

Chapter 3. Results

In the following results, “k” refers to the number of studies, “t” refers to the number of treatment arms, and “n” refers to the number of patients.

Searches

The numbers of abstracts obtained from all searches are displayed in Figure 2. The primary search in Medline (search window: 1988-2001) yielded 3200 citations and the primary search in Current Contents (search window: 1988-2001) yielded 154 additional citations. PsychINFO was also searched and yielded an additional 398 citations, and 88 citations were identified by manual bibliography checks of accepted studies and recent review articles.

A total of 3,840 abstracts identified from electronic searches and bibliography checks were screened against protocol-defined exclusion criteria. After screening of abstracts for exclusion criteria (Level I screening), 420 were accepted and these full-text papers were retrieved for more in-depth screening (Level II). During Level II screening of full-text papers, 346 were rejected, resulting in a total of 53 accepted studies and 21 kin studies meeting all criteria. The bibliography of accepted studies may be found in Appendix H. Appendix I contains full citations for rejected studies, organized by rejection reason. The most common reason for rejection was lack of data on work or disability status (k=124).

Studies

Evidence Table 1 summarizes the main study-level characteristics of the 53 studies accepted for data extraction, which described a total of 4,558 patients with CFS. In addition, 22 of these studies described healthy controls (n=775). Information on other comparator groups, such as groups of patients with multiple sclerosis or fibromyalgia, was not extracted.

Most studies were conducted in North America (k=30; n=1,942). Twenty were performed in Western Europe (n=1,807), and two in Australia or New Zealand (n=65). One study was multicontinental (n=744).³⁷

Studies of all designs were accepted. Of the 53 accepted studies, 36 were observational (n=3,210) and 17 were interventional (n=1,348). Thirty-one studies were cross-sectional; i.e., reported results at just one timepoint (n=2,664). One study was a retrospective case series (n=94), and there were 21 prospective studies, which included ten RCTs (n=1,042), eight UCSs (n=366), two case control studies (n=321), and one nRCT (n=71).

For acceptance into the database, studies were required to use at least one of the four accepted diagnostic criteria for CFS. Many studies used more than one definition. Twenty-three studies required patients to fulfill the 1988 CDC criteria for CFS, 20 required that patients fulfill the 1994 CDC diagnostic criteria, and 18 studies required that patients meet the Oxford 1991 diagnostic criteria. Only one study used the Australian criteria, but it used the other three criteria as well.³⁷

Study Quality and Validity

Two distinct methods of study quality assessment were performed, and results are displayed in Table 2. In quality scoring, studies were divided into longitudinal vs. cross-sectional design,³⁸ and demonstrated a great deal of variation in quality within each stratum. Many studies did not receive high scores due to lack of sufficient sample size or lack of well-validated measurement instruments. 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. The mean quality score for the ten RCTs was 3.3, on a scale of 0-5, where 5 represents the most robust evidence.³⁹

Patients

Evidence Table 3 shows baseline patient characteristics of all accepted studies. The majority of patients (76 percent) were female. Mean age was reported in 48 studies (n=4,372), and ranged from 24.7 to 46.1 years, with a mean of 38.4 years. Mean duration of CFS in all studies that reported this parameter (k=40, n=3,976) was 5.5 years, and ranged from 1.9 to 8.5 years. Years of education were reported in 14 studies (n=1,310), and ranged from 11.8 to 16.0 years, with a mean of 14.1 years. As shown in Evidence Table 3, the demographic information of the healthy controls was similar to that of the patients with CFS.

To be accepted into the database, studies were required to report data pertaining to employment, but their methods of reporting this parameter varied greatly. Evidence Table 3 summarizes disability information in all of the studies in the database. The total number of employed CFS patients was reported in 35 studies (n=2,652; 42 percent employed). The number of unemployed patients was reported in 37 studies (n=2,720; 54 percent unemployed). The number of studies reporting percent unemployed exceeds the number of studies reporting percent of patients employed by two because one study reported the number of CFS participants not working, and stated that the remainder were either working or not reporting their employment status.⁴⁰ Another study reported the percent of patients disabled, and presumed to not be working, but did not give any information pertaining to the percentage of non-disabled patients who were working.⁴¹ Nine of these studies also reported the total number of healthy controls who were employed and unemployed (n=340; 90 percent employed, 9 percent unemployed). These results do not total to 100 percent 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 CFS patients and controls. In 16 studies reporting this measure, only 19 percent of 967 CFS patients worked full-time, while in two of these studies, 75 percent of 53 controls worked full-time.

Ten studies (n=511) reported the number of patients who were on disability or temporary sick leave (55 percent), compared with 1 percent of healthy controls (k=2, n=89).

Twenty studies (n=1,919) reported the number of patients who had work limitations due to illness (64 percent), compared with 0 percent of 38 controls in the single study that reported this measure for healthy controls (n=38).

Impairment Domains

Twenty-seven studies reported data in the cognitive domain (including POMS and WAIS), 39 in the disease or symptom severity domain (including POMS and CIS), 12 in exercise testing, nine in the functional domain (including SIP), 15 in the general health domain (including MOS SF-36), 32 in the mental (psychiatric or affective) domain (including BDI and MOS SF-36), and 14 in the physical activity domain (including MOS SF-36 and actometer results).

Key Question 1: Disability and Impairment in CFS Patients

What is the evidence that some individuals with CFS have discrete impairments that are associated with disability? (Note that impairments include both physical and mental impairments).

As summarized in Table 3, 17 studies (n=1,830) reported the incidence of current psychiatric diagnoses in their patients (39 percent). Twelve studies reported the lifetime incidence of psychiatric diagnoses in their CFS patients (65 percent). The most common psychiatric diagnosis was depression. In contrast, four studies (n=200) reported the lifetime incidence of psychiatric diagnosis in their healthy controls (12 percent). While this does not prove an association, it does suggest that patients with CFS have a higher lifetime incidence of psychiatric diagnoses than healthy controls. However, the small sample size prevents drawing any definitive conclusions, and no relationship of psychiatric diagnoses to disability may be established.

Few studies reported the incidence of medical diagnoses in CFS patients. Substance abuse was reported in four studies,^{19, 42-44} in a total of 24 of 250 patients (9.6 percent). Fibromyalgia was reported in four studies,⁴⁵⁻⁴⁸ in a total of 245 of 806 patients (30 percent). One study reported the presence of allergies, in 66 percent of 47 patients; and irritable bowel syndrome, in nine percent of 47 patients.⁴⁸ Mitral valve prolapse was reported in a single study, and occurred in three of 18 patients.⁴⁹ The same study reported hyperlipidemia, in one of 18 patients. Sparse reporting of medical conditions suggests that CFS patients in these studies either do not have concurrent medical diagnoses, or their medical diagnoses are not reported. This may also relate to the fact that certain medical conditions are exclusionary factors in the consideration of CFS.

Evidence Table 4 shows studies that reported both employment status and impairment scales. This table was compiled to see if associations could be demonstrated between employment status and impairment domains in CFS patients. Figures 3 through 6 show scatter plots exploring possible relationships between employment status and scores on various impairment scales, organized by domain. Each scale was standardized to a 0-100 range. For the disease severity scale, high scores corresponded to increased severity. For general health and physical activity, high scores corresponded to improved health or activity. Figure 3 shows the percentage of patients unemployed vs. disease severity, as measured on POMS fatigue and several fatigue severity scales. Figure 4 shows percentage of patients with work limitations vs. disease severity, as measured on POMS fatigue and several fatigue severity scales. Figure 5 shows percentage of patients unemployed vs. scores on general health, as measured on MOS SF-36, self-rating wellness score, and perceived health score. Figure 6 shows percentage of patients unemployed vs. scores on physical activity scales (MOS SF-36, basic Activities of Daily Living, and

actometer). All of these figures display absence of an apparent association between work status and any self-reported impairment domain.

Evidence Table 5 shows the eight studies that reported both impairment in physical domains (physical activity, general health, disease severity, or exercise testing) and percentage of subjects employed, in both CFS patients and healthy controls.^{30, 41, 42, 47, 50-53} Employment data were reported in other studies, but did not include both CFS patients and healthy controls. Significant differences were found between CFS patients and healthy controls on several scales in the physical domain: the MOS SF-36 physical function,^{47, 52} general health,⁴⁷ health perception,⁵² the POMS for fatigue and vigor,^{41, 42, 50} the Profile of Fatigue-Related Symptoms (PFRS) for fatigue and somatic symptoms,⁵¹ SIP for mobility and walking,⁵³ and the CIS for activity.⁵³ The mean scores are shown in Table 5, along with *p* values, when reported. Measures of dispersion were frequently reported in papers, but were omitted from the table because the authors believed that including these extra values would add minimal interpretive value to the table and would do little to enhance the readability of the text. Although CFS patients had significantly different scores from healthy controls in these studies, it should be remembered that all of these scales may be abnormal in patients who are fatigued for any reason. All but three of these eight studies represent estimates of physical impairment based only on self-reported scales by the patient. Only two of the eight studies describe formal objective exercise testing. No significant differences were found between CFS patients and healthy controls in VO₂ max³⁰ or maximal voluntary contraction (MVC) during hand grip exercises.⁵⁰ The percentage of CFS patients who were employed ranged from 13 to 49 percent in these studies, while the percentage of healthy controls employed ranged from 71 to 100 percent. Most of these employment rates include both full-time and part-time work, but the lowest values, for both CFS patients and healthy controls, were from one study that only reported full-time work.⁵¹ No statistical pooling is possible, due to widely divergent study designs and outcomes measured, but the table does suggest that a lower percentage of CFS patients with abnormalities on physical function and fatigue scales are employed compared to healthy controls with normal scores on these scales.

In two studies,^{47, 52} the MOS SF-36 physical function scores showed similar differences between CFS patients and controls. In three studies,^{41, 42, 50} the POMS fatigue scores were also similar in CFS patients. These two measures of physical impairment represent the best available evidence of physical impairment in CFS patients at this time.

In summary, the evidence suggests that some individuals with CFS have self-reported discrete physical and mental impairments, and some individuals with CFS have decreased ability to work. It is not possible, however, to correlate impairments with disability based on the published literature.

Key Question 2: Neuropsychological Tests Associated With Impairment in CFS Patients

What is the evidence that in the CFS population, current neuropsychological tests reliably detect cognitive or affective impairments associated with decreased ability to work?

Evidence Table 6 lists the nine studies that reported both neuropsychological impairment scales and work data in both CFS patients and healthy controls.^{30, 41, 42, 47, 50-53} Significant differences were found between CFS patients and healthy controls on MOS SF-36 mental

health,^{47, 52} POMS confusion and depression,^{41, 42, 50} EAQ and PFRS for emotional distress and cognitive difficulty,⁵¹ SCL 90R depression,⁵² and SIP and CIS concentration.⁵³ POMS for anger/hostility and tension/anxiety were significantly different in CFS patients vs. healthy controls in one study,⁴¹ but not in another.⁴² Cognitive function was significantly different in CFS patients vs. healthy controls in the WAIS digit span forward in one study,⁵⁴ but not in another, in the Hopkins verbal learning.³⁰ One study reported that the POMS tension/anxiety and anger/hostility scores were not significantly different between CFS patients and healthy controls.⁴² The percentage of CFS patients who were employed ranged from 13 to 49 percent in these studies, while the percentage of healthy controls employed ranged from 71 to 100 percent. No statistical pooling is possible, due to widely divergent study designs and outcomes measured, but the table does suggest that CFS patients have a higher frequency of abnormalities on confusion, depression, and concentration scales and lower levels of employment compared to healthy controls.

In two studies,^{47, 52} MOS SF-36 mental health scores revealed similar differences between CFS and healthy controls. In three other studies,^{41, 42, 50} POMS confusion scores and differences with healthy controls are also of similar magnitude. POMS depression is comparable in only two of these same three studies.^{41, 42} This best available evidence suggests that MOS SF-36 mental health and POMS confusion may be the most promising measures of neuropsychiatric status in CFS patients, and may relate to employment status. Individual patient data would be needed to further research this hypothesis.

Figure 7 shows a scatter plot of the percent of patients unemployed vs. the mean depression score, as measured on the BDI, POMS depression, and MOS SF-36 – mental health. The depression scores were standardized to 0 to 100, and lower scores correspond to greater depression. Most of the studies in Evidence Table 6 are represented in this figure, in addition to studies that reported scales in the cognitive or mental domain for CFS patients but not for healthy controls. This figure suggests an association between greater degree of depression and greater percentage of unemployment. It is not possible, however, to determine whether there is a causal linkage between depression and unemployment.

In summary, the evidence suggests that some individuals with CFS have self-reported discrete cognitive or affective mental impairments, and some individuals with CFS also report decreased ability to work. We found no reports examining the relationship (if any) between the patient's perception of potential consequences (e.g., financial gain) and the results of these self-reported impairment instruments.

Key Question 3: Treatments Effective in Restoring Ability To Work in CFS Patients

What is the evidence that in individuals with CFS, treatments are effective in restoring the ability to work?

Evidence Table 7 shows the interventional trials in the database, organized by type of intervention and impairment scale domains. This table was compiled to see if a sufficient number of studies were available to permit study of any associations between intervention and work or impairment domains. However, in no cell of the matrix was there a sufficient number of studies to allow any assessment of association. The most commonly reported scales were in the domains

of disease severity and symptoms (e.g., POMS and CIS) and mental impairment (e.g., BDI and SCL 90R). The most commonly reported interventions were drug therapy (e.g., corticosteroids, mineralocorticoids, and antidepressants) and behavioral therapy. Even for cells in this matrix with three or more studies, there were no apparent consistent associations between domains measured and interventions studied.

Two British studies of CBT^{55, 56} reported work scale data before and after an intervention. In one study,⁵⁵ in which 32 patients received CBT and a tricyclic antidepressant (dothiepin), the mean baseline ability to work score \pm SD (scale range 0-8; decrease = improvement) was 6.31 ± 1.96 , and the mean followup score, six weeks later, was 2.72 ± 2.44 . The number of patients employed at baseline and followup was not reported, but it is possible (although not explicitly demonstrated), that improvement in the ability to work score would be associated with an increase in the number of patients employed.

In the other study,⁵⁶ which was an RCT comparing CBT to relaxation, the Work and Social Adjustment score was reported at baseline and followup, six months later. Again, the scale range was 0-8, with lower scores corresponding to improvement. In the CBT group, the baseline \pm SD was 6.0 ± 1.2 , and the followup score was 3.3 ± 2.2 , while in the relaxation group, the scores were 6.1 ± 1.3 and 5.4 ± 1.8 , respectively. The improvement in the CBT work score was significantly greater than that in the relaxation group work score ($p < .001$). Again, it is likely that improvement in the ability to work score would be associated with an increase in the number of patients employed, although this was not demonstrated.

Only six longitudinal studies reported percentage employment at baseline and followup, as shown in Evidence Table 8.^{26, 57-61} Percentage of CFS patients employed at baseline ranged from zero to 39 percent, and at followup (three to 42 months after baseline), employment ranged from 23 to 53 percent. Interventions associated with increased percentage of employment at outcome included individualized rehabilitation programs,^{57, 58, 60} CBT,⁵⁷ and exercise therapy.⁵⁹ The studies are not comparable, however, due to differences in study design, duration of followup, and types of intervention. Furthermore, up to 29 percent of patients were lost to followup.

Only one study⁵⁷ with a substantial number of patients ($n=51$) and a high validity score (6) showed a substantial increase in percentage of patients working after an intervention, in this case, CBT. We also note that the two observational studies (no specific therapeutic interventions) reporting work outcomes showed a decrease over time in the proportion of CFS patients employed. These two studies, however, had a large percentage of drop-outs at the followup assessment.

In summary, some CFS patients who underwent a variety of interventions ranging from no treatment to individualized rehabilitation programs were able to return to work, but the sample sizes are too small and the study designs too disparate to allow comparisons of different treatments in their association with returning CFS patients to work.

Key Question 4: Characteristics Associated With Improvement in CFS Patients

What patient characteristics best define improvement in functioning or positive outcomes in the CFS population? Where it occurs, how is improvement in functioning related to the ability to engage in work activity?

Evidence Table 9 describes the nine studies that reported the number of CFS patients who were reported by investigators to be improved over time. The table details the interventions used, and compares the baseline characteristics of the patients who improved to those who did not improve.^{26, 43, 45, 49, 55, 56, 61-63} Specific characteristics of interest were mean age, gender, 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 parameters.

Shorter duration of disease was associated with improvement in two studies,^{26, 49} but not in three others.^{55, 61, 62} Gender was associated with improvement in two studies,^{49, 62} but not in two others.^{55, 61} Age was associated with improvement in one study,²⁶ but not in two others.^{61, 62} Education was not associated with improvement in two studies^{61, 62} and marital status was not associated with improvement in one study.⁶²

In four studies, work status was discussed with regard to patient characteristics. These studies were examined to seek characteristics associated with positive work outcomes in the CFS population (Evidence Table 10). In one US study,⁴⁵ 226 CFS patients were contacted 1.5 years after their initial evaluation, and asked to fill out a questionnaire pertaining to their working and level of functioning. None of the baseline demographic, clinical, or psychiatric characteristics were predictive of returning to work. In another US study,⁶⁴ 32 CFS patients were evaluated to identify traits associated with working. Working patients with CFS were more likely to be male, younger, never married, had less severe muscle and joint pain, higher activity levels, and better physical functioning than non-working patients. In the third study, from New Zealand,⁶⁵ 53 CFS patients were questioned regarding their perceptions of health, illness attributions, self esteem, and coping skills, and were followed for six months. Work dysfunction was associated with increased CFS-related symptoms. In a multinational study,³⁷ 744 CFS patients filled out questionnaires that included questions on functional impairment and 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.