



Improving the diagnostic criteria and procedures for chronic fatigue syndrome

Caroline King^{a,*}, Leonard A. Jason^b

^a *Spinal Cord Injury Service (128), Hines VA Hospital, P.O. Box 5000, Hines, IL 60141-5128, USA*

^b *Department of Psychology, Northwestern Medical School, DePaul University,
2219 N. Kenmore Ave., Chicago, IL 60614, USA*

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Abstract

Since the publication of the case definition for chronic fatigue syndrome (CFS) in 1988 the diagnostic criteria have been revised twice in the U.S. None of the case definitions were derived empirically. As a result, there is concern regarding the sensitivity, specificity, and reliability of the criteria. The goal of the present study was to identify methods for improving the diagnostic criteria for CFS. Three groups of 15 participants each were recruited: participants with (1) CFS, (2) major depressive disorder (MDD), and (3) healthy controls. Using statistical procedures, three methods for improving the diagnostic criteria were explored: identification of new diagnostic symptoms, the use of severity ratings for symptomatology, and the identification of standardized measures that differentiate cases of CFS from other conditions. Results of the present study suggest that these three methods hold promise for improving the sensitivity, specificity, and reliability of the diagnostic criteria for CFS.

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One of the main goals of classifying any disease or illness is to group together patients who have an illness that may have many manifestations, but a common underlying pathophysiological pathway (Hartz et al., 1998). The benefit of classifying patients into diagnostic categories is that it facilitates communication among clinicians/researchers, selection of treatment methods, and prediction of response to treatment. Past experience has shown that even in cases where the underlying pathophysiological pathway has not been identified,

* Corresponding author.

E-mail addresses: cpking@rcn.com (C. King), ljason@depaul.edu (L.A. Jason).

research on the etiology and treatment of the illness has been facilitated by simply classifying these illnesses as syndromes of signs and symptoms (e.g., systemic lupus erythematosus or tuberculosis). This has been the case with chronic fatigue syndrome. Although the etiology of this illness remains unknown, researchers have been able to examine and better understand the nature of this illness primarily through the use of clinical classification approaches (i.e., classification criteria developed through clinical experience and observation).

In 1988, a team of experienced clinicians led by the Centers for Disease Control and Prevention developed the first set of clinically derived diagnostic criteria for chronic fatigue syndrome. These criteria, developed through the consensus of an expert committee, provided health care professionals with the first set of systematic criteria to follow when assessing patients presenting with unexplained chronic fatigue. Shortly following the publication of the Holmes et al. (1988) case definition, researchers and clinicians in the United States became dissatisfied with this set of diagnostic criteria (Jason et al., 1997). Since then, the case definition has been revised twice: once in 1992 by a group who attended the 1991 National Institute of Allergy and Infectious Disease/National Institute of Mental Health workshop on CFS, and a second time in 1994 by the NIH/CDC CFS study group (Fukuda et al., 1994). The criteria published by the NIH/CDC CFS study group (Fukuda et al., 1994) is the current U.S. case definition for CFS.

It is important to note that neither the original U.S. case definition nor the revised U.S. case definitions for CFS were derived empirically (Jason et al., 1997). Over the past 4–5 years researchers have become interested in attempting to validate the current U.S. case definition through empirical and statistical approaches. Overall, the results of these studies have suggested that there is moderate to strong empirical support for the current CFS case definition (Hartz et al., 1998; Jason and Taylor, 2002; Jason et al., 2002a,b; Komaroff et al., 1996; Nisenbaum et al., 1998). There is some concern, however, regarding the sensitivity (i.e., ability to identify those who have the disease), specificity (i.e., ability to correctly identify those who do not have the disease), and diagnostic reliability of the Fukuda et al. (1994) criteria.

Some CFS researchers are concerned that the specificity of the current U.S. case definition is poor (Jason et al., 1997). Even Fukuda, one of the primary authors of the U.S. case definition, has stated that the current CFS diagnostic criteria might not exclude people who have purely psychosocial stress, or many psychiatric reasons for their fatigue (Fukuda, personal communication, August 30, 1995). As a result, individuals with purely psychiatric disorders and psychological explanations for their fatigue might be included within the CFS rubric. Although it is possible for some individuals with CFS to have psychiatric problems before or after the onset of CFS, or even both, the inclusion of individuals with purely psychiatric disorders may seriously complicate the interpretation of epidemiological and treatment studies (Jason et al., 1997).

One approach to improving the specificity as well as the sensitivity of the diagnostic criteria for CFS is through the development of empirically derived symptom criteria. Researchers attempting to empirically validate the current U.S. case definition have already made some initial suggestions regarding specific symptoms that should be added or removed to improve the overall sensitivity and specificity of the criteria. In a study conducted by Komaroff et al. (1996), patients meeting the major criteria of both the original CFS case definition (Holmes et al., 1988) and the most recently revised CFS case definition (Fukuda

et al., 1994) were compared to healthy controls and two clinical populations with fatigue: patients with multiple sclerosis (MS), and patients with depression. Komaroff et al. (1996) examined the occurrence of the minor symptom criteria as well as the occurrence of several other medical symptoms not included in the case definition between the four study groups. Results of the study revealed that most of the minor criteria symptoms of the U.S. case definition were found to discriminate patients with CFS from patients with MS, depression, and healthy controls. However, the following three diagnostic symptoms were identified as being poor discriminators among the four study groups: muscle weakness, arthralgias, and sleep disturbances. Komaroff et al. (1996) therefore recommended that these items be omitted from future revisions of the CSF case definition. The authors also found that two additional symptoms currently not included in the case definition had good discriminatory power among the four study groups: anorexia and nausea. Komaroff et al. (1996) suggested adding these two symptoms to the case definition to improve the specificity and sensitivity of the diagnostic criteria.

In a separate study, Hartz et al. (1998) examined persons with CFS and compared them to persons with idiopathic fatigue and persons with no symptoms of fatigue. Similar to Komaroff et al. (1996), Hartz and colleagues found support for the symptoms included in the current case definition. However, Hartz et al. (1998) also found additional symptoms that separated participants with CFS from participants with idiopathic fatigue and controls: frequent fever and chills, muscle weakness, and sensitivity to alcohol. Based on their findings, the authors recommended including these additional symptoms in the current U.S. case definition.

Lastly, a study conducted by Jason et al. (2002b) found additional support for the current case definition. In comparison to controls, individuals with CFS reported significantly higher frequencies of all eight Fukuda et al. (1994) definitional symptoms. However the authors found several other symptoms that occurred with higher frequency and uniquely differentiated the CFS group from controls that are not included within the Fukuda et al. (1994) criteria. These symptoms included: shortness of breath, chest pain, dizziness after standing, skin sensations, general dizziness, dizzy moving the head, and alcohol intolerance.

A second approach to improving the sensitivity and specificity of the criteria is the use symptom severity ratings. At present, the symptom criteria for the case definition are scored as either being present or absent with no consideration given to the severity of the symptoms. Research suggests that this scoring system is problematic because many of the symptoms included in the diagnostic criteria for CFS are commonly experienced by people at one time or another (Denche et al., 1996). For example, symptoms of fatigue, sore throat, headache, muscle pain, and post-exertional malaise are frequently experienced by people who have a cold or the flu. Denche et al. (1996) demonstrated the potential for control participants to be misdiagnosed with CFS when using Fukuda et al. (1994) symptom criteria alone. In a sample of healthy adults, 15% met Fukuda et al. (1994) symptom criteria for CFS (i.e., complained of four or more of the eight specified symptoms) (Denche et al., 1996).

The symptoms included in the CFS case definition are also common to many other fatiguing medical illnesses and psychiatric conditions. For example, symptoms of fatigue, headache, unrefreshing sleep, muscle pain, and impaired memory and concentration frequently experienced by people with multiple sclerosis and major depression. Again, because of the degree of symptom overlap, it is very possible for a person with either MS or major

depression to fulfill the symptomatic criteria of the current CFS case definition when only symptom occurrence is measured. Although many of the symptoms of CFS are common to many conditions, it is possible that the severity at which these symptoms are experienced by individuals with CFS is not. Use of symptom severity ratings with cutoff scores may therefore help to differentiate CFS from other illnesses with similar symptoms.

There is preliminary evidence that the use of severity ratings may provide a way to improve the specificity of the current case definition. Jason et al. (2000) found that symptom severity ratings were useful for distinguishing individuals with CFS from individuals with a fatiguing psychiatric illness (i.e., melancholic depression). Jason et al. (2000) found when comparing the symptomatic criteria of participants with CFS to participants with melancholic depression, only one significant difference emerged between the groups. In other words, the occurrence of the Fukuda et al. (1994) symptomatic criteria was very similar between the two groups. However, when a symptom severity ratings were used, and a rating of 40 or higher was used as a scoring rule for determining whether the symptom fulfilled the diagnostic criteria, four significant differences emerged between the two groups. These results demonstrate the utility of severity ratings as a means for improving the specificity of the diagnostic criteria.

Lastly, the absence of objective assessment approaches for the diagnostic criteria has generated concern regarding the reliability of the U.S. case definition. Researchers have noted that the case definition for CFS has been “frequently modified in practice because some of the criteria are difficult to interpret or to comply with” (Fukuda et al., 1994; p. 954). Because no laboratory tests or objective indicators for CFS exist, case identification depends primarily on information obtained through clinical interviews. Although the clinical interview is often an integral component to any assessment process, if the interview does not follow a standardized format, the results of the interview can be quite variable across examiners and different diagnostic conclusions may be reached (Matarazzo, 1983). One approach to improving the diagnostic reliability of the current U.S. CFS case definition is the identification of standardized measures with scoring guidelines to be used in conjunction with the clinical interview. The addition of standardized measures with scoring guidelines would likely improve the reliability of diagnostic decisions by providing clinicians with objective standards to follow when assessing the various features of this syndrome.

In an effort to identify an objective method for discriminating CFS from major depression, Johnson et al. (1995) administered the Beck depression inventory (BDI) to people with CFS and people with major depression. Items from the BDI were categorized into one of four symptom categories (mood, self-reproach, somatic, and vegetative) and compared among the two groups. Significant differences were found in the qualitative nature of the symptoms endorsed on the BDI by people with CFS and people with major depression. The BDI scores of people with CFS were comprised mainly of items concerning physical complaints and somatic symptoms of fatigue. Symptoms of disturbed mood and self-reproach, two cardinal signs of depression, were not reported as frequently by the participants with CFS as by the participants with depression (Johnson et al., 1995). These findings demonstrate that while depressive symptoms are common in samples of people with CFS and depression, the types of items involved are qualitatively different. The results of this study suggest that incorporating a standardized measure, such as the BDI, into the diagnostic procedure for CFS may help clinicians distinguish cases of CFS from case of major depression.

The use of other standardized measures of functioning would likely improve the diagnostic accuracy and reliability of CFS. For example, the SF-36 Health Survey (Ware and Sherbourne, 1992) is a standardized questionnaire that has been widely used to assess functioning in patients who have a variety of medical conditions. For many conditions, distinct SF-36 profiles have been identified (e.g., cardiovascular disease, major depression). Buchwald et al. (1996) have demonstrated that the SF-36 may also be a useful and reliable instrument for assessing functional status in patients with CFS as well as distinguishing such patients from patients with other fatiguing conditions. Additional studies replicating the results of the Buchwald et al. (1996) study are needed to establish a unique SF-36 profile for CFS patients.

The present study was conducted to explore three methods for improving the diagnostic criteria and procedures for CFS. First, symptomatology was compared among patients with CFS, major depressive disorder (MDD), and healthy controls to explore which symptoms currently included in the case definition differentiate cases of CFS from MDD and controls, and to identify new symptoms (i.e., not currently included in the case definition) that differentiate CFS from these conditions. Second, the use of symptom severity ratings was examined as an additional means for distinguishing CFS from MDD and controls. Third, the use of two standardized measures, the BDI and SF-36 was evaluated to determine whether these instruments were useful for identifying cases of CFS and differentiating CFS from MDD and controls.

1. Method

1.1. Research participants

A total of 45 individuals (15 with CFS, 15 with major depression, and 15 healthy controls) were recruited from the Greater Chicago area for the present study. Fifteen participants with CFS were solicited to participate in the present study. Participants were drawn from two sources, a local CFS support group in Chicago and previous research studies conducted at DePaul University. Participants were required to have been diagnosed with CFS, using the Fukuda et al. (1994) diagnostic criteria, by a Board-certified physician and were required to have a current (active) case of CFS. All participants had been seen by their physician in the past year. Individuals who reported having uncontrolled/untreated medical illnesses (e.g., untreated anemia) were excluded. All participants were screened with the SCID-IV (to be described later) to ensure that they did not have any exclusionary psychiatric illnesses as stipulated by the Fukuda et al. (1994) case definition.

Fifteen participants with a diagnosis of major depression were solicited from a local chapter of the National Depressive and Manic Depressive support group in Chicago. Participants were required to have been diagnosed with major depression by a licensed psychologist or psychiatrist. All participants were screened with the SCID-IV to ensure that they met criteria for a current (active) case of major depression and did not have any other current psychiatric illnesses. Individuals who had other current psychiatric conditions in addition to major depression were excluded. Individuals who reported having uncontrolled/untreated medical illnesses (e.g., anemia, diabetes) were also excluded.

Finally, fifteen healthy control participants were solicited from the Greater Chicago area. Individuals who did not have any medical illnesses or who did not have any uncontrolled/untreated illnesses were allowed to participate. Individuals with uncontrolled/untreated medical illnesses (e.g., anemia, diabetes) were excluded. All participants were screened with the SCID-IV to ensure that they did not have any current psychiatric illnesses. Individuals with current psychiatric conditions were excluded.

1.2. Procedure

All 45 participants were initially screened by a trained interviewer to determine if they met the inclusion and exclusion criteria for the group condition they were being considered for (i.e., CFS, depression, healthy control). As part of this screening process, all participants were administered the SCID-IV to assess for psychiatric conditions.

Participants who met criteria for participation were asked to complete a battery of questionnaires that measured demographics, social, emotional, and physical functioning, activity level, depression, and a comprehensive list of physical, cognitive, and emotional symptoms.

1.3. Measures

1.3.1. Demographic variables

Basic demographic data was gathered, including age, ethnicity, marital status, gender, occupation, work status, and educational level.

1.3.2. Socioeconomic status (SES)

This was measured by using occupation and highest educational level to compute the revised Hollingshead scale (Wasser, *in press*) of socioeconomic status. The scores on the Hollingshead scale ranged from 5 to 54, with lower scores indicating lower socioeconomic status, and higher scores indicating higher socioeconomic status.

1.3.3. Beck depression inventory (BDI)

This is a self-rating scale which evaluates 21 symptoms related to depression on a scale of 0 (absent) to 3 (most severe). Internal consistency for the BDI ranges from 0.73 to 0.92 with a mean of 0.86. (Beck et al., 1988). The BDI demonstrates high internal consistency, with alpha coefficients of 0.86 and 0.81 for psychiatric and non-psychiatric populations, respectively (Beck et al., 1988). The BDI has a split-half reliability coefficient of 0.93 (Beck et al., 1988).

Research has shown that the individual questions on the BDI can be divided into four categories: mood, self-reproach, somatic, and vegetative characteristics of depression (Huber et al., 1990, 1993). The mood category included six items: #1, #2, #4, #10, #11, and #12. The self-reproach category included seven items: #3, #5, #6, #7, #8, #9, and #13. The somatic category consisted of the following three items: #14, #15, and #20; and the vegetative category consisted of the following four items: #16, #18, #19, and #21.

1.3.4. Medical outcomes study SF-36 (SF-36)

The SF-36 is 36-item instrument that is comprised of multi-item scales that assess physical functioning, role limitations, social functioning, bodily pain, general mental health, vitality,

and general health perceptions. Higher scores indicate better health, lower disability, or less impact of health on functioning. Reliability and validity studies have demonstrated that the 36-item version of the SF-36 has high reliability and validity in a wide variety of patient populations (Stewart et al., 1989). The SF-36 has also shown adequate psychometric properties as a measure of functional status in a population of CFS participants and is capable of distinguishing CFS from other fatiguing illnesses (Buchwald et al., 1996).

Principal component analytic studies of the MOS SF-36 have revealed that the eight scales of MOS SF-36 comprise two distinct factors, a physical component and a mental component. These two components have been found to be valid and reliable summary measures of the MOS SF-36 and account for 80–85% of the reliable variance in the eight SF-36 scales.

The physical component scale (PCS) is a summary measure of the following SF-36 scales: physical functioning, role-physical, bodily pain, and general health. The physical component correlates most highly with the physical functioning, role-physical, and bodily pain scales, which contribute most to scoring of the PCS measure of that component. The mental health component scale (MCS) is a summary measure of the following SF-36 scales: vitality, social functioning, role-emotional, and mental health. Three scales (social functioning, role-emotional, and mental health) correlate most highly with the mental component and contribute most to scoring of the MCS measure of that component. Three of the SF-36 scales have notable correlations with both components. The vitality scale correlates highly with both components. The general health scale correlates with both components, but has a stronger correlation with the physical component. The social functioning scale also correlates with both components, however it is more highly correlated with the mental component.

1.3.5. Physical, cognitive, and emotional symptom checklist

Participants were asked to indicate whether or not they had a number of somatic, cognitive, and emotional symptoms commonly experienced by people with CFS. Symptoms on this list were taken from a variety of sources, including a measure developed by Komaroff et al. (1996), the current U.S. CFS case definition (Fukuda et al., 1994), and the results of studies by Hartz et al. (1998) and Komaroff et al. (1996) that suggested the inclusion of new symptoms in the case definition.

For each symptom, participants were asked to indicate if the symptom had been present for 6 months or longer, if the symptom began before the onset of their fatigue or health problems, and how often the symptom is experienced. Participants were also asked to rate the intensity of each symptom they endorsed on a scale of 0–100, where 0 = no problem and 100 = the worst problem possible.

Included in this list were fatigue and the eight diagnostic symptoms specified by Fukuda et al. (1994). Again, participants were asked to report if each symptom had been present for 6 months or longer, began before the onset of their fatigue or health problems, how often it is experienced, and rate the intensity of each symptom on the same scale of 0–100.

1.3.6. The structured clinical interview for the DSM-IV (SCID)

The SCID is a valid and reliable semi-structured interview guide that closely resembles a traditional psychiatric interview (First et al., 1996). The SCID is designed to identify current,

past, and lifetime (chronic or reoccurring, current, and past) diagnoses for a majority of DSM-IV, Axis I psychiatric disorders. The SCID is commonly administered during a single session lasting from 45 min to 1 h. Diagnostic decisions generated by the SCID are based on all possible sources of historical, symptomatic, and behavioral information. The SCID begins with a semi-structured interview portion designed to yield a tentative diagnosis. The tentative diagnosis is then systematically assessed during the structured portion of the interview through the use of embedded questions that conform to the exact, Axis I criteria set forth by the DSM-IV.

2. Results

Demographic characteristics of the three groups of participants are shown in Table 1. Sociodemographic data were compared across the three groups using Pearson's Chi-square for dichotomous and multinomial data and analysis of variance for age and SES. Exact significance levels were used for the Chi-square analyses because of the occurrence of low cell frequencies in many of the analyses. Exact significance is the significance level based on the exact distribution of a test statistic. Exact significance levels are preferable when the data set is small, sparse, contains many ties, or is poorly distributed (Norusis, 2000). There were no significant differences between groups with respect to gender, race, age, SES, education, marital status, occupation, work status, and additional roles.

In regard to psychiatric co-morbidity, in the CFS group 3 (20%) participants met DSM-IV diagnostic criteria for dysthymia. No other current diagnoses were detected in the CFS group. In the MDD group all 15 (100%) participants met DSM-IV diagnostic criteria for MDD. None of the participants in the MDD group met criteria for MDD with catatonic, melancholic, psychotic, or atypical features. Participants in the MDD group did not meet criteria for any other Axis I disorders. None of the participants in the control group met criteria for any Axis I disorder.

2.1. Comparison of symptomatology between groups and use of severity ratings

Two series of analyses were conducted to identify symptoms with the potential to discriminate CFS from MDD and healthy controls. In the first series of analyses, frequencies of the 66 symptoms from the physical, cognitive, and emotional symptom checklist were compared among the three study groups using pairwise Fisher's exact test. These comparisons are also shown in Table 2. Only differences at the $P < 0.01$ level were reported to control for the high number of comparisons. The CFS group differed most from the control group in that 37 of the 66 symptoms were found to occur significantly more frequently in the CFS group. In comparing the CFS group to the MDD group, 16 of the 66 symptoms were occurred significantly more frequently in the CFS group. Lastly, in comparing the MDD group to the control group, five symptoms occurred significantly more frequently in the MDD group.

When looking specifically at the occurrence of fatigue and the eight symptoms of the current U.S. case definition, only one symptom, post-exertional malaise, was found to occur significantly more frequently in the CFS group in comparison to the MDD group. When comparing the CFS and control group, fatigue and all eight of the symptoms were found

Table 1
Demographic variables across groups

	CFS (<i>n</i> = 15)	Depression (<i>n</i> = 15)	Control (<i>n</i> = 15)
Gender			
Women	13	13	14
Men	2	2	1
Race			
White	11	12	12
African–American	3	2	3
Latino	1	1	0
Age	44.5	43	42.7
SES	41	37.9	41.1
Education			
H.S. or GED	2	1	0
Partial college	2	1	2
Vocational/trade	0	3	2
College degree	7	7	5
Graduate degree	4	3	6
Marital status			
Married	7	8	8
Divorced	7	3	2
Never married	1	4	5
Occupation			
Semi-skilled/workers	1	2	1
Semi-professional/technician	3	4	5
Minor professional/lessor professional	9	8	9
Major professional/higher executive	2	1	2
Work status			
Retired	0	0	1
Unemployed	1	1	1
Disabled	8	3	0
Part-time	3	2	2
Full-time	1	7	9
None of above	2	2	2
Additional roles			
Student	3	2	2
Homemaker	6	6	1
Neither	6	7	12

to occur significantly more often in the CFS group. Comparisons between the MDD and control group revealed that fatigue, unrefreshing sleep, impaired memory and concentration, headaches, and muscle pain all occurred significantly more in the MDD group.

None of the 66 symptoms from the physical, cognitive, and emotional symptom checklist (shown in Table 2) were found to separate all three groups when looking at symptom occurrence. However, three symptoms in the fatigue/weakness group (post-exertional malaise, muscle weakness, feeling unsteady on feet), five symptoms in the neuropsychological category (need to focus on one thing at a time, confusion/disorientation, difficulty finding

Table 2
Percent of participants reporting symptom as present for 6 months or longer and pairwise Fisher's exact test comparisons across the three groups

	CFS (<i>n</i> = 15) (%)	MDD (<i>n</i> = 15) (%)	Control (<i>n</i> = 15) (%)	Significance
Fatigue/weakness				
Fatigue	100 ^b	93 ^c	13 ^{b,c}	**
Post-exertional malaise	100 ^{a,b}	20 ^a	6 ^b	**
Muscle weakness	93 ^{a,b}	33 ^a	6 ^b	**
Need to nap each day	93 ^b	60	13 ^b	**
Feeling unsteady on feet	60 ^{a,b}	6 ^a	6 ^b	**
Disturbed sleep				
Unrefreshing sleep	100 ^b	93 ^c	20 ^{b,c}	**
Difficulty staying asleep	73 ^b	53	13 ^b	**
Difficulty falling asleep	60 ^b	47	6 ^b	**
Waking up early in the morning	47	6	27	
Neuropsychiatric				
Impaired memory and concentration	93 ^b	87 ^c	20 ^{b,c}	**
Headaches	93 ^b	67	20 ^b	**
Need to focus on one thing at a time	87 ^{a,b}	27 ^a	20 ^b	**
Confusion/disorientation	80 ^{a,b}	20 ^a	6 ^b	**
Difficulty finding the right word	80 ^{a,b}	6 ^a	13 ^b	**
Frequently lose train of thought	80 ^{a,b}	13 ^a	13 ^b	**
Difficulty retaining information	80 ^b	60 ^c	0 ^{b,c}	**
Difficulty recalling information	80 ^b	40	6 ^b	**
Slowness of thought	73 ^{a,b}	13 ^a	6 ^b	**
Absent-mindedness	73 ^b	60	6 ^b	**
Forgetting what you are saying	73 ^b	33	6 ^b	**
Difficulty following things	60 ^b	13	6 ^b	**
Difficulty comprehending information	60 ^b	20	6 ^b	**
Trouble expressing thoughts	60 ^b	13	6 ^b	**
Difficulty reasoning	53	20	6	
Slow to react	47	20	6	
New trouble with math	47	6	6	
Frequently getting words in the wrong order	40	6	6	
Concern with driving	33	13	6	
Infectious				
Hot/cold spells	67 ^{a,b}	6 ^a	6 ^b	**
Feeling like have a temperature	67 ^{a,b}	6 ^a	0 ^b	**
Sore throat	60 ^b	20	6 ^b	**
Chilled/shivery	60 ^{a,b}	6 ^a	6 ^b	**
Temperature lower than normal	53 ^a	13 ^a	13	**
Tender/sore lymph nodes	47 ^b	13	0 ^b	**
Allergies	47	13	27	
Fever and chills	27	0	0	
Chemical sensitivity	33	13	6	
Rash	27	13	6	
Fever	13	0	0	
Rheumatological				
Muscle pain	93 ^b	73 ^c	13 ^{b,c}	**

Table 2 (Continued)

	CFS (<i>n</i> = 15) (%)	MDD (<i>n</i> = 15) (%)	Control (<i>n</i> = 15) (%)	Significance
Pain in multiple joints without swelling or redness	73 ^b	33	13 ^b	**
Tense muscles	67 ^b	40	13 ^b	**
Night sweats	53 ^a	0 ^a	6	**
Cardiopulmonary				
Chest pain	60 ^{a,b}	6 ^a	6 ^b	**
Racing heart	47	6	6	
Shortness of breath	47 ^a	0 ^a	6	**
Sweating hands	6	0	0	
Gastrointestinal				
Upset stomach	33 ^{a,b}	20 ^a	6 ^b	**
Weight change	33	40	13	
Poor appetite	33	20	0	
Abdominal pain	27	6	0	
Nausea	20	20	6	
Neurological				
Tingling feeling	53	27	6	
Dizziness	47	6	6	
Blurred vision	47	6	6	
Abnormal sensitivity to light	47 ^b	13	0 ^b	**
Sensitivity to alcohol	33	27	0	
Eye pain	33	13	0	
Poor hand to eye coordination	27	13	6	
Ringing in ears	27	13	6	
Blind spots	27	0	0	
Paralysis	6	0	0	
Psychological				
Depression	80 ^b	87 ^c	6 ^{b,c}	**
Irritability	87 ^b	53	20 ^b	**
Anxiety/tension	67 ^b	40	6 ^b	**
Mood swings	60 ^b	40	6 ^b	**

If small letter occurs for two groups, they are significantly different.

** $P < 0.01$.

the right word, frequently losing train of thought, slowness of thought), three symptoms in the infectious category (hot and cold spells, feeling like having a temperature, feeling chilled/shivery), one in the cardiopulmonary (chest pain), and one in the gastrointestinal category (upset stomach), were found to occur significantly more in the CFS group than either the MDD or control group.

2.2. Severity ratings

A second series of analyses was conducted to further explore symptoms that differentiate the three study groups. For these analyses, symptom severity ratings were compared across the three groups for 66 symptoms using one-way ANOVAs. Tukey Honest significant

difference (HSD) post hoc analyses were performed on all significant ANOVAs at the $P < 0.01$ level. The results of these analyses are shown in Table 3. Once again, the CFS group differed most from the control group in that 31 of the 66 symptoms were reported as being significantly more severe in the CFS group. In comparison to the MDD group, 17 symptoms were reported as being significantly more severe in the CFS group. Only three symptoms were reported as being significantly more severe in the MDD group in comparison to the control group.

In examining the symptom severity ratings for fatigue and the eight symptoms of the U.S. case definition, six symptoms were reported as being significantly more severe in the CFS group than the MDD group: fatigue, post-exertional malaise, unrefreshing sleep, sore throat, tender/sore lymph nodes, muscle pain, and pain in multiple joints without swelling or redness. In comparing the CFS and control group, fatigue and all eight symptoms were found to be significantly more severe in the CFS group. Comparisons between the MDD and control group revealed that two symptoms were reported as significantly more severe in the MDD group: unrefreshing sleep and impaired memory and concentration.

Only one symptom, unrefreshing sleep, was found to be significantly different across all three groups. Comparing the CFS group against the MDD group and control group revealed significant differences for the following items: four symptoms in the fatigue/weakness group (fatigue, post-exertional malaise, muscle weakness, need to nap each day), three symptoms in the neuropsychological category (frequently losing train of thought, difficulty finding the right word, confusion/disorientation), four symptoms in the infectious category (sore throat, tender lymph nodes, hot and cold spells, feeling chilled/shivery), three in the rheumatological category (muscle pain, pain in multiple joints without swelling, night sweats), one in the cardiopulmonary (shortness of breath), and one symptom in the neurological category (blurred vision).

2.3. Comparison of standardized measures between groups

Overall composite and subscale scores on the BDI and SF-36 were compared between groups to test these instruments ability to distinguish cases of CFS, MDD, and healthy controls.

2.4. BDI analyses

ANOVA was used to examine differences in the total BDI score across the three groups. A significant main effect for group membership on total BDI score was found ($F(2, 42) = 17.39$, $P = 0.01$). The MDD group had the highest mean total BDI score ($M = 17.67$), indicative of moderate to severe depression, while the control group had the lowest score ($M = 4.20$) and were not clinically depressed. The CFS group had an intermediate score ($M = 14.53$) indicating mild depression according to the BDI classification system. Post hoc analysis using Tukey HSD test at the 0.05 level revealed that the control group's total BDI score was significantly lower from the CFS and MDD group ($P < 0.00$). Significant differences were not found between the total BDI scores for the CFS and MDD groups.

A second analysis on the BDI was conducted to examine possible differences in the type of depressive symptoms (mood, self-reproach, somatic, and vegetative) endorsed

Table 3
ANOVA: one-way analysis of variance for symptom severity ratings across the three groups, means and Tukey HSD post hoc comparisons

	CFS (<i>n</i> = 15)	MDD (<i>n</i> = 15)	Control (<i>n</i> = 15)	Significance
Fatigue/weakness				
Fatigue	79.80 ^{a,b}	46.67 ^a	11.00 ^b	**
Post-exertional malaise	73.33 ^{a,b}	8.67 ^a	4.67 ^b	**
Need to nap each day	58.33 ^{a,b}	26.67 ^a	9.67 ^b	**
Muscle weakness	55.33 ^{a,b}	13.33 ^a	9.00 ^b	**
Feeling unsteady on feet	29.00 ^b	7.33	2.00 ^b	**
Disturbed sleep				
Unrefreshing sleep	75.60 ^{a,b}	44.33 ^{a,c}	5.33 ^{b,c}	**
Difficulty staying asleep	49.00 ^b	28.00	2.67 ^b	**
Difficulty falling asleep	33.67	31.67	3.33	
Waking up early in the morning	31.00	10.67	5.33	
Neuropsychiatric				
Impaired memory and concentration	61.67 ^b	41.33 ^c	7.00 ^{b,c}	**
Headaches	52.33 ^b	30.67	19.33 ^b	**
Absent-mindedness	45.67 ^b	26.67	4.67 ^b	**
Slowness of thought	43.67	8.33	4.00	
Forgetting what you are saying	40.67 ^b	18.00	2.33 ^b	**
Difficulty retaining information	39.00 ^b	31.67 ^c	2.67 ^{b,c}	**
Frequently lose train of thought	38.67 ^{a,b}	7.00 ^a	2.14 ^b	**
Need to focus on one thing at a time	38.33 ^b	20.33	3.30 ^b	**
Difficulty finding the right word	37.33 ^{a,b}	5.33 ^a	4.67 ^b	**
Difficulty recalling information	33.67 ^b	26.67	2.67 ^b	**
Confusion/disorientation	32.67 ^{a,b}	6.33 ^a	1.33 ^b	**
Difficulty reasoning	27.67 ^b	8.67	1.33 ^b	**
Trouble expressing thoughts	25.33	6.00	1.33	
Difficulty comprehending information	22.67	14.33	1.33	
Slow to react	22.33	12.00	1.33	
Difficulty following things	21.67	10.67	1.33	
New trouble with math	20.87	4.67	1.00	
Frequently getting words in the wrong order	19.33	2.33	1.33	
Concern with driving	18.67	26.0	7.67	
Infectious				
Sore throat	36.67 ^{a,b}	8.67 ^a	2.33 ^b	**
Chilled/shivery	29.67 ^{a,b}	7.33 ^a	2.67 ^b	**
Tender/sore lymph nodes	27.67 ^{a,b}	3.33 ^a	0.00 ^b	**
Hot/cold spells	26.67 ^{a,b}	7.30 ^a	2.67 ^b	**
Allergies	25.33	12.00	9.33	
Feeling like have a temperature	23.33 ^b	5.33	0.67 ^b	**
Temperature lower than normal	17.33	8.00	7.33	
Chemical sensitivity	15.00	12.00	5.33	
Rash	8.00	10.67	2.67	
Fever and chills	7.33	0.00	0.67	
Fever	3.67	0.67	0.00	
Rheumatological				
Muscle pain	60.67 ^{a,b}	28.67 ^a	10.67 ^b	**
Pain in multiple joints without swelling or redness	39.00 ^{a,b}	11.00 ^a	6.67 ^b	**

Table 3 (Continued)

	CFS (<i>n</i> = 15)	MDD (<i>n</i> = 15)	Control (<i>n</i> = 15)	Significance
Tense muscles	35.00	7.33	2.67	
Night sweats	21.07 ^{a,b}	2.86 ^a	2.00 ^b	**
Cardiopulmonary				
Shortness of breath	30.00 ^{a,b}	3.57 ^a	3.33 ^b	**
Chest pain	27.69	11.79	2.00	
Racing heart	17.67	7.33	3.00	
Sweating hands	5.00	0.67	0.00	
Gastrointestinal				
Upset stomach	17.00	11.00	6.67	
Weight change	16.33	17.33	7.33	
Poor appetite	12.67	5.33	0.00	
Abdominal pain	12.67	6.67	0.67	
Nausea	11.67	8.00	4.67	
Neurological				
Blurred vision	32.33 ^{a,b}	4.00 ^a	1.33 ^b	**
Abnormal sensitivity to light	7.33	10.00	0.67	
Tingling feeling	23.33	11.07	1.33	
Dizziness	22.00	7.33	1.33	
Sensitivity to alcohol	20.33	18.33	1.33	
Eye pain	16.07	0.67	0.00	
Blind spots	16.07	0.67	0.00	
Poor hand to eye coordination	14.33	3.67	1.33	
Ringling in ears	12.00	9.00	8.00	
Paralysis	0.00	0.00	0.00	
Psychological				
Irritability	39.67 ^b	31.33	8.00 ^b	**
Mood swings	36.00 ^b	17.33	3.33 ^b	**
Depression	34.67 ^b	53.67 ^c	2.67 ^{b,c}	**
Anxiety/tension	28.67	26.00	7.67	

If small letter occurs for two groups, they are significantly different.

** $P < 0.01$.

by participants in the CFS, MDD, and control groups. Specifically, multivariate analysis of variance (MANOVA) was used to examine whether of group membership influenced participants' scores on the four symptom categories (mood, self-reproach, somatic, and vegetative). Group membership was found to have a significant effect on all outcome variables, as measured by Wilks' Lambda ($F(2, 42) = 6.11, P = 0.01$). Significant differences were found between the three groups in reporting mood, self-reproach, somatic, and vegetative symptoms of depression. Tukey HSD post hoc analysis at the 0.05 level was used to examine group differences on the four symptom categories. The CFS group reported significantly less severe symptoms of self-reproach ($M = 3.33$) in comparison to the MDD group ($M = 6.33$), yet comparable levels of mood (CFS group $M = 3.67$, MDD group $M = 4.73$), somatic (CFS group $M = 4.33$, MDD group $M = 3.93$), and vegetative symptomatology (CFS group $M = 3.20$, MDD group $M = 2.67$). In comparison to the control

group, the CFS group exhibited significantly higher levels of symptomatology for all four symptom categories. The MDD group in comparison to the control group had significantly higher levels of self-reproach (control group $M = 0.53$), mood (control group $M = 0.93$), and somatic symptomatology (control group $M = 1.47$), but did not differ with respect to vegetative symptoms (control group $M = 1.27$).

2.5. SF-36 analyses

The effect of group membership on level of functioning was examined using MANOVA with the eight subscales of the SF-36 as outcome variables. In examining the main effect of the independent variable, group membership was found to have a significant effect on the outcome variables, as measured using Wilks' Lambda ($F(2, 42) = 7.45, P = 0.01$). Between-subject tests found that group membership predicted all eight outcome variables. Tukey HSD post hoc tests at the 0.05 level were used to examine the differences between the three groups (CFS, depressed, and controls) on all eight dependent variables. Using Tukey HSD to compare differences between the three groups for the physical functioning scale, significant differences were found between the CFS group and the two other groups. CFS participants were found to have significantly lower scores on the physical functioning scale ($M = 44$) in comparison to the MDD group ($M = 70.33, P = 0.01$) and the control group ($M = 88.0, P = 0.01$). Significant differences were not found between the MDD and control group on this scale.

When using the Tukey HSD post hoc test to examine differences between the three groups on the physical role functioning scale, significant differences were found between all three groups. Participants with CFS had the lowest score on this scale ($M = 13.33$), followed by participants with MDD who had an intermediate score ($M = 43.33, P = 0.039$), with control participants having the highest score on this scale ($M = 90.0, P = 0.01$).

Post hoc analysis of the general health scale revealed significant differences between all three groups. The CFS group had the lowest score on this scale ($M = 31.60$), followed by MDD participants who had an intermediate score ($M = 49.93$), with the control group having the highest score on this scale ($M = 66.67$).

Similarly, post hoc analysis of the vitality scale revealed significant differences between all three groups. Specifically, the CFS group ($M = 14.0$) scored significantly lower on the vitality scale than the MDD group ($M = 44.0, P = 0.01$). In turn, the MDD group scored significantly lower on the vitality scale than the control group ($M = 66.67, P = 0.01$).

Tukey HSD post hoc analysis of the social functioning scale also revealed significant differences between all three groups. The CFS group ($M = 35.0$) scored significantly lower on the social functioning scale than the MDD group ($M = 60.83, P = 0.01$). In turn, the MDD group scored significantly lower on the social functioning scale than the control group ($M = 90.83, P = 0.01$).

Post hoc analysis of the emotional role functioning scale revealed significant differences between the control group and the other two groups. Control participants were found to have significantly higher scores on this scale ($M = 91.11$) in comparison to CFS participants ($M = 48.89, P = 0.01$) and MDD participants ($M = 37.78, P = 0.01$). The CFS and MDD group did not differ significantly from one another on this scale.

Significant differences were also found between the control group and the other two groups on the bodily pain scale. Using the Tukey HSD test, control participants were found to have significantly higher scores on this scale ($M = 76.27$) in comparison to CFS participants ($M = 38.53$, $P = 0.01$) and MDD participants ($M = 55.60$, $P = 0.041$). The CFS and MDD group did not differ significantly from one another on this scale.

Using the Tukey HSD test, significant differences were found between the control group and the other two groups on the mental health scale. The control group scored significantly higher ($M = 79.73$) on the mental health scale than both the CFS group ($M = 39.27$, $P = 0.04$) and the MDD group ($M = 39.13$, $P = 0.17$). Significant differences were not found between the CFS and the MDD group on the mental health scale.

A second MANOVA was run on to evaluate the influence of group membership the two summary scale scores of the SF-36: the physical component scale and the mental component scale. The results of this analysis revealed that group membership did have a significant main effect on the outcome variables, as measured using Wilks' Lambda statistic ($F(2, 42) = 13.69$, $P = 0.01$) Between-subject tests found that group membership predicted both the physical component and mental component scale scores.

Tukey HSD post hoc analyses were conducted to compare differences between the three groups on the physical component and mental component scales. Examination of group differences on the physical component scale revealed that the CFS group ($M = 28.52$) scored significantly lower on this scale in comparison to the MDD group ($M = 42.32$, $P = 0.01$) and the control group ($M = 51.21$, $P = 0.01$). The MDD group and control group did not differ significantly from one another.

Tukey HSD post hoc analysis of group differences on the standardized mental component scale revealed that the control group scored significantly higher on this scale (53.37) than the CFS group ($M = 39.27$) and the MDD group ($M = 39.13$). Significant differences were not found between the CFS and MDD group.

3. Discussion

The overarching goal of the present study was to identify methods for improving the diagnostic reliability of CFS. Three approaches for improving the diagnostic reliability of CFS were explored. First, the identification of new symptoms that differentiate CFS from other conditions (i.e., MDD, healthy controls) was explored. Interestingly, results of the analyses examining differences between the groups for the symptom occurrence and severity data did not provide support for previous research in this area by Komaroff et al. (1996). Komaroff et al. (1996) suggested that symptoms of muscle weakness, arthralgias, and sleep disturbances be eliminated from the diagnostic criteria. In the present study, reports of muscle weakness, arthralgias, and sleep disturbances were significantly different amongst the three study groups.

Muscle weakness was reported by 93% of the CFS group and was found to occur significantly more in the CFS than either the MDD or controls groups. Muscle weakness was also significantly more severe in the CFS group in comparison to the MDD or control groups. Muscle weakness was therefore found to be a good discriminator among the three groups. Pain in multiple joints without swelling or redness (arthralgias) was reported by 73% of the

CFS group and was found to occur significantly more in the CFS group than the control group. Severity ratings for pain in multiple joints without swelling or redness were also significantly higher in the CFS group as compared to the MDD and controls groups. Thus, when looking at severity data, this symptom also discriminated among the three groups. Lastly, unrefreshing sleep was reported by 100% of the CFS group and difficulty staying asleep was reported by 73% of the CFS group. Problems with unrefreshing sleep occurred significantly more in the CFS group than the control group and were rated as being significantly more severe in the CFS group in comparison to the MDD and controls groups. Again, when using severity data, unrefreshing sleep discriminated among the three groups. Overall, these findings suggest that muscle weakness, pain in multiple joints without swelling or redness, and unrefreshing sleep may be key symptoms for distinguishing CFS from other conditions, especially when symptom severity is taken into consideration.

Komaroff et al. (1996) also suggested the addition of nausea as one of the diagnostic symptoms. Results of the present study do not support the inclusion of nausea as this symptom was reported by only 20% of the CFS group and differences between the three groups were not found in terms of symptom occurrence and severity. Hartz et al. (1998) also made recommendations regarding the inclusion of fever and chills, and sensitivity to alcohol. Neither symptoms of fever and chills nor sensitivity to alcohol were found to discriminate between the CFS, MDD, and control groups in the present study. These results do not support the inclusion of these latter two symptoms in the case definition.

The second approach taken in the present study to improve the specificity and reliability of the diagnostic criteria for CFS was the use of symptom severity ratings. In the present study symptom occurrence and symptom severity were examined to explore differences in the ability of occurrence data and severity ratings to discriminate among the three groups, and to explore whether there are symptoms which differentiate the three groups that are not currently included in the diagnostic criteria for CFS. Symptom occurrence was examined first for fatigue and the eight symptoms of the current U.S. case definition.

The analyses examining differences in symptom occurrence of fatigue and the eight symptoms of the current U.S. case definition amongst individuals with CFS, MDD, and healthy controls revealed several interesting findings. First, both the CFS group and the MDD group reported significantly more symptoms than the control group. Fatigue and all eight of the symptoms were found to occur significantly more often in the CFS group than control group and fatigue and four other symptoms occurred significantly more in the MDD group than control group. Second, only one symptom, post-exertional malaise, was found to occur significantly more frequently in the CFS group in comparison to the MDD group. Thus, in comparison to the control group and with one another, the CFS and MDD groups were similar. Third, when looking at symptom occurrence alone, some individuals in the MDD group met the inclusionary criteria for the current U.S. case definition for CFS (i.e., the presence of fatigue plus at least four of the eight symptoms diagnostic symptoms). Taken together, these findings strongly suggest that when using symptom occurrence alone, there is a strong potential for individuals with MDD to be misclassified as having CFS.

The analyses examining differences in symptom severity ratings for fatigue and the eight symptoms of the U.S. case definition amongst individuals with CFS, MDD, and healthy controls demonstrated an improved ability to distinguish the CFS group from the MDD group than when symptom occurrence was used. Six symptoms were reported as being

significantly more severe in the CFS group than the MDD group. These results are quite different from the occurrence data in which only one symptom distinguished the CFS group from the MDD group. Comparisons between the MDD and control group revealed that only two symptoms were reported as significantly more severe in the MDD group as opposed to four symptoms when the occurrence data was used. This finding is important and represents an improvement over the use of the occurrence data because the MDD group no longer meets the inclusionary criteria for CFS. These results suggest that the use of symptom severity ratings may improve the diagnostic specificity of the current U.S. case definition for CFS.

In an effort to identify new symptoms that might help distinguish CFS from other conditions, group differences were examined for symptom occurrence and symptom severity using the remaining 57 symptoms from the physical, cognitive, and emotional checklist. When looking at symptom occurrence, the following 12 symptoms were found to occur more frequently in the CFS group than either the MDD or control group: muscle weakness, feeling unsteady on feet, need to focus on one thing at a time, confusion/disorientation, difficulty finding the right word, frequently losing train of thought, slowness of thought, hot and cold spells, feeling like having a temperature, feeling chilled/shivery, chest pain, and upset stomach. However, when looking at symptom severity, only 10 symptoms were found to occur more frequently in the CFS group than either the MDD or control group: muscle weakness, need to nap each day, frequently losing train of thought, difficulty finding the right word, confusion/disorientation, hot and cold spells, feeling chilled/shivery, night sweats, shortness of breath, and blurred vision. Because severity ratings were demonstrated in the previous set of analyses to be superior discriminators, it is suggested that emphasis be given to the results of the analyses examining severity ratings for the additional 57 symptoms rather than the analyses looking at occurrence data. Future research is needed to test whether these symptoms would indeed improve the specificity and sensitivity of the current U.S. diagnostic criteria for CFS.

The third approach taken in the present study to improve the diagnostic reliability of CFS was the identification of standardized measures to assist clinicians in the identification of cases of CFS. Two standardized measures were evaluated in the present study, the BDI and SF-36. Components of each of these instruments were found to discriminate CFS, MDD, and healthy controls. Items measuring self-reproach on the BDI were found to distinguish CFS from MDD and controls. Applied use of this information could help prevent cases of CFS being diagnosed as primary depression and vice versa. With respect to the SF-36, five of the eight scales were found to distinguish CFS from MDD and controls. Clinical use of these SF-36 scales could help clinicians evaluate the diagnostic criteria for CFS, which require “substantial reductions” in functioning, as well as aid them in distinguishing cases of CFS from other conditions on the basis of levels of functioning. The above findings support previous research by Johnson et al. (1995) examining the BDI and research by Buchwald et al. (1996) examining the SF-36. These results strongly suggest the inclusion of standardized measures in the diagnostic assessment process for CFS.

A limitation of the present study involves the small sample size. Small sample size typically leads to problems with low statistical power, failure to obtain normal distributions, and failure to obtain a sample that is representative of the larger population. These problems may threaten the accuracy of statistical findings and limit the external validity of results.

Even when sample size is not large, mild to moderate violations of the assumptions of normality are not strong reasons for choosing a nonparametric test over a parametric test (McCall, 1996). In the present study, because the violations of normality were only mild to moderate in nature, parametric tests were used to analyze the data (i.e., ANOVA).

A second concern regarding the results of the present study involves the problem of experiment-wise type I error. Experiment-wise type I error concerns the overall level of type I error for an experiment. According to the Bonferroni inequality, the overall alpha level for a study will be less than or equal to the sum of alpha levels associated with each individual test (Grimm and Yarnold, 1998). In the present study an alpha level of 0.01 was used to try and reduce type I error.

The current case definition for CFS was developed by consensus, that is, based on the opinions and anecdotal experience of a group of “experts” assembled by the CDC in 1994 (Komaroff et al., 1996). Since this time a number of studies have found varying degrees of empirical support for the case definition (Hartz et al., 1998; Jason and Taylor, 2002; Jason et al., 2002a,b; Komaroff et al., 1996). However, many clinicians and researchers are not completely satisfied with the current case definition and have questioned the specificity and sensitivity of the current criteria. Future research should therefore focus on the development of an empirical case definition for CFS.

The development of an empirical case definition for CFS would entail a large scale study with many sites across the country. Important methodological considerations for such a study would include: (1) the use of a randomly collected community-based sample, (2) use of at least two physicians to examine each participant and confirm his or her diagnosis to ensure the diagnostic accuracy and validity of the study sample, and (3) use of multiple assessment measures (e.g., physical examination, clinical interview, and standardized self-report measures). Statistical methods would likely include the use of factor analysis to identify the most salient predictors of CFS, followed by discriminant function analyses to examine the ability of the predictors to discriminate and classify cases of CFS within the context of other medical conditions.

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