Table 2 shows that patients with CFS, FM, and TMD all tended to have more symptoms of multiple chemical sensitivity compared with control subjects. In total, patients with CFS exhibited significantly more symptoms than controls for 5 conditions (CFS, FM, IBS, multiple chemical sensitivities, and chronic tension-type headache); patients with FM reported symptoms consistent with 7 conditions (CFS, FM, IBS, interstitial cystitis, multiple chemical sensitivities, chronic tension-type headache, and chronic low back pain); and patients with TMD reported more symptoms than controls for 5, including TMD, of the conditions (CFS, FM, IBS, and chronic tension-type headache). Patient groups did not differ from the control group with regard to the frequencies for post-concussive syndrome or chronic pelvic pain.

Table 2. Symptom Scores for Clinical Conditions as Determined by Expert-Based Criteria*

Condition	Maximum Score	Mean (SD) Score				P
		CFS (n = 25)	FM (n = 22)	TMD (n = 25)	Control (n = 22)	
CFS	12	11.0 (0.9)	8.6 (2.2)	5.2 (3.0)	1.0 (1.1)	≤.001†‡§
FM	6	5.2 (0.9)	5.0 (0.9)	3.2 (1.7)	0.4 (0.9)	≤.001†‡§
TMD	25	11.6 (4.8)	14.6 (5.0)	16.0 (4.6)	9.3 (4.6)	.009§
IBS	7	5.3 (1.5)	4.9 (2.5)	3.8 (2.6)	1.5 (2.3)	≤.001†‡§
Interstitial cystitis	5	1.1 (1.1)	1.6 (1.5)	0.7 (0.9)	0.6 (1.1)	.05‡
Post-concussive syndrome	5	4.3 (1.4)	4.3 (1.5)	2.5 (1.6)	0.7 (1.2)	.02
Multiple chemical sensitivities	21	14.5 (2.1)	15.5 (3.7)	13.0 (0.9)	4.3 (3.2)	.05†‡
Chronic tension-type headache	4	2.2 (1.9)	1.7 (1.7)	2.2 (1.6)	0.1 (0.6)	≤.001†‡§
Chronic pelvic pain	22	12.9 (3.7)	10.8 (4.8)	11.8 (5.0)	15.8 (0.9)	.29
Chronic low back pain	11	3.6 (3.9)	5.8 (3.6)	2.4 (3.8)	1.4 (2.9)	≤.001‡#

*CFS indicates chronic fatigue syndrome; FM, fibromyalgia; TMD, temporomandibular disorder; and IBS, irritable bowel syndrome.

†CFS > controls, P ≤ .01.

‡FM > controls, P ≤ .01.

§TMD > controls, P ≤ .01.

||FM > controls, P ≤ .05.

||TMD > controls, P ≤ .05.

#CFS > controls, P ≤ .05.

Table 3. Diagnostic Classifications Using Published Criteria*

Diagnosis	Criteria	No. (%) of Subjects				P
		CFS	FM	TMD	Controls	
CFS	1994 CDC	25 (100)	14 (64)	5 (20)	0	<.001†‡§
FM	1990 ACR	5 (20)	5 (71)	3 (13)	0	<.001†‡§
IBS	1978 Manning ¹⁷	23 (92)	17 (77)	16 (64)	4 (18)	<.001†‡
Chronic tension-type headache	1988 IHS	3 (12)	1 (5)	2 (8)	0	.37

*Total number of subjects in each group may vary due to missing values. CFS indicates chronic fatigue syndrome; FM, fibromyalgia; TMD, temporomandibular disorder; IBS, irritable bowel syndrome; CDC, Centers for Disease Control and Prevention; ACR, American College of Rheumatology; and IHS, International Headache Society.

†CFS > controls, P ≤ .01.

‡FM > controls, P ≤ .01.

§TMD > controls, P ≤ .05.

||TMD > controls, P ≤ .01.

Table 3 presents the percentage of subjects in each group who met Research Diagnostic Criteria for CFS, FM, IBS, and chronic tension-type headache. Not surprisingly, patients with CFS and FM were significantly more likely than control subjects to meet stringent criteria for their respective disorders. A greater percentage of patients with TMD also tended to meet criteria for CFS (20%) and FM (13%) compared with healthy subjects, none of whom met criteria for these diagnoses. Most striking, the large majority of all patients met lifetime criteria for IBS according to the Manning criteria,¹⁷ in contrast to only 18% of controls (all P values ≤ .001). There were no significant differences among the groups with respect to percentage of subjects meeting the 1988 International Headache Society definition for chronic tension-type headache. The most common reason among the CFS, FM, and TMD patients for failing to meet the research criteria was the endorsement of both sensitivity to lights and noise during a typical headache, symptoms that are considered more characteristic of migraine-type headaches.

Table 4 displays both common and distinguishing individual symptoms derived from 138 items contained on the symptom checklist encompassing the 10

conditions. Consistent with the results shown in Table 2, symptoms common to CFS, FM, and TMD patients included those characteristic of CFS, FM, and IBS. Especially prominent among these were muscle and abdominal pain and sleep and concentration difficulties. Patients with CFS and FM were distinguished from patients with TMD and control subjects by symptoms of fatigue, joint aches, and burning or shooting muscle pain. Unique features for CFS included fever or sore throat; for FM, a more frequent history of low back pain that was made better by heat or massage and was exacerbated with sitting or standing; and patients with TMD were best distinguished by a history of facial ache or pain in jaw muscles or joints.

Finally, differences were found in the mean number of tender points on the physical examination among control subjects (0.9) compared with patients with CFS (7.4, P < .001), FM (11.0, P < .001), and TMD (5.2, P ≤ .001). Patients with FM also were found to have more tender points than either CFS or TMD patients (both P ≤ .001). However, patient groups did not differ from the control group with respect to the total number of swollen and/or tender lymph nodes present on physical examination (P values, .18-.78).

Table 4. Common and Distinguishing Symptoms of CFS, FM, and TMD*

Symptoms†	Illness Category	No. (%) of Subjects			
		CFS	FM	TMD	Controls
Symptoms Common to All 3 Conditions					
Muscle pain, aching, or discomfort	FM	25 (100)	22 (100)	22 (88)	2 (9)
Problems falling or staying asleep, or sleeping too much	CFS	23 (92)	21 (96)	20 (83)	6 (32)
Wake up feeling tired, unrefreshed after a full night's rest	CFS	22 (88)	20 (91)	17 (68)	4 (20)
Difficulty concentrating or thinking, forgetfulness	CFS	24 (100)	20 (91)	18 (72)	3 (15)
Abdominal pain relieved by a bowel movement	IBS	16 (64)	15 (68)	16 (64)	4 (18)
Hard, loose, or watery stools	IBS	25 (100)	18 (82)	16 (67)	7 (32)
Symptoms That Distinguish CFS and FM From TMD					
Fatigue >6 mo	CFS	25 (100)	19 (86)	14 (56)	2 (9)
Fatigue resulting in a 50% reduction of normal activity	CFS	25 (100)	16 (73)	7 (28)	1 (4)
Unexplained weakness in muscles	CFS	25 (100)	16 (73)	3 (13)	0
Migratory arthralgias without redness or swelling	CFS	22 (88)	22 (100)	11 (44)	1 (5)
Burning, shooting, or throbbing muscle pain	FM	18 (72)	16 (73)	11 (44)	1 (5)
Symptoms That Distinguish CFS From FM and TMD					
Mild fever (37.5°C-38.6°C) or chills	CFS	23 (92)	13 (59)	9 (38)	0
Sore throat	CFS	25 (100)	10 (48)	13 (52)	3 (15)
Symptoms That Distinguish FM From CFS and TMD					
Pain made better by heat or massage	Low back pain	10 (40)	16 (76)	8 (32)	4 (18)
Pain made worse by sitting or standing	Low back pain	12 (48)	15 (75)	8 (32)	4 (18)
Symptoms That Distinguish TMD From CFS and FM					
Pain in jaw muscles, temporomandibular joint, or inside the ear	TMD	14 (58)	11 (50)	25 (100)	6 (27)

* CFS indicates chronic fatigue syndrome; FM, fibromyalgia; TMD, temporomandibular disorder; and IBS, irritable bowel syndrome.

† Individual symptoms derived from 138 items comprising "expert" criteria for 10 disorders. Symptoms must have differentiated group(s) by more than 25% and P ≤ .01.

COMMENT

In this study we assessed the degree of overlap of 10 clinical conditions among patients with CFS, FM, and TMD, and healthy control subjects using several complementary approaches. We examined the lifetime occurrence of each syndrome as diagnosed by a health care provider, as well as patients' endorsement of individual symptoms comprising these conditions as determined by experts in the field and the existing literature. Published diagnostic criteria were also applied for a subset of overlapping conditions. Finally, symptoms common to CFS, FM, and TMD, as well as those that distinguish them from each other were described. With the exception of TMD, interstitial cystitis, post-concussive syndrome, and chronic pelvic pain, all patient-reported health care provider diagnoses were more commonly reported by CFS and FM patients compared with controls. Differences between patients with TMD and controls were less striking. In contrast, using the symptom checklist, patients in the 3 groups generally scored much higher than healthy control subjects with regard to the total number of symptoms comprising each condition. Application of the published case definitions yielded similar findings. Thus, by investigating the clinical syndromes from a variety of perspectives, differences in the types of information obtained, discrepancies, probable missed diagnoses, and variable rates of illness could be observed.

In the case of CFS, 80% of patients reported a history of clinician-diagnosed FM, the FM symptom score was high, yet on examination only 20% met American College of Rheumatology criteria for FM. An opposite trend was ob-

served for IBS, multiple chemical sensitivities, post-concussive syndrome, and chronic tension-type headaches in relation to CFS where we found low rates of clinician diagnoses and moderate symptom scores. When published criteria were applied, the apparent rate of missed diagnoses was relatively high for IBS (92%) and chronic tension-type headaches (12%) among patients with CFS. A similar situation existed for FM with respect to these disorders. However, in contrast to patients with CFS and concurrent FM, only 18% of FM patients carried a diagnosis of CFS, although 64% actually met the Centers for Disease Control criteria. These findings are surprising given the substantial overlap between CFS and FM in studies that have used both symptom-based and diagnostic criteria for the disorders.^{2,5} The reason for discrepancies in rates of clinician diagnoses and symptom reporting compared with the application of diagnostic criteria is unclear. Explanations might include the requirement of tender points in the FM case definition vs the symptom-based criteria for CFS, and clinicians' tendency to focus on particular conditions depending on the presenting symptom(s) and/or familiarity with alternative conditions.

Among patients with TMD, 0% and 9% had received a health care provider diagnosis of CFS and FM, respectively. Nevertheless, patients with TMD had many symptoms in common with CFS and FM, such as muscle pain, sleep problems, difficulty concentrating, and debilitating headaches. Thirteen percent of our TMD patients satisfied the American College of Rheumatology criteria for FM, which is comparable to the rate of 18% recently reported.⁷ The mean number of tender points for patients

with TMD found in this study also was similar to previously published values (5.2 vs 6.3).⁷ In comparing our results with epidemiological data on pain, it is interesting to note that these values approximate the number of tender points found in community residents with widespread pain (6.2).¹⁸ Although TMD is believed to represent a localized pain syndrome, this relatively high number of tender points suggests that TMD may represent one manifestation of a more global pain sensitivity disorder.¹⁹

Regardless of the method of inquiry, the lifetime rate of IBS was common in the 3 patient groups relative to control subjects. In the medical literature, IBS has most frequently been reported to co-occur with FM.^{3,20} In the present study, however, patients with CFS and TMD also were more likely than control subjects to report a previous diagnosis of IBS, meet diagnostic criteria for IBS, and experience IBS-related symptoms. The rates of IBS among patients with CFS, FM, and TMD (92%, 77%, and 64%, respectively) were well above the frequency both in our control group (18%) and in the general population (9%-21%) as estimated using the Manning criteria.²¹ The only study examining the overlap of IBS and chronic fatigue used identical standard diagnostic criteria and similarly reported a high prevalence of IBS among patients with chronic fatigue over a 1-year retrospective evaluation period (73%).²² It should be noted that the prevalence of IBS in community surveys is typically assessed using a 3-month time frame, whereas this study ascertained lifetime prevalence. However, when we examined whether subjects currently met criteria for IBS (ie, >2 Manning symptoms endorsed on the day of questionnaire completion), we also found significantly higher rates of IBS among patients (17%-40%) compared with control subjects (5%). Thus, while IBS is certainly common in the general population, our patient groups were disproportionately affected with IBS. These results suggest that a common pathogenic mechanism related to bowel dysfunction may underlie CFS, FM, and TMD disorders. In this regard, some investigators have speculated that the serotonin abnormalities observed in patients with FM may be the result of defective absorption of the precursor amino acid tryptophan from the gut.²³

The rates of several other clinical conditions of interest were found to occur more frequently in the 3 patient groups. Patients with FM had a significantly greater number of symptoms characteristic of interstitial cystitis compared with patients with CFS or TMD or control subjects but were no more likely to report a past diagnosis of this disorder than any other group. These results are consistent with a survey of 2682 patients with interstitial cystitis, 25% of whom reported having comorbid FM.²⁴ Additional support for clinical similarities comes from a recent study demonstrating that patients with interstitial cystitis and patients with FM were more similar to each other than to controls with regard to decreased pain thresholds and comparability of symptoms.¹ Few patients in the present study reported a past diagnosis of multiple chemical sensitivity syndrome, although their symptom checklist scores were high for this diagnosis. Previous studies have indicated that 55% of patients with FM reported symptoms consistent with multiple chemical sensitivities and 30% of patients with multiple chemical sensitivities met the Centers for Disease Control criteria for CFS.^{2,8} To our

knowledge, there are no data available on the overlap between TMD and multiple chemical sensitivities.

Collectively, the findings of this study provide additional evidence that patients with CFS, FM, and TMD share symptoms including generalized pain sensitivity, sleep and concentration difficulties, and bowel complaints. It also is apparent that other localized and systemic conditions, particularly IBS, interstitial cystitis, and multiple chemical sensitivities may frequently co-occur with CFS, FM, and TMD. Although this study was not designed to assess either the temporal relationships among these conditions or potential mechanism(s) that link them, these are among the most intriguing questions that arise. In this regard, prospective studies that examine the onset of these disorders could improve our understanding of the underlying pathophysiological mechanisms. For example, a localized injury might trigger a sensitization of the central nervous system to afferent pain signals leading to decreased pain thresholds at other body sites. A similar process, known as neurogenic inflammation, occurs when an exogenous agent combines with chemical irritant receptors on sensory nerves, and the subsequent release of inflammatory neuropeptides sensitizes local and central structures.

While such mechanisms have been proposed to account for the development of both multiple chemical sensitivities and FM,²⁵ they cannot alone account for illness in patients whose onset did not follow a physical injury or chemical exposure. Indeed, many patients report a gradual onset, onset in conjunction with acute or chronic emotionally stressful events, or a combination of physical and emotional events that appear to have precipitated their illness.²⁶⁻²⁸ These events may initiate perturbations in the hypothalamic-pituitary-adrenal axis and the autonomic system and result in sensitization of the central nervous system via neuropeptides, ultimately altering the processing of nociceptive signals as has been suggested in the case of FM.²⁹ However, such theories as applied to the development of other related conditions require further testing as key differences in hypothalamic-pituitary-adrenal axis and neuromodulatory functioning have been reported only for CFS and FM.^{30,31} In light of the present study's findings, it may be important in future studies investigating underlying pathophysiological mechanisms to identify patients who also meet criteria for comorbid related conditions and to either screen them out or subgroup patients with similar comorbidities. Otherwise, shared vs dissimilar pathophysiological features among these conditions may be obscured due to illness confounding.

The present study has several limitations. First, we relied on physician referrals for the identification of subjects. Thus, we did not independently confirm the diagnoses of FM and TMD prior to study participation (eg, TMD requires a specialized examination) nor were subjects guaranteed to meet criteria on the day of the study examination. This methodological point likely explains why only 77% of previously diagnosed FM patients fulfilled the case definition upon enrollment. Second, we relied on the subjects' self-report of previous diagnoses of overlapping conditions and did not confirm these with review of medical records. However, in most cases, the frequency of past diagnoses were lower than one might expect given the scores on the symptom checklist, consistent with underdiagnoses of these illnesses. Third, the nonblinded methodology

of the physical examinations might have influenced the examiner's findings. However, the examination represented only a small portion of the overall data presented. Fourth, the results from this study may not be generalizable to patients with CFS, FM, and TMD who do not seek treatment for their disorder as persons with multiple comorbidities may be overrepresented in tertiary care clinics. Last, our study design relied primarily on patients' subjective complaints and not on objective clinical or laboratory findings, which, for the most part, are not yet available for the conditions of interest. Thus, as noted by others, this approach is heavily influenced by patients' perceptions and symptom appraisals rather than representing functional impairment or other more objective outcomes.³²

In summary, we investigated the degree of overlap for a variety of conditions believed to commonly occur among patients with CFS, FM, and TMD in a case-control study. We found that patients were more likely than control subjects to meet lifetime symptom and/or diagnostic criteria for many of these conditions including CFS, FM, IBS, multiple chemical sensitivities, and chronic tension-type headache, among others. Given the association of CFS, FM, and TMD with poor functional status^{13,26,33} and psychiatric illness,^{2,27,34,35} future research should evaluate physical impairments, potential mechanisms, and psychiatric comorbidities among patients with overlapping conditions. In addition, clinical trials might examine whether systematically identifying and targeting comorbid conditions for treatment produces superior outcomes compared with usual care or to a more general type of intervention (eg, education, stress management). The evaluation of such interventions seems particularly important in light of recent findings demonstrating that higher health care costs and utilization were independently associated with the number of self-reported comorbid conditions in patients with FM,³² and patients diagnosed as having both CFS and FM were significantly more likely to be unemployed and to use more health care services than those with only one disorder.³³

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