ORIGINAL INVESTIGATION

Disability and Chronic Fatigue Syndrome

A Focus on Function

Susan D. Ross, MD, FRCPC; Rhonda P. Estok, RN, BSN, CNOR; Diana Frame, MEM; Linda R. Stone, RN, MS, CPNP; Veronica Ludensky, BA; Cindy B. Levine, MD

Background: Evidence was sought in the published literature on how best to measure, monitor, and treat disability in patients with chronic fatigue syndrome (CFS).

Methods: A systematic review was performed of English-language literature published between January 1, 1988, and November 15, 2001. Interventional and observational studies of adults with CFS were eligible if they reported measures of disability and employment. A qualitative synthesis of results relating impairment measures to employment was performed.

Results: Of 3840 studies identified, 37 reported employment status and some measure of mental or physical impairment associated with disability. Most patients with CFS in these studies were unemployed. In 22 studies, the employment status of control subjects was also available. Only depression seemed to be associated with unemployment in patients with CFS. No other measurable impairment seemed to be consistently associated with disability or work outcomes. Only cognitive behavior therapy, rehabilitation, and exercise therapy interventions were associated with restoring the ability to work. No specific patient characteristics were identified as best predictors of positive employment outcomes. No quantitative syntheses of results were performed.

Conclusions: For questions of disability and employment in CFS, the limitations inherent in the current literature are extensive. Methodologically rigorous, longitudinal, and interventional studies are needed to determine baseline characteristics that are associated with the inability to work and interventions that are effective in restoring the ability to work in the CFS population. Simple and consistent evaluations of functional capacity in patients with CFS are needed.

Arch Intern Med. 2004;164:1098-1107

CHRONIC FATIGUE SYNdrome (CFS) poses a difficult challenge to the medical community. Although there are at least 4 different and well-accepted operational definitions of CFS,[1-4] all rely on subjective reports, and there are no objective diagnostic findings. Chronic fatigue syndrome is defined by the Centers for Disease Control and Prevention (CDC) as a syndrome of severe, disabling physical and mental fatigue lasting for at least 6 months, exacerbated by minimal exertion, and unexplained by a conventional medical diagnosis. As such, CFS is a purely subjective condition and is a diagnosis of exclusion because no diagnostic laboratory marker or pathognomonic biopsy specimen has yet been identified.[5] The prevalence of CFS is difficult to quantify owing to the lack of validated diagnostic tests and the heterogeneity of the CFS population.[6] No treatment for CFS has proved to be effective at reversing the condition, although cognitive behavior therapy may provide symptomatic improvement.[7]

The objective of this study is to evaluate the best available evidence on detecting and managing disability in persons with CFS. This topic was funded by the Agency for Healthcare Research and Quality after nomination by the Social Security Administration, which defines disability as "the inability to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment (or combination of impairments) which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than twelve months."[8] Patients with disabilities must have a severe impairment that makes them "unable to do (their) previous work or any other substantial gainful activity."[8] The impairment "must result from anatomical, physiological, or psychological abnormalities which can be shown by medically accept-

From MetaWorks Inc, Medford, Mass. *The authors have no relevant financial interest in this article.*

able clinical and laboratory diagnostic techniques. A physical or mental impairment must be established by medical evidence consisting of signs, symptoms, and laboratory findings, not only by a statement of symptoms."[8]

Although these requirements may be readily documented for some illnesses, the assessment and documentation of disability in CFS present an enormous challenge. The core complaint, fatigue, is entirely subjective, and it does not readily fit the Social Security Administration definition of "anatomical, physiological, or psychological abnormalities"[8] that can be demonstrated by objective testing. The goal of this study, therefore, is to review the best available evidence regarding questions of disability in persons with CFS.

METHODS

In general, standard best methods of systematic review research were used.[9,10] With the help of a multidisciplinary expert panel, 4 specific questions were developed to guide the review: (1) What is the evidence that some individuals with CFS have discrete impairments that are associated with disability? (2) What is the evidence that in the CFS population, current neuropsychological tests reliably detect cognitive or affective impairments associated with decreased ability to work? (3) What is the evidence that in individuals with CFS, treatments are effective in restoring the ability to work? (4) What are the patient characteristics that best define improvement or positive outcomes in the CFS population such that they experience improvement in functioning? Where it occurs, how is this improvement in functioning related to the ability to engage in work activity?

The published literature between January 1, 1988 (the year the first operational definition of CFS was published by the CDC), and November 15, 2001, was searched using the MEDLINE, Current Contents, Cochrane Library, and PsychINFO databases. In addition, the bibliographies of all accepted studies and review articles from January 1, 1999, through December 31, 2001, were searched for potentially relevant citations. The retrieval cutoff date was March 15, 2002.

Only English-language literature was sought, using the following search strategy: *fatigue syndrome, chronic* (MeSH) or *chronic fatigue (syndrome)*. Limitations were English language and human subjects.

The following study designs were accepted: observational (prospective, retrospective, and cross-sectional) and interventional. To be accepted for this review, studies were required to report CFS diagnosed according to 1 of the 4 CFS definitions (CDC 1988,[2] CDC 1994,[1] Oxford 1991,[3] or Australia 1990[4]) in adults. Studies had to report at least 1 medically determinable measure of physical or mental impairment (measures of symptom severity, functional or cognitive impairment, physical activity, exercise testing, general health, or psychiatric impairment related to disability) per Social Security Administration guidelines in relation to work or employment status.

Key data from each eligible study were extracted by one reviewer (R.P.E. or L.R.S.) and reviewed by another (C.B.L.), checking all data elements against the published article. Data elements sought for extraction from each study included study characteristics (such as location and design), patient characteristics (such as age, sex, and duration of CFS), and previous interventions (pharmacologic treatment, cognitive or exercise therapy, etc). Impairment scale results were captured for baseline and follow-up observations. The reviewers categorized each scale according to 1 of 7 impairment domain categories: cognitive, symptoms, exercise, functional, general health, mental, or physical. Some scales, such as the Checklist of Individual Strength,[11] the Sickness Impact Profile,[12] and the Medical Outcomes Study 36-Item Short-Form Health Survey (MOS SF-36),[13] had subscales in multiple domains.

Table 1. Study Quality Criteria*

Grade	Criteria
1a	Prospective longitudinal study with sufficient patient numbers, well-matched groups, and well-validated measurement instruments.
1b	Prospective longitudinal study with low patient numbers, but well-matched groups, and well-validated measurement instruments.
2a	Cross-sectional study with sufficient patient numbers, well-matched groups, and well-validated measurement instruments.
2b	Cross-sectional study with low patient numbers, but well-matched groups, and well-validated measurement instruments.
3a	Prospective longitudinal study with sufficient patient numbers, but poorly matched groups or less well-validated measurement instruments.
3b	Prospective longitudinal study with low patient numbers, poorly matched groups or less well-validated measurement instruments.
4a	Cross-sectional study with sufficient patient numbers, but poorly matched groups or less well-validated measurement instruments.
4b	Cross-sectional study with low patient numbers, poorly matched groups, or less well-validated measurement instruments.

*Data from MacMahon and Lip.[14]

Because many articles used different scales, organizing them by domain was a necessary first step before attempting to combine data from different studies. For each study, results from a maximum of 3 scales in each of the domains available were extracted; when more than 3 scales in a given domain were reported for the same study, the scales chosen for extraction were those with the highest number of patients evaluated, those with group means and measures of dispersion, and those with named scales previously published or validated. When, in a single domain, total and component scale results were reported, the total was extracted preferentially.

Study quality was graded according to design (**Table 1**). A scale to measure the internal and external validity of all eligible studies was developed. For internal validity, points were awarded (0 indicates absent; 1, present) if the following criteria were met: all patients with CFS studied were diagnosed according to at least 1 of the acceptable criteria, tests for medically determinable physical or mental impairment were specified and reported, control groups were similar to patients with CFS in clinically important demographic factors at the start of the study, all patients and controls enrolled were accounted for in follow-up, 95% confidence intervals or *P* values were reported for numerical results, and work activity or disability status was reported. For external validity, studies received points depending on whether the patient sample was self-selected (0 points), a random sample from a CFS cohort (1 point), or all patients from a CFS cohort (2 points).

RESULTS

STUDIES

From a total of 3840 abstracts identified from electronic searches and bibliography checks, 53 studies and 19 kin studies met all of the eligibility criteria (see Box). The most common reason for rejection was lack of data on work or disability status (124 studies).

Table 2 summarizes the main study-level characteristics of the 53 accepted studies (4558 patients). Con-

Table 2. Characteristics of the 53 Accepted Studies

	Studies, No. (n = 53)	Patients, No. (n = 4558)
Publication year		
1988-1994	11	1030
1995-2001	42	3528
Accrual years reported	13	1226
Study location		
United States	28	1869
Canada	2	73
Western Europe	20	1807
Australia/New Zealand	2	65
Multicontinental	1	744
Study design		
Prospective		
RCT	10	1042
nRCT	1	71
Case control	2	321
UCS	8	366
Retrospective case series	1	94
Cross sectional	31	2664
Interventional	17	1348
Observational	36	3210
CFS diagnostic criteria used*		
CDC 1988	23	2267
CDC 1994	20	1912
Oxford 1991	18	2173
Australia 1990	1	744
MetaWorks internal validity score (2-6 points)		
2	2	136
3	5	424
4	15	1779
5	21	950
6	10	1269
MetaWorks external validity score (0-2 points)		
0	35	1737
1	3	403
2	15	2418
MetaWorks total validity score, mean (range, 2-8)†	5.2	4558

Abbreviations: CDC, Centers for Disease Control and Prevention; CFS, chronic fatigue syndrome; nRCT, nonrandomized controlled trial; RCT, randomized controlled trial; UCS, uncontrolled case series.

*Numbers sum to greater than the total number of studies as some studies used more than 1 of these criteria.

†Higher scores indicate better validity.

trol subjects were also available in 22 of these studies (775 controls). Information on other comparator groups, such as patients with multiple sclerosis or fibromyalgia, was not extracted. Of the 53 accepted studies, 36 were observational (3210 patients) and 17 were interventional (1348 patients). Fourteen of the 17 interventional studies reported a work or impairment domain result at follow-up, after intervention. The interventions in these 17 studies were behavioral (4 studies), psychologic (2 studies), drugs (5 studies), occupational or physiotherapy (2 studies), or mixed (4 studies). In 6 studies, a placebo intervention was also used.

Twenty-three studies required that patients fulfill the 1988 CDC criteria for CFS, 20 required that patients satisfy the 1994 CDC diagnostic criteria, and 18 required that patients meet the Oxford 1991 diagnostic criteria. Several studies used more than 1 set of criteria. Only 1 study[15] used the Australian criteria, but it used the other 3 criteria as well.

Using the validity assessment tool defined specifically for this project, studies scored well overall for internal validity but poorly for external validity, suggesting that the results of this sample of studies may not be generalizable to the entire population of patients with CFS.

PATIENTS

Table 3 gives baseline patient characteristics for all accepted studies. Most patients (76%) were women. Mean age was reported in 48 studies (4372 patients) and ranged from 24.7 to 46.1 years, with a mean of 38.4 years. Mean duration of CFS in the 40 studies (3976 patients) that reported this variable was 5.5 years (range, 1.9-8.5 years). Years of education were reported in 14 studies (1310 patients) and ranged from 11.8 to 16.0 years, with a mean of 14.1 years. The demographic information of controls was generally similar to that of patients with CFS.

Table 3 also summarizes the highly variable employment information available in the accepted studies. The total number of employed patients with CFS was reported in 35 studies (2652 patients; 42% employed). The number of unemployed patients was reported in 37 studies (2720 patients; 54% unemployed). The number of studies reporting the percentage of patients unemployed exceeds the number of studies reporting the percentage of patients employed because 2 studies reported[16] or implied[17] the number unemployed but not the number employed. Nine of these studies also reported the total number of controls who were employed and unemployed (340 controls; 90% employed and 9% unemployed). These results do not sum to 100% due to incomplete reporting in some studies.

Some studies divided employment into full-time vs part-time, and in these studies, an even greater difference was seen between patients with CFS and controls. In 16 studies reporting this measure, only 19% of 967 patients with CFS worked full-time, whereas 75% of 53 controls worked full-time in the 2 studies with this information. Ten studies (511 patients) reported that 55% of patients were on disability or temporary sick leave compared with 1% of controls (2 studies and 89 patients). Twenty studies (1919 patients) reported that 64% of patients had work limitations due to CFS compared with none of 38 controls in the single study that reported this measure.

PROJECT QUESTIONS

What Is the Evidence That Some Individuals With CFS Have Discrete (Mental or Physical) Impairments That Are Associated With Disability?

Seventeen studies reported the incidence of current psychiatric diagnoses in 1830 patients with CFS (40%). The lifetime incidence of psychiatric diagnoses was even higher in the 12 studies with this information: 65% of 930 patients with CFS. The most common psychiatric diagnosis was depression, which was reported in 45% of 1718 patients with CFS. In contrast, 4 studies reported the lifetime incidence of psychiatric diagnosis in 200 controls

Table 3. Baseline Patient Demographics and Employment Status

	Patients With CFS			Controls		
	Value*	Studies, No. (n = 53)	Patients, No.† (n = 4507)	Value	Studies, No. (n = 22)	Controls, No.† (n = 775)
Demographics						
Women, %	76	49	4378	73	19	605
Age, mean, y	38.4	48	4372	37.7	19	596
CFS or symptom duration, mean, y	5.5	40	3976	NA	NA	NA
Education, mean, y	14.1	14	1310	14.4	6	212
Employment status, %‡						
Total employed§	42	35	2652	90	9	340
Employed full-time	19	16	967	75	2	53
Unemployed‖	54	37	2720	9	9	340
Disability benefits	51	6	364	4	1	47
Disability or temporary sick leave	55	10	511	1	2	89
Work limitations due to illness	64	20	1919	0	1	38

Abbreviations: CFS, chronic fatigue syndrome; NA, not applicable.
*For studies in which the value is known.
†Number of patients in studies contributing data (less than the total number of patients enrolled at the study level because some studies did not account for, or present demographic information for, all patients).
‡Employed + unemployed does not sum to 100% of patients because complete employment data could not be extracted for all patients. Number of studies reporting number of patients employed does not equal number of studies reporting number of patients unemployed because 2 studies only reported number unemployed, and the remainder of the patients were either employed or unaccounted for.
§Employed includes working or in school.
‖Unemployed includes retired, not working, or unable to continue schooling.

Table 4. Employment and Physical Impairments*

Source	Validity Score	Patients With CFS, No.	Patients With CFS Employed, %	Controls, No.	Controls Employed, %	Scale Score: Patients With CFS vs Controls	*P* Value
Buchwald et al,[20] 1996	7	185	46	99	91	MOS SF-36 physical function: 40 vs 96	≤.001
						MOS SF-36 general health: 32 vs 81	≤.001
Claypoole et al,[18] 2001	5	22	41	22	86	$\dot{V}O_{2max}$ 18.9 vs 20.5 mL/kg per minute	NS
Garcia-Borreguero et al,[19] 1998	5	42	27†	41	100	POMS fatigue: 19.9 vs 6.3	.0001
						POMS vigor/activity: 8.0 vs 19.0	.0001
Lloyd et al,[21] 1994	5	12	42	13	100	POMS fatigue: 18.1 vs 2.2	<.05
						MVC (decline after exercise): 61.8% vs 63.8%	NS
Natelson et al,[17] 1995	6	41	18‡	36	100	POMS vigor: 6 vs 21	NR
						POMS fatigue: 21 vs 2	NR
Ray et al,[22] 1993	5	24	13§	24	71§	PFRS fatigue: 4.0 vs 0.7	<.001
						PFRS somatic symptons: 2.6 vs 0.4	<.001
Schmaling et al,[23] 1998	4	15	13	11	91	MOS SF-36 health perception: 23.3 vs 95.8	<.001
						MOS SF-36 physical function: 37.0 vs 95.8	<.001
Vercoulen et al,[24] 1997	7	51	49	53	89	CIS Actometer: 23.3 vs 35.5	<.05
						SIP mobility: 26.2 vs 33.5	<.05
						SIP walking: 31.6 vs 40.8	<.05

Abbreviations: CFS, chronic fatigue syndrome; CIS, Checklist of Individual Strength for activity; MOS SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; MVC, maximal voluntary contraction; NR, not reported, but the difference was significant; NS, not significant; PFRS, Profile of Fatigue-Related Symptoms; POMS, Profile of Mood States; SIP, Sickness Impact Profile, $\dot{V}O_{2max}$, maximum oxygen consumption.
*Measures of dispersion are not included.
†This study reported the number of patients with vocational disability. It was assumed that the remainder of the patients were employed. For controls, vocational disability was reported as not applicable, and 100% employment was assumed.
‡This study reported the number of patients with disability, and it was assumed that the remainder of the patients were employed.
§This study reported only the number of patients and controls employed full-time.

(12%). Patients with CFS in these studies thus seem to have a higher lifetime incidence of psychiatric diagnoses than controls. However, no relationship of psychiatric diagnoses to disability can be established in these studies.

Therefore, we next explored the subset of studies that reported employment status and either physical or mental impairment scales, after categorizing the scales by domain. Using scatterplots, we observed no apparent association between work status and any single impairment domain (data not shown). We then further grouped studies by similar impairment domains. **Table 4** displays the 8 studies[17-24] that reported impairment in any physical domain (physical, general health, symptoms, or exercise) and the percentage of individuals employed for patients with CFS and controls. Statistically significant differences were found between patients with CFS and controls on several scales in the physical

Table 5. Neuropsychologic Tests and Work Status*

Source	Validity Score	Patients With CFS, No.	Patients With CFS Employed, No.	Controls, No.	Controls Employed, No.	Scale Score: Patients With CFS vs Controls	*P* Value
Buchwald et al,[20] 1996	7	185	46	99	91	MOS SF-36 mental health: 57 vs 83	<.001
Claypoole et al,[18] 2001	5	22	41	22	86	Hopkins verbal learning: 26.1 vs 27.4	NS
Garcia-Borreguero et al,[19] 1998	5	42	27†	41	100	POMS confusion: 12.0 vs 5.9	.0001
						POMS depression: 9.2 vs 5.4	<.05
						POMS tension/anxiety (scores not reported)	NS
						POMS anger/hostility (scores not reported)	NS
Lloyd et al,[21] 1994	5	12	42	13	100	POMS confusion: 14.8 vs 2.4	<.1
						POMS depression: 21.5 vs 0.6	<.001
Michiels et al,[25] 1996	5	35	26	33	100	WAIS digit span forward: 45.3 vs 52.6	.0005
Natelson et al,[17] 1995	6	41	18‡	6	100	POMS depression/dejection: 10 vs 3	NR
						POMS confusion: 14 vs 2	NR
Ray et al,[22] 1993	5	24	13§	24	71§	EAQ: 35.6 vs 49.3	<.001
						PFRS emotional distress: 3.5 vs 1.2	<.001
						PFRS congnitive difficulty: 3.8 vs 1.0	<.001
Schmaling et al,[23] 1998	4	15	13	11	91	SCL-90-R depression: 59.3 vs 25.8	<.001
						MOS SF-36 mental health: 69.1 vs 85.5	<.001
Vercoulen et al,[24] 1997	7	51	49	53	89	SIP concentration: 35.0 vs 2.2	.0001
						CIS concentration: 5.2 vs 1.9	.0001

Abbreviations: CFS, chronic fatigue syndrome; CIS, Checklist of Individual Strength; EAQ, Everyday Attention Questionnaire; MOS SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; NR, not reported, but the difference was significant; NS, not significant; PFRS, Profile of Fatigue-Related Symptoms; POMS, Profile of Mood States; SCL-90-R, Symptom Checklist-90–Revised; SIP, Sickness Impact Profile; WAIS, Wechsler Adult Intelligence Scale.

*Measures of dispersion are not included.

†This study reported the number of patients with vocational disability. It was assumed that the remainder of the patients were employed. For controls, vocational disability was reported as not applicable, and 100% employment was assumed.

‡This study reported the number of patients with disability, and it was assumed that the remainder of the patients were employed.

§This study reported only the number of patients and controls employed full-time.

domain: the MOS SF-36 for physical function,[20,23] general health,[20] and health perception[23]; the Profile of Mood States (POMS) for fatigue and vigor[17,19,21]; the Profile of Fatigue-Related Symptoms for fatigue and somatic symptoms[22]; the Sickness Impact Profile for mobility and walking[24]; and the Checklist of Individual Strength for activity.[24] Although patients with CFS had statistically significantly different scores from controls in these studies, it should be remembered that all of these scores may be abnormal in patients who are fatigued for any reason. In all but 3 of these 8 studies, estimates of physical impairment are based only on self-reported scales by the patient. Only 2 of the 8 studies described formal exercise testing. No statistically significant differences were found between patients with CFS and controls in maximum oxygen consumption[18] or maximal voluntary contraction during hand grip exercises.[21] The percentage of patients with CFS who were employed ranged from 13% to 49% in these studies, whereas the percentage of controls who were employed ranged from 71% to 100%. Most of these employment rates include full-time and part-time work, but the lowest values, for patients with CFS and controls, were from a study[22] that limited results to full-time employment. No statistical pooling is possible owing to widely divergent study designs and outcomes measured, but the data in Table 4 suggest that a lower percentage of patients with CFS who have abnormalities on physical function and fatigue scales are employed compared with controls who have normal scores on these scales.

Furthermore, 2 instruments relate discrete physical impairments with disability in more than 1 study and thus provide more convincing evidence. For example, in 2 studies,[20,23] the MOS SF-36 physical function scores showed consistent differences between patients with CFS and controls. In 3 studies,[17,19,21] the POMS fatigue scores were also similar in patients with CFS. These 2 measures of physical impairment thus seem to represent the best available evidence of physical impairment in patients with CFS at this time. It is not possible, however, to relate these physical or mental impairments to employment in these few studies.

What Is the Evidence That in the CFS Population, Current Neuropsychological Tests Reliably Detect Cognitive or Affective Impairments Associated With Decreased Ability to Work?

Table 5 lists the 9 studies[17-25] that reported neuropsychological impairment scales and work data in patients with CFS and controls. Statistically significant differences were found between patients with CFS and controls on MOS SF-36 mental health,[20,23] POMS confusion and depression,[17,19,21] Everyday Attention Questionnaire and Profile of Fatigue-Related Symptoms for emotional distress and cognitive difficulty,[22] Symptom Checklist-90–Revised depression,[23] and Sickness Impact Profile and Checklist of Individual Strength concentration.[24] The POMS scores for anger/hostility and tension/anxiety were statistically significantly different in patients with CFS vs controls in one study[17] but not in another.[19] Cognitive function was statistically significantly different in patients with CFS vs controls in the Wechsler Adult Intelligence Scale digit span forward in one study[25] but not in Hopkins verbal learning in another study.[18] One study[19] reported that the POMS tension/anxiety and anger/

Table 6. Interventions Restoring the Ability to Work in Patients With Chronic Fatigue Syndrome

Source	Validity Score	Intervention	Time of Follow-up Assessment, mo	Patients Enrolled, No.	Dropouts, %	Patients Employed at Baseline, %	Patients Employed at Follow-up, %*
Akagi et al,[26] 2001	6	Cognitive behavior therapy	6	51	0	29	53
Dyck et al,[27] 1996	3	Rehabilitation program	3	2	0	0	50
Fulcher and White,[28] 1997	5	Exercise therapy	15	66	29	39	47
Marlin et al,[29] 1998	2	Individualized programs	6	71	28	0	44
Tiersky et al,[30] 2001	4	None	42	47	26	32	23
Vercoulen et al,[11] 1994	7	None	18	298	17	31	24

*Based on the number of patients enrolled.

hostility scores were not significantly different between patients with CFS and controls. These data suggest that patients with CFS have a higher frequency of abnormalities on confusion, depression, and concentration scales and lower levels of employment compared with controls. However, no statistical pooling is possible in these studies owing to widely divergent study designs and outcome measures.

Although no single neuropsychological test has been validated to reliably detect either cognitive or affective impairments associated with employment status in patients with CFS, 2 measures may have promise. In 2 studies,[20,23] MOS SF-36 mental health scores revealed consistent differences between patients with CFS and controls. In 3 other studies,[17,19,21] POMS confusion scores and differences with controls were also of similar magnitude. The POMS depression score was comparable in only 2 of these same 3 studies.[17,19] This best available evidence thus suggests that MOS SF-36 mental health and POMS confusion may be the most promising measures of neuropsychiatric status in patients with CFS and may relate to employment status.

What Is the Evidence That in Individuals With CFS, Treatments Are Effective in Restoring the Ability to Work?

Among the 14 interventional trials with work or impairment results after intervention, there were too few of any single intervention with any specific impairment domain to allow any assessment of association. Only 4 longitudinal studies[26-29] reported employment at baseline and follow-up after intervention (**Table 6**). Two additional studies[11,30] reported employment at both times with no interventions. In the 4 studies with interventions, the percentage of patients with CFS who were employed at baseline ranged from 0% to 39%; at follow-up (3-42 months after baseline), employment ranged from 44% to 53%. Interventions associated with increased employment at follow-up included individualized rehabilitation programs,[27,29] cognitive behavior therapy,[26] and exercise therapy.[28] The studies are not comparable, however, owing to differences in study design, duration of follow-up, and types of intervention. Furthermore, up to 29% of patients were lost to follow-up. Still, all 4 studies showed improved employment outcomes, whereas the 2 studies[11,30] with no interventions showed worsening of employment outcomes.

What Are the Patient Characteristics That Best Define Improvement in the CFS Population Such That They Experience Improvement in Functioning That Is Related to Ability to Engage in Work Activity?

Table 7 describes the 9 studies[11,30-37] that reported the proportion of patients with CFS in whom symptomatic improvement was noted over time. Specific characteristics of interest were mean age, sex, mean duration of CFS symptoms, mean number of years of education, and incidence of depression. Studies did not show any consistent trend with regard to these baseline variables as predictors of improvement. For example, shorter duration of disease was associated with improvement in 2 studies[11,33] but not in 3 others.[30,34,36] Sex was associated with improvement in 2 studies[33,36] but not in 2 others.[30,34] Age was associated with improvement in 1 study[11] but not in 2 others.[30,36] Education was not associated with improvement in 2 studies,[30,36] and marital status was not associated with improvement in 1 study.[36]

Last, in 4 studies, work status was examined with regard to patient characteristics. These studies were examined to seek characteristics associated with positive work outcomes in the CFS population. In a US study,[32] 226 patients with CFS were contacted 1½ years after their initial evaluation to report on their work and functional status. None of the baseline demographic, clinical, or psychiatric characteristics were predictive of returning to work. In another US study,[38] 32 patients with CFS were evaluated to identify traits associated with working. Working patients with CFS were more likely to be men, younger, and never married, and they had less severe muscle and joint pain, higher activity levels, and better physical functioning than nonworking patients. In the third study,[39] from New Zealand, 53 patients with CFS were questioned regarding their perceptions of health, illness attributions, self-esteem, and coping skills, and they were followed for 6 months. Work dysfunction was associated with increased somatic illness identity and limited coping skills. Last, in a multinational study,[15] 744 patients with CFS filled out questionnaires that included questions about functional impairment and the ability to work. Greater severity of symptoms was associated with inability to work, but depression was not.

In summary, no patient characteristics in any impairment domain have been consistently identified that best define or predict improvement or positive work or functional outcomes in the CFS population.

Table 7. Baseline Characteristics Reported as Improved in Patients With Chronic Fatigue Syndrome*

Source	Validity Score	Intervention	Time of Outcome Assessment, mo	Patients Enrolled, No.	Patients Evaluated for Improvement, No.	Patients Improved, %	Baseline Characteristics of Improved vs Unimproved Patients
Bombardier and Buchwald,[32] 1995	4	None	18	226	226	61	Absence of dysthymia ($r = 0.15$, $P<.03$)
Butler et al,[34] 1991	5	CBT	1.5	32	27	85	Absence of treatment-resistant affective disorder (BDI: 8.3 vs 11.7) Same sex, disease severity, disease duration (number not reported)
Deale et al,[35] 1997	6	CBT	6	60	27	70	No significant difference on any pretreatment characteristic (numbers not reported)
Kruesi et al,[31] 1989	4	Acyclovir or placebo therapy	6	28	24	88	No significant difference in clinical, chemical, immunologic, or serologic features (numbers not reported)
Lerner et al,[33] 1997	4	Ganciclovir therapy	6	38	18	72	Male sex (3 men in study, all improved) Shorter mean duration of symptoms (1.6 vs 2.8 y)
Peterson et al,[36] 1991	6	None	Onset of illness	177	177	12	Female sex: 61.9% vs 80.1% ($P = .09$) Employed at presentation: 66.7% vs 49.4% ($P = .06$) Physical functioning scores: 68.5 vs 58.9 ($P = .01$) Social functioning scores: 3.2 vs 42.8 ($P = .02$) SCL-90 anxiety scores: 0.43 vs 0.66 ($P = .01$) SCL-90 obsessive/compulsive scores: 0.93 vs 1.34 ($P = .04$)
Saltzstein et al,[37] 1998	4	None	24	15	15	12	Perception that physician's prognosis was positive, social support (numbers not reported)
Tiersky et al,[30] 2001	4	None	42	47	35	57	Higher median anxiety score 38 vs 27 ($P = .02$) Ability to perform light duty No significant differences in age, education, illness severity or duration, employment status, sex, or level of depression (all $P>.05$)
Vercoulen et al,[11] 1994	7	None	18	298	246	20	Self-reported improvement was related to younger age, shorter disease duration, less symptom severity, less functional impairment, and more sense of control over symptoms (numbers not reported) Demographic variables were not predictive

Abbreviations: BDI, Beck Depression Inventory; CBT, cognitive behavior therapy; SCL-90, Symptom Checklist-90.
*Measures of dispersion are not included. *P* values are listed when reported.

COMMENT

For patients with CFS, we have no diagnostic tests and no proven treatments. Yet, "whatever one presumes CFS to be, people suffer with it and because of it."[40] Can we serve patients with CFS better by focusing less on the medical mystery per se and more on the functional consequences? This is the main premise underlying this review. This best available evidence suggests that unemployment in patients with CFS is high. Physical and mental impairments are demonstrable, albeit with instruments that have not been validated in a compensation setting, or as measures of disability, or in patients with CFS. The MOS SF-36 physical and mental functions and the POMS confusion, fatigue, and depression scales provide the strongest evidence in this regard. It is not possible, however, to yet determine whether patients with CFS who have discrete impairments are those who are unemployed. Also, no specific demographic, clinical, or psychiatric traits have been shown to be consistently predictive of the ability of patients with CFS to return to work.

Thus, the major limitation of this review is that the studies we identified as the best available evidence were not designed to answer the types of questions posed in this review. And owing to the variety of study designs, scales used, and outcomes reported, results of different studies could not be combined in meaningful ways. Researchers did not report consistent information about impairment and work status at both baseline and follow-up. Neither did they consistently describe employment status as full- or part-time work, previous or new work, or duration before return to work. Standardized measurements of impairment in patients with CFS are not available, and neither is the impact of impairment on employability. The validity and reliability of self-reported measures of impairment and disability are needed specifically for patients with CFS, as they are often formerly high-functioning individuals, unlike chronically

Akagi H, Klimes I, Bass C. Cognitive behavioral therapy for chronic fatigue syndrome in a general hospital-feasible and effective. *Gen Hosp Psychiatry*. 2001;23:254-260.

Anderson JS, Ferrans CE. The quality of life of persons with chronic fatigue syndrome. *J Nerv Ment Dis*. 1997;185:359-367.

Antoni MH, Brickman A, Lutgendorf S, et al. Psychosocial correlates of illness burden in chronic fatigue syndrome. *Clin Infect Dis*. 1994;18(suppl 1):S73-S78.

Arpino C, Carrieri MP, Valesini G, et al. Idiopathic chronic fatigue and chronic fatigue syndrome: a comparison of two case-definitions. *Ann Ist Super Sanita*. 1999;35:435-441.

Bombardier CH, Buchwald D. Chronic fatigue, chronic fatigue syndrome, and fibromyalgia: disability and health-care use. *Med Care*. 1996;34:924-930.

Bombardier CH, Buchwald D. Outcome and prognosis of patients with chronic fatigue vs chronic fatigue syndrome. *Arch Intern Med*. 1995;155:2105-2110.

Bou-Holaigah I, Rowe PC, Kan J, Calkins H. The relationship between neurally mediated hypotension and the chronic fatigue syndrome. *JAMA*. 1995;274:961-967.

Buchwald D, Pearlman T, Kith P, Schmaling K. Gender differences in patients with chronic fatigue syndrome. *J Gen Intern Med*. 1994;9:397-401.

Buchwald D, Pearlman T, Umali J, Schmaling K, Katon W. Functional status in patients with chronic fatigue syndrome, other fatiguing illnesses, and healthy individuals. *Am J Med*. 1996;101:364-370.

Butler S, Chalder T, Ron M, Wessely S. Cognitive behaviour therapy in chronic fatigue syndrome. *J Neurol Neurosurg Psychiatry*. 1991;54:153-158.

Claypoole K, Mahurin R, Fischer ME, et al. Cognitive compromise following exercise in monozygotic twins discordant for chronic fatigue syndrome: fact or artifact. *Appl Neuropsychol*. 2001;8:31-40.

Creswell C, Chalder T. Defensive coping styles in chronic fatigue syndrome. *J Psychosom Res*. 2001;51:607-610.

Cruess SE, Klimas N, Antoni MH, et al. Immunologic status correlates with severity of physical symptoms and perceived illness burden in chronic fatigue syndrome patients. *J Chronic Fatigue Syndr*. 2000;7:39-52.

Daly E, Komaroff AL, Bloomingdale K, Wilson S, Albert MS. Neuropsychological function in patients with chronic fatigue syndrome, multiple sclerosis, and depression. *Appl Neuropsychol*. 2001;8:12-22.

Deale A, Chalder T, Marks I, Wessely S. Cognitive behavior therapy for chronic fatigue syndrome: a randomized controlled trial. *Am J Psychiatry*. 1997;154:408-414.

Dyck D, Allen S, Barron J, et al. Management of chronic fatigue syndrome: case study. *AAOHN J*. 1996;44:85-92.

Fiedler N, Kipen HM, DeLuca J, Kelly-McNeil K, Natelson B. A controlled comparison of multiple chemical sensitivities and chronic fatigue syndrome. *Psychosom Med*. 1996;58:38-49.

Fischler B, Cluydts R, De Gucht Y, Kaufman L, De Meirleir K. Generalized anxiety disorder in chronic fatigue syndrome. *Acta Psychiatr Scand*. 1997;95:405-413.

Fulcher KY, White PD. Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. *BMJ*. 1997;314:1647-1652.

Fulcher KY, White PD. Strength and physiological response to exercise in patients with chronic fatigue syndrome. *J Neurol Neurosurg Psychiatry*. 2000;69:302-307.

Garcia-Borreguero D, Dale JK, Rosenthal NE, et al. Lack of seasonal variation of symptoms in patients with chronic fatigue syndrome. *Psychiatry Res*. 1998;77:71-77.

Hill NF, Tiersky LA, Scavalla VR, Lavietes M, Natelson BH. Natural history of severe chronic fatigue syndrome. *Arch Phys Med Rehabil*. 1999;80:1090-1094.

Jason LA, Fricano G, Taylor RR, Halpert J, Fennell PA, Klein S, et al. Chronic fatigue syndrome: An examination of the phases. *J Clin Psychol*. 2000;56:1497-508.

Jason LA, Richman JA, Rademaker AW, et al. A community-based study of chronic fatigue syndrome. *Arch Intern Med*. 1999; 159:2129-2137.

Jason LA, Taylor RR, Kennedy CL, et al. Chronic fatigue syndrome: sociodemographic subtypes in a community-based sample. *Eval Health Prof*. 2000;23:243-263.

Jason LA, Taylor RR, Kennedy CL. Chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities in a community-based sample of persons with chronic fatigue syndrome-like symptoms. *Psychosom Med*. 2000;62:655-663.

Kruesi MJ, Dale J, Straus SE. Psychiatric diagnoses in patients who have chronic fatigue syndrome. *J Clin Psychiatry*. 1989;50: 53-56.

Lane TJ, Manu P, Matthews DA. Depression and somatization in the chronic fatigue syndrome. *Am J Med*. 1991;91:335-344.

Lerner AM, Zervos M, Dworkin HJ, et al. New cardiomyopathy: pilot study of intravenous ganciclovir in a subset of the chronic fatigue syndrome. *Infect Agents Dis*. 1997;6:110-117.

Lloyd A, Gandevia S, Brockman A, Hales J, Wakefield D. Cytokine production and fatigue in patients with chronic fatigue syndrome and healthy control subjects in response to exercise. *Clin Infect Dis*. 1994;18:S142-S146.

MacDonald KL, Osterholm MT, LeDell KH, et al. A case-control study to assess possible triggers and cofactors in chronic fatigue syndrome. *Am J Med*. 1996;100:548-554.

Marcel B, Komaroff AL, Fagioli LR, Kornish RJ, Albert MS. Cognitive deficits in patients with chronic fatigue syndrome. *Biol Psychiatry*. 1996;40:535-541.

Marlin RG, Anchel H, Gibson JC, Goldberg WM, Swinton M. An evaluation of multidisciplinary intervention for chronic fatigue syndrome with long-term follow-up, and a comparison with untreated controls. *Am J Med*. 1998;105:110S-114S.

McKenzie R, O'Fallon A, Dale J, et al. Low-dose hydrocortisone for treatment of chronic fatigue syndrome: a randomized controlled trial. *JAMA*. 1998;280:1061-1066.

Michiels V, Cluydts R, Fischler B, Hoffmann G, Le Bon O, De Meirleir K. Cognitive functioning in patients with chronic fatigue syndrome. *J Clin Exp Neuropsychol*. 1996;18:666-677.

Morriss RK, Wearden AJ, Battersby L. The relation of sleep difficulties to fatigue, mood and disability in chronic fatigue syndrome. *J Psychosom Res*. 1997;42:597-605.

Morriss RK, Wearden AJ, Mullis R. Exploring the validity of the Chalder Fatigue scale in chronic fatigue syndrome. *J Psychosom Res*. 1998;45:411-417.

Morriss RK, Wearden AJ. Screening instruments for psychiatric morbidity in chronic fatigue syndrome. *J R Soc Med*. 1998;91:365-368.

Moss-Morris R, Petrie KJ. Discriminating between chronic fatigue syndrome and depression: a cognitive analysis. *Psychol Med*. 2001;31:469-479.

Myers C, Wilks D. Comparison of Euroqol EQ-5D and SF-36 in patients with chronic fatigue syndrome. *Qual Life Res*. 1999;8:9-16.

Natelson BH, Johnson SK, DeLuca J, et al. Reducing heterogeneity in chronic fatigue syndrome: a comparison with depression and multiple sclerosis. *Clin Infect Dis*. 1995;21:1204-1210.

Peterson PK, Schenck CH, Sherman R. Chronic fatigue syndrome in Minnesota. *Minn Med*. 1991;74:21-26.

Peterson PK, Shepard J, Macres M, et al. A controlled trial of intravenous immunoglobulin G in chronic fatigue syndrome. *Am J Med*. 1990;89:554-560.

Pheley AM, Melby D, Schenck C, Mandel J, Peterson PK. Can we predict recovery in chronic fatigue syndrome? *Minn Med*. 1999;82:52-56.

Powell P, Bentall RP, Nye FJ, Edwards RH. Randomised controlled trial of patient education to encourage graded exercise in chronic fatigue syndrome. *BMJ*. 2001;322:387-390.

Prins JB, Bleijenberg G, Bazelmans E, et al. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. *Lancet*. 2001;357:841-847.

Ray C, Jefferies S, Weir WR. Coping and other predictors of outcome in chronic fatigue syndrome: a 1-year follow-up. *J Psychosom Res*. 1997;43:405-15.

Ray C, Jefferies S, Weir WR. Coping with chronic fatigue syndrome: illness responses and their relationship with fatigue, functional impairment and emotional status. *Psychol Med*. 1995;25:937-945.

Ray C, Jefferies S, Weir WR. Life-events and the course of chronic fatigue syndrome. *Br J Med Psychol*. 1995;68:323-331.

Ray C, Phillips L, Weir WR. Quality of attention in chronic fatigue syndrome: subjective reports of everyday attention and cognitive difficulty, and performance on tasks of focused attention. *Br J Clin Psychol*. 1993;32:357-364.

Rowe PC, Calkins H, DeBusk K, et al. Fludrocortisone acetate to treat neurally mediated hypotension in chronic fatigue syndrome: a randomized controlled trial. *JAMA*. 2001;285:52-59.

Saltzstein BJ, Wyshak G, Hubbuch JT, Perry JC. A naturalistic study of the chronic fatigue syndrome among women in primary care. *Gen Hosp Psychiatry*. 1998;20:307-316.

Scheffers MK, Johnson RJ, Grafman J, Dale JK, Straus SE. Attention and short-term memory in chronic fatigue syndrome patients: an event-related potential analysis. *Neurology*. 1992;42:1667-1675.

Schmaling KB, Hamilos DL, DiClementi JD, Jones JF. Pain perception in chronic fatigue syndrome. *J Chronic Fatigue Syndr*. 1998;4:13-22.

Schmaling KB, Smith WR, Buchwald DS. Significant other responses are associated with fatigue and functional status among patients with chronic fatigue syndrome. *Psychosom Med*. 2000;62:444-450.

Shanks MF, Ho-Yen DO. A clinical study of chronic fatigue syndrome. *Br J Psychiatry*. 1995;166:798-801.

Sharpe M, Hawton K, Simkin S, et al. Cognitive behaviour therapy for the chronic fatigue syndrome: a randomized controlled trial. *BMJ*. 1996;312:22-26.

Sisto SA, LaManca J, Cordero DL, et al. Metabolic and cardiovascular effects of a progressive exercise test in patients with chronic fatigue syndrome. *Am J Med*. 1996;100:634-640.

Straus SE, Dale JK, Tobi M, et al. Acyclovir treatment of the chronic fatigue syndrome: lack of efficacy in a placebo-controlled trial. *N Engl J Med*. 1988;319:1692-1698.

Swanink CM, Vercoulen JH, Bleijenberg G, Fennis JF, Galama JM, van der Meer JW. Chronic fatigue syndrome: a clinical and laboratory study with a well matched control group. *J Intern Med*. 1995;237:499-506.

Tiersky LA, DeLuca J, Hill N, et al. Longitudinal assessment of neuropsychological functioning, psychiatric status, functional disability and employment status in chronic fatigue syndrome. *Appl Neuropsychol*. 2001;8:41-50.

Tuck I, Wallace D. Chronic fatigue syndrome: a woman's dilemma. *Health Care Women Int*. 2000;21:457-466.

Vercoulen JH, Bazelmans E, Swanink CM, et al. Physical activity in chronic fatigue syndrome: assessment and its role in fatigue. *J Psychiatr Res*. 1997;31:661-673.

Vercoulen JH, Bazelmans E, Swanink CM, et al. Evaluating neuropsychological impairment in chronic fatigue syndrome. *J Clin Exp Neuropsychol*. 1998;20:144-156.

Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res*. 1994;38:383-392.

Vercoulen JH, Swanink CM, Zitman FG, et al. Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome. *Lancet*. 1996;347:858-861.

Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Prognosis in chronic fatigue syndrome: a prospective study on the natural course. *J Neurol Neurosurg Psychiatry*. 1996;60:489-494.

Vercoulen JH, Swanink CM, Galama JM, et al. The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: development of a model. *J Psychosom Res*. 1998;45:507-517.

Wearden AJ, Morriss RK, Mullis R, et al. Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. *Br J Psychiatry*. 1998;172:485-490.

Wessely S, Powell R. Fatigue syndrome: a comparison of chronic "postviral" fatigue with neuromuscular and affective disorders. *J Neurol Neurosurg Psychiatry*. 1989;52:940-948.

Wilson A, Hickie I, Hadzi-Pavlovic D, et al. What is chronic fatigue syndrome? heterogeneity within an international multicentre study. *Aust N Z J Psychiatry*. 2001;35:520-527.

Yeomans JD, Conway SP. Biopsychosocial aspects of chronic fatigue syndrome (myalgic encephalomyelitis). *J Infect*. 1991;23:263-269.

ill patients, who have served as the benchmark population for the development and validation of existing impairment and disability measures to date. Also, further research is needed to determine whether there are characteristics of care providers or previous work experiences that relate to ongoing CFS disability. Last, longitudinal, interventional studies are mandatory to determine baseline characteristics that are associated with the inability to work and interventions that are effective in restoring the ability to work.

In conclusion, this systematic review of the current published research related to CFS disability demonstrates that some individuals with CFS have self-reported physical or mental impairments, but these results are not consistent and are not specific to CFS. The relationship of these impairments to work status has not been well demonstrated. No specific interventions have been proved to be effective in restoring the ability to work. No specific patient characteristics have been defined that best predict positive employment outcomes in patients with CFS. Nevertheless, the results of these studies suggest that some patients with CFS are impaired and that some are disabled, according to the Social Security Administration definition. In future research and practice, a routine functional capacity evaluation should prove useful in defining what a patient can or cannot do and as an objective measure of change over time, with or without specific interventions.

Accepted for publication June 30, 2003.

This research was conducted by the MetaWorks Evidence-based Practice Center under contract 290-97-0016 with the Agency for Healthcare Research and Quality, Rockville, Md.

We thank our multidisciplinary expert panel and the many peer reviewers who provided invaluable feedback throughout this project. In particular, we thank Nelson Gantz, MD, for his friendly advice and clinician's perspective.

The authors of this article are responsible for its contents, including any clinical or treatment recommendations. No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or the US Department of Health and Human Services.

Corresponding author and reprints: Susan D. Ross, MD, FRCPC, MetaWorks Inc, 10 President's Landing, Medford, MA 02155.

REFERENCES

1. Fukuda K, Straus S, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med.* 1994;121:953-959.
2. Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: a working case definition. *Ann Intern Med.* 1988;108:387-389.
3. Sharpe MC, Archard LC, Banatvala JE, et al. A report: chronic fatigue syndrome: guidelines for research. *J R Soc Med.* 1991;84:118-121.
4. Lloyd AR, Hickie I, Boughton CR, Spencer O, Wakefield D. Prevalence of chronic fatigue syndrome in an Australian population. *Med J Aust.* 1990;153:522-528.
5. Working group convened under the auspices of the Royal Australian College of Physicians. Chronic fatigue syndrome: clinical practice guidelines—2002. *Med J Aust.* 2002;176(suppl):S23-S56.
6. Michiels V, Cluydts R. Neuropsychological functioning in chronic fatigue syndrome: a review. *Acta Psychiatr Scand.* 2001;103:84-93.
7. Mulrow CD, Ramirez G, Cornell JE, et al. *Defining and Managing Chronic Fatigue Syndrome.* Rockville, Md: Agency for Healthcare Research and Quality; September 2001. AHRQ publication 01-E061.
8. Employees benefits, *Federal Register* 1501-1568 (2000) (20 CFR § 404).
9. Mulrow CD, Oxman AD, eds. Cochrane collaboration handbook [Cochrane Review on CD-ROM]. Oxford, England: Cochrane Library, Update Software; 1997; issue 1.
10. Sacks HS, Berrier J, Reitman D, Pagano D, Chalmers T. Meta-analyses of randomized control trials: an update of the quality and methodology. In: Bailar JC III, Mosteller F, eds. *Medical Uses of Statistics.* 2nd ed. Boston, Mass: NEJM Books; 1992:427-442.
11. Vercoulen JH, Swanink C, Fennis J, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res.* 1994; 38:383-392.
12. Bergner M, Bobbitt RA, Kressel S, Pollard WE, Gilson BS, Morris JR. The Sickness Impact Profile: conceptual formulation and methodology for the development of a health status measure. *Int J Health Serv.* 1976;6:393-415.
13. Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36). *Med Care.* 1992;30:473-483.
14. MacMahon K, Lip G. Psychological factors in heart failure: a review of the literature. *Arch Intern Med.* 2002;162:509-516.
15. Wilson A, Hickie I, Hadzi-Pavlovic D, et al. What is chronic fatigue syndrome? heterogeneity within an international multicentre study. *Aust N Z J Psychiatry.* 2001;35:520-527.
16. Cruess S. Immunologic status correlates with severity of physical symptoms and perceived illness burden in chronic fatigue syndrome patients. *J Chronic Fatigue Syndr.* 2000;7:39-52.
17. Natelson BH, Johnson SK, DeLuca J, et al. Reducing heterogeneity in chronic fatigue syndrome: a comparison with depression and multiple sclerosis. *Clin Infect Dis.* 1995;21:1204-1210.
18. Claypoole K, Mahurin R, Fischer ME, et al. Cognitive compromise following exercise in monozygotic twins discordant for chronic fatigue syndrome: fact or artifact. *Appl Neuropsychol.* 2001;8:31-40.
19. Garcia-Borreguero D, Dale JK, Rosenthal NE, et al. Lack of seasonal variation of symptoms in patients with chronic fatigue syndrome. *Psychiatry Res.* 1998;77:71-77.
20. Buchwald D, Pearlman T, Umali J, Schmaling K, Katon W. Functional status in patients with chronic fatigue syndrome, other fatiguing illnesses, and healthy individuals. *Am J Med.* 1996;101:364-370.
21. Lloyd A, Gandevia S, Brockman A, Hales J, Wakefield D. Cytokine production and fatigue in patients with chronic fatigue syndrome and healthy control subjects in response to exercise. *Clin Infect Dis.* 1994;18:S142-S146.
22. Ray C, Phillips L, Weir W. Quality of attention in chronic fatigue syndrome: subjective reports of everyday attention and cognitive difficulty, and performance on tasks of focused attention. *Br J Clin Psychol.* 1993;32:357-364.
23. Schmaling KB, Hamilos DL, DiClementi JD, et al. Pain perception in chronic fatigue syndrome. *J Chronic Fatigue Syndr.* 1998;4:13-22.
24. Vercoulen JH, Bazelmans E, Swanink CM, et al. Physical activity in chronic fatigue syndrome: assessment and its role in fatigue. *J Psychiatr Res.* 1997;31:661-673.
25. Michiels V, Cluydts R, Fischler B, Hoffmann G, LeBon O, DeMeirleir K. Cognitive functioning in patients with chronic fatigue syndrome. *J Clin Exp Neuropsychol.* 1996;18:666-677.
26. Akagi H, Klimes I, Bass C. Cognitive behavioral therapy for chronic fatigue syndrome in a general hospital: feasible and effective. *Gen Hosp Psychiatry.* 2001; 23:254-260.
27. Dyck D, Allen S, Barron J, et al. Management of chronic fatigue syndrome: case study. *AAOHN J.* 1996;44:85-92.
28. Fulcher KY, White PD. Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. *BMJ.* 1997;314:1647-1652.
29. Marlin RG, Anchel H, Gibson JC, Goldberg WM, Swinton M. An evaluation of multidisciplinary intervention for chronic fatigue syndrome with long-term follow-up, and a comparison with untreated controls. *Am J Med.* 1998;105:110S-114S.
30. Tiersky LA, DeLuca J, Hill N, et al. Longitudinal assessment of neuropsychological functioning, psychiatric status, functional disability and employment status in chronic fatigue syndrome. *Appl Neuropsychol.* 2001;8:41-50.
31. Kruesi MJ, Dale J, Straus SE. Psychiatric diagnoses in patients who have chronic fatigue syndrome. *J Clin Psychiatry.* 1989;50:53-56.
32. Bombardier CH, Buchwald D. Outcome and prognosis of patients with chronic fatigue vs chronic fatigue syndrome. *Arch Intern Med.* 1995;155:2105-2110.
33. Lerner AM, Zervos M, Dworkin HJ, et al. New cardiomyopathy: pilot study of intravenous ganciclovir in a subset of the chronic fatigue syndrome. *Infect Agents Dis.* 1997;6:110-117.
34. Butler S, Chalder T, Ron M, et al. Cognitive behaviour therapy in chronic fatigue syndrome. *J Neurol Neurosurg Psychiatry.* 1991;54:153-158.
35. Deale A, Chalder T, Marks I, Wessely S. Cognitive behavior therapy for chronic fatigue syndrome: a randomized controlled trial. *Am J Psychiatry.* 1997;154: 408-414.
36. Peterson PK, Schenck CH, Sherman R. Chronic fatigue syndrome in Minnesota. *Minn Med.* 1991;74:21-26.
37. Saltzstein BJ, Wyshak G, Hubbuch JT, Perry JC. A naturalistic study of the chronic fatigue syndrome among women in primary care. *Gen Hosp Psychiatry.* 1998; 20:307-316.
38. Jason LA, Fricano G, Taylor RR, et al. Chronic fatigue syndrome: an examination of the phases. *J Clin Psychol.* 2000;56:1497-1508.
39. Moss-Morris R, Petrie KJ. Discriminating between chronic fatigue syndrome and depression: a cognitive analysis. *Psychol Med.* 2001;31:469-479.
40. Straus SE. Caring for patients with chronic fatigue syndrome: conclusions in CMO's report are shaped by anecdote not evidence [editorial]. *BMJ.* 2002;324:124-125.