

Non-pharmacologic Interventions for CFS: A Randomized Trial

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Abstract Non-pharmacological behavioral treatments for CFS have been suggested as promising. These trials have tested protocols composed of behavioral, cognitive and cognitive-behavioral interventions but there have been few efforts to differentially evaluate their outcomes. The primary purpose of the current study was to evaluate the effectiveness of nurse delivered non-pharmacologic interventions. In the present study, 114 participants diagnosed with CFS were randomly assigned to four 6-month interventions. The interventions were: cognitive-behavior therapy, cognitive therapy, anaerobic activity, and a relaxation control group. The study found that these interventions led to increases in several areas of functioning, with more consistent changes occurring among those participants in the cognitive condition. For the 25 variables in this study, significant change occurred for 28%, 20%, 16%, and 12% of the variables for the cognitive, cognitive behavior therapy, anaerobic activity, and relaxation conditions, respectively. However, the majority of participants

continued to be diagnosed with CFS following the treatment trial. Implications of these findings are discussed.

Keywords CFS · ME · Non-pharmacologic · Treatment · Trial · Cognitive-behavior therapy

Cognitive behavior therapy with graded exercise (CBT) constitutes a non-pharmacologic form of treatment for chronic fatigue syndrome (CFS). This treatment was featured in an influential review article (Whiting et al., 2001). CBT encourages participants to consider the role of social and psychological factors in maintaining symptoms. Using this approach, individuals with CFS are encouraged to engage in gradual and consistent increases in activity and to attempt active strategies in place of activity avoidance as methods to manage symptoms (Surawy, Hackmann, Hawton, & Sharpe, 1995). Other components of this treatment include modifying excessive perfectionism and self-criticism and maintaining an active problem-solving approach when coping with interpersonal and occupational difficulties.

Two randomized controlled trials of CBT (Deale, Chalder, Marks, & Wessely, 1997; Sharpe et al., 1996) reported substantial improvements in physical and role functioning for the majority of treated participants with CFS. In the Sharpe et al. study (1996), 63% of the subjects in the CBT condition (versus 20% of the control group) improved significantly in work status and had considerable reductions in fatigue severity as well. Similarly, in the Deale et al. (1997) clinical trial, 70% of CBT completers (versus 19% of the control group) achieved substantial improvements in physical and role functioning.

In an effort to generalize these findings within less specialized settings using newly trained therapists, Prins

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et al. (2001) found that CBT was more effective than guided support groups for patients with CFS. However, when this study was compared to others that employed more highly skilled therapists, there was a lower percentage of improvement. Severens, Prins, Van Wilt, Van Meer, and Bleijenberg (2004) also reported that a CBT condition was less costly and more effective than guided support groups for patients with CFS. In another intervention study, Powell, Bentall, Nye, and Edwards (2001) compared four conditions: two face-to-face CBT treatment sessions; a similar intervention plus an additional seven sessions by phone; a third intervention that included nine face-to-face sessions; and a control condition. No significant differences were found between the three treatment conditions (69% achieved a satisfactory outcome in physical functioning), but participants with CFS receiving any of the treatments did significantly better than the control group receiving standardized medical care (among controls, only 6% achieved a satisfactory outcome).

Despite improvements found in a number of behavioral intervention studies, other studies have been less successful. A non-randomized CBT group therapy trial (Bazelmans, Prins, Lulofs, van der Meer, & Bleijenberg, 2005) found improvements in fatigue for patients with CFS, but higher functional improvements for the waiting list control condition. Furthermore, physician delivered CBT for CFS participants has not shown efficacy in two studies (Huibers et al., 2004; Whitehead & Campion, 2002). The somewhat different aspects of study design in these trials (i.e., use of a group intervention; physician therapists) may account for the poor outcomes.

Other non-pharmacological intervention studies have emphasized the role of aerobic exercise as the primary intervention. For example, Fulcher and White (1997) compared graded aerobic exercise to flexibility/relaxation training and found that patients with CFS in the exercise group were more likely to rate themselves as “improved” when compared to those in the flexibility/relaxation group (52% vs. 27%). In a later study, Wearden et al. (1998) randomly assigned participants with CFS to receive graded exercise and fluoxetine, graded exercise and a placebo drug, exercise placebo and fluoxetine, or exercise placebo and drug placebo. There was an 18% improvement with aerobic exercise and a 6% improvement with placebo controls. Edmonds, McGuire, and Price (2004) reviewed five randomized controlled trials using exercise and concluded that, although some patients with CFS might benefit from aerobic exercise, these treatments are less acceptable to patients than other approaches such as rest and pacing. They concluded that further randomized studies are needed to determine whether patients who respond to aerobic exercise interventions maintain their gains over time. While aerobic programs often involve efforts to increase

levels of aerobic exercise (e.g., walking), anaerobic intervention programs differ in that they reinforce gradual increases in activity such as stretching and strengthening, where the goal is to increase a person’s ability to become more functional (e.g., being able to stretch to reach a cupboard in the kitchen). Anaerobic programs have not been formally tested in CFS nor have they been compared to graded activity or exercise, which carries the possibility of symptom exacerbation in the view of many patients (e.g., Clapp et al., 1999). If an anaerobic program is more acceptable to patients and holds promise for efficacy, then it would constitute a desirable comparison group to a standard CBT condition.

Only a few studies have compared the relative effectiveness of CBT and exercise interventions for patients with CFS. One published study (Ridsdale, Darbishire, & Seed, 2004) compared two active behavioral interventions, i.e., CBT and graded exercise therapy. This study randomized a diverse group of fatigued patients to graded exercise or CBT in primary care. At an 8-month follow-up, there were no significant differences between the two conditions. In the USA, Donta et al. (2003) randomly assigned over 1,000 individuals with multi-symptom illnesses to one of two groups: CBT plus exercise alone or CBT alone and usual care. There were no significant differences in the proportion of individuals who reported an improvement in physical functioning at a one-year follow-up. The reduced effectiveness of this intervention might have been caused by differences in training and supervision of therapists or use of a heterogeneous group of individuals with both CFS and Gulf War Syndrome.

A third approach to CFS non-pharmacological intervention has used a cognitive therapy model. In contrast to CBT and graded exercise therapy, cognitive therapy (COG) for patients with CFS is designed to reduce stress and re-evaluate maladaptive cognitions which, in principle, might facilitate pleasurable low effort activities, lead to better social relationships, and result in a healthier balance between activity, rest, and leisure. COG might modify the way stressful circumstances are appraised and diminish the way negative emotional responses influence immune dysregulation. Regular relaxation, emotional-regulation training, and learning more adaptive coping responses might also decrease negative emotions. Antoni and Weiss (2003) suggest that these interventions increase a person’s sense of self-efficacy and control. Further, reductions in distress can improve immunologic functioning, perhaps in turn reducing virally associated infections.

In an early study of a narrowly focused cognitively oriented coping skills intervention, Friedberg and Krupp (1994) found a near-significant trend towards reduced depression scores and a significant reduction in maladaptive illness beliefs among patients with CFS. In addition,

Soderberg and Evengard (2001) found that more than half of patients experiencing CFS who were provided with group therapy exhibited improved psychological well-being after adjusting their ambitions and improved symptom coping. In one of the few comparative studies, Ridsdale et al. (2001) found that counseling was as effective as CBT with fatigue patients. Thus, a more generalized type of psychological intervention, such as cognitive coping skills, may hold promise for patients with CFS.

Given the mixed results for these various cognitive and behavioral interventions reported above, it is unclear which type of non-pharmacologic intervention is most effective for participants with CFS. Understanding how non-pharmacological interventions differentially affect participants with CFS might provide insights into the pathophysiology of this illness. This investigation evaluated the differential effectiveness of a comprehensive cognitive behavioral treatment with a graded activity component (CBT), a cognitive therapy treatment (COG), an anaerobic activity treatment (ACT), and an active relaxation (RELAX) intervention. This investigation evaluated the relative effectiveness of these interventions in addressing the physical and emotional symptoms of CFS and overall levels of physical functioning.

Method

Participant Recruitment

Participants were recruited from a variety of sources in the Chicago metropolitan area, including physician referrals. Information about the non-pharmacologic treatment trial study was disseminated to medical colleagues through mailings, phone communication, and invited grand rounds. In addition, study announcements for new participants were placed in local newspapers and recruitment offers were made at local CFS support group meetings. These efforts were continued throughout the study period until the target enrollment numbers were achieved. One hundred and fourteen individuals were recruited and enrolled in the study.

Of the 114 individuals, 46% were referred by physicians, 34% were recruited by media (e.g., newspapers, TV, radio), and 20% stemmed from other sources (e.g., heard about the study from a friend, family member, person in the study). There were no significant demographic differences for participants recruited from these varying sources. Approaches to reduce attrition included use of letters and telephone reminders for all appointments, flexibility regarding working around vacations and medical and other crises, reimbursement for transportation costs, and participant honoraria. Participants received \$75 for completing

the baseline interviews and assessments, and \$75 upon completion of the 12-month follow-up evaluation.

Initial Screening

All participants were required to be at least 18 years of age, not pregnant, able to read and speak English, and considered to be physically capable of attending the scheduled sessions. Persons who used wheelchairs and those who were bedridden or housebound were excluded due to the practical difficulties of keeping therapy appointments. Referrals to local physicians who treat CFS and to support groups were offered to these individuals. After a consent form was filled out, prospective participants were initially screened by the second author using a structured questionnaire. The study was approved by the DePaul University Institutional Review Board.

The CFS Questionnaire

This screening scale was initially validated by Jason et al. (1997). This scale is used to collect demographic, health status, medication usage, and symptom data, and it uses the definitional symptoms of CFS (Fukuda et al., 1994). Hawk, Jason, and Torres-Harding (2007) recently revised this CFS Questionnaire and administered the questionnaire to three groups (CFS, major depressive disorder, and healthy controls). The revised instrument, which was used in the present study, evidences good test–retest reliability and has good sensitivity and specificity.

The CFS Questionnaire was designed to assess the diagnostic criteria for CFS as specified by Fukuda et al. (1994). For each symptom, participants were asked to indicate if the symptom had been present for six months or longer, if the symptom began before the onset of their fatigue or health problems, and how often (never, seldom, often/usually, or always) the symptom is experienced. Participants were also asked to rate the severity of each symptom they endorsed on a scale of 0 to 100, where 0 = no problem and 100 = the worst problem possible. This is a numerical rating scale, which has been shown to be a consistently valid measure of symptom intensity, particularly for pain intensity (Jensen & Karoly, 1992). To be diagnosed with the Fukuda et al. (1994) CFS criteria, participants were required to experience persistent or relapsing fatigue for a period of six or more months concurrent with at least four of eight specific minor symptoms that did not predate the illness. In assessing case definition symptoms, items were designed to measure the severity of the eight minor symptoms (i.e., impaired memory or concentration, sore throat, tender lymph nodes, muscle pain,

multi-joint pain, new headaches, unrefreshing sleep, and post-exertion malaise) as specified by the Fukuda et al. case definition.

Structured Clinical Interview for DSM-IV. Next, a semi-structured psychiatric interview, the Structured Clinical Interview for DSM-IV (SCID) (Spitzer, Williams, Gibbon, & First, 1995) was administered in order to establish Axis I psychiatric diagnoses. The professionally administered SCID allows for clinical judgment in the assignment of symptoms to psychiatric or medical categories, a crucial distinction in the assessment of symptoms that overlap between CFS and psychiatric disorders, e.g., fatigue, concentration difficulty, and sleep disturbance (Friedberg & Jason, 1998). A psychodiagnostic study (Taylor & Jason, 1998) validated the use of the SCID in a sample of CFS patients. Because CFS is a diagnosis of exclusion, prospective participants were screened for identifiable psychiatric and medical conditions that may explain CFS-like symptoms.

These measures were completed at DePaul University and took approximately 2 h. After the initial interview was completed, the participants' information was reviewed to ensure that they met all eligibility requirements. If an individual was eligible for the study, a medical appointment was set up. Conversely, if an individual was not eligible, alternate treatment options were discussed.

Medical Assessment of CFS

The physician screening evaluation included an in-depth medical and neurological history and a general and neurological physical examination. The evaluation also included a structured instrument, a modified version of the CFS questionnaire (Komaroff et al., 1996). This instrument assesses the signs, symptoms, and medical history to rule out other disorders. Relevant medical information was gathered to exclude possible other medical causes of chronic fatigue, including exposure histories to tuberculosis, AIDS, and non-AIDS sexually transmitted diseases. Information on prescribed and illicit drug use was also assessed and recorded. Finally the histories of all symptoms related to CFS were gathered.

Laboratory tests included a chemistry screen (which assesses liver, renal, and thyroid functioning), complete blood count with differential and platelet count, erythrocyte sedimentation rate, arthritic profile (which includes rheumatoid factor and antinuclear antibody), hepatitis B, Lyme disease screen, HIV screen and urinalysis. A tuberculin skin test was also performed. The project physician performed a detailed medical examination to detect evidence of diffuse adenopathy, hepatosplenomegaly, synovitis, neuropathy, myopathy, cardiac or pulmonary

dysfunction. These laboratory tests in the battery were used to rule out other illnesses (Fukuda et al., 1994); in other words, they are used as exclusionary criteria rather than as inclusionary criteria. Twenty-four individuals who were screened were excluded due to a variety of reasons (i.e., lifelong fatigue, less than the required four secondary symptoms of CFS, BMI > 45, melancholic depression or bipolar depression, alcohol or substance abuse disorder, autoimmune thyroiditis, cancer, lupus, rheumatoid arthritis).

Randomization to Study Treatments

After enrollment into the study, each participant was randomly assigned to one of the four non-pharmacologic intervention conditions. Random assignment was done using a random number generator in statistical software (SPSS version 12).

Functional Status

Medical Outcomes Study-Short Form-36 (MOS-SF-36)

The MOS-SF-36 is a 36 item broadly-based self-report measure of functional status related to health (Ware & Sherbourne, 1992). A higher score indicates better health or less impact of health on functioning. An example of a question on this form follows: Does your health now limit you in these activities? Walking one block (Yes, limited a lot; Yes, limited a little; No, not limited at all). Test construction studies for the SF-36 (McHorney, Ware, Lu, & Sherbourne, 1994) have shown adequate internal consistency, significant discriminate validity among subscales, and substantial differences between patient and non-patient populations in the pattern of scores. The SF-36 has also demonstrated sufficient psychometric properties as a measure of functional status in a CFS population (Buchwald, Pearlman, Umali, Schmalings, & Katon, 1996). The MOS Physical Functioning scale was utilized in the present investigation as it has been used in several other CFS outcomes studies (Deale et al., 1997).

Employment Status

This measure of role function consisted of work status (working versus nonworking). Employed included those who were working at least 20 h per week or in school full-time. Unemployed included those who were retired, working fewer than 20 h per week, not in school, or part-time student.

Six-minute Walking Test

As an in vivo behavioral measure of physical functioning, the six-minute walking test (Butland, Pang, Gross, Woodcock, & Geddes, 1982) was used. The test measures the distance walked during a six-minute interval. The test is a useful and reproducible measure of exercise tolerance, provides a simple practical guide to everyday disability, and does not require expensive apparatus (Butland et al., 1982). Exercise intolerance is a key symptomatic feature of CFS (Friedberg & Jason, 1998). Significant improvements in exercise tolerance as measured by the six minute walking test were associated with the successful clinical outcome of a graded activity intervention in CFS (Sharpe et al., 1996).

Fatigue and Pain

Fatigue Severity Scale (FSS)

The Krupp, LaRocca, Muir-Nash, and Steinberg (1989) Fatigue Severity Scale was used to measure fatigue. This scale includes nine items rated on 7-point scales and is sensitive to different aspects and gradations of fatigue severity. Most items are related to behavioral consequences of fatigue. An example of a question from this scale is the following: Fatigue interferes with my work, family, or social life (1 = strongly disagree to 7 = strongly agree). Previous findings have demonstrated the utility of the FSS (Krupp et al., 1989) to discriminate between individuals with CFS, MS, and primary depression (Pepper, Krupp, Friedberg, Doscher, & Coyle, 1993). In addition, the FSS (Krupp et al., 1989) was normed on a sample of individuals with multiple sclerosis, systemic lupus erythematosus, and healthy controls. A study by Taylor, Jason, and Torres (2000) compared the Fatigue Scale (Chalder, Berelowitz, Pawlikowska, Watts, & Wessely, 1993) with the FSS (Krupp et al., 1989) with a sample of healthy controls and a CFS-like group. Within a CFS-like group, the Fatigue Severity Scale (Krupp et al., 1989) was more closely associated with severity ratings for the eight Fukuda et al. (1994) CFS symptoms as well as with functional outcomes related to fatigue.

Brief Pain Inventory

The Brief Pain Inventory (Cleeland & Ryan, 1994) was administered to measure the intensity of pain (pain severity) and the interference of pain in the patient's life (pain interference). Higher scores indicate more severe levels of persistent pain and higher levels of interference with

functioning. An example of an item from this scale follows: During the past 24 h pain has interfered with your general activity (0 = does not interfere to 10 = completely interferes). This measure exhibits adequate levels of reliability to assess pain in non-cancer samples, with coefficient alphas of .70 and above. It also evidences good concurrent validity with other generic pain measures, and has been shown to be sensitive to changes in pain status over time (Keller et al., 2004).

Psychological/Well-Being Assessments

Beck Depression Inventory (BDI-II)

Because depression is the most commonly diagnosed psychiatric disorder in CFS (Friedberg, 1996), a quantitative measure of depression severity was used. Depressive symptomatology was measured with the BDI-II (Beck, Steer, & Brown, 1996), a 21-item self-report instrument with well-established psychometric properties. An example of an item follows: Pick out a statement that best describes the way you have been feeling during the past two weeks, including today: Sadness (I do not feel sad; I feel sad much of the time; I am sad all the time; I am so sad or unhappy I can't stand it). This version of the BDI is more consistent with DSM-IV criteria for major depressive disorder than the earlier version. The BDI-II is the only depression rating scale to be empirically tested and interpreted for both individuals with CFS who were depressed and those that were not depressed (Johnson, DeLuca & Natelson, 1996). Also the BDI-II has shown sensitivity to treatment changes in two cognitive behavioral treatment studies of CFS (Deale et al., 1997).

Beck Anxiety Inventory (BAI)

Anxiety symptoms were measured with the BAI, a 21-item self-report measure with established and replicated construct validity (Hewitt & Norton, 1993; Steer, Clark, Beck, & Ranieri, 1995). An example of an item follows: Indicate how much you have been bothered by each symptom during the past week, including today: Nervousness (Not at all, Mildly, Moderately, Severely). Factor analysis of the BAI and BDI yielded a first-order factor labeled anxiety that had salient loadings for all 21 items on the BAI, but only one item on the BDI. Anxiety symptoms at intake was a predictor of treatment outcome in two cognitive behavioral treatment studies of CFS (Sharpe et al., 1996). Also there is a high frequency of anxiety disorders reported in psychodiagnostic studies of CFS (e.g., Pepper et al., 1993).

Self-efficacy

This self-efficacy measure focused on how much control a person feels with respect to CFS complaints. The ratings from each of the five questions are added, and higher scores indicate higher levels of self-efficacy. An example of an item follows: I think I can positively influence my fatigue (Completely disagree, disagree, neutral, agree, completely agree). Cronbach's alpha reliability ranges from .70 to .77 (Prins et al., 2001). This scale has been used in one of the major trials involving CFS and CBT (Prins et al., 2001).

Perceived Stress Scale

The Perceived Stress Scale (PSS) is a four-item revised version of a previous 14-item measure of global perceived stress. One example of an item is: In the last month, how often have you felt that you were unable to control the important things in your life? (Never, almost never, sometimes, fairly often, very often). The time period that this instrument measured was the previous month (Cohen, Kamarck, & Mermelstein, 1983). The authors report a coefficient alpha reliability of .72 for the four-item short version. The Total Stress score was used in the present study. It has a range from 0 to 16, with higher scores indicating more stress.

Quality of Life Scale

The Quality of Life Scale measures satisfaction with different life activities for individuals with various chronic illnesses (Burckhardt & Anderson, 2003). The scale consists of 16 items answered on a Likert type 1 to 7 scale which measures six conceptual domains of quality of life: material and physical well-being; relationships with other people; social, community and civic activities; personal development and fulfillment; recreation; and independence. Higher scores mean more overall life satisfaction. Participants were asked to circle the number that best describes how satisfied they are at this time (e.g., close relationships with spouse or significant other; choices ranging from terrible to delighted). This scale demonstrated high test–retest reliability for this 16-item scale, and convergent and discriminate construct validity in groups of individuals with various stable chronic illnesses, including post-ostomy surgery, osteoarthritis, rheumatoid arthritis, fibromyalgia, COPD, and insulin-dependent diabetes (Burckhardt & Anderson, 2003).

Global Impression of Change Rating

Overall change was assessed on a 7-point clinician rating scale, ranging from “very much improved” to “very much

worse” (Sharpe et al., 1996). Participants also provided a rating of the treatment effectiveness (ranging from “worse” to “much improved”), satisfaction with treatment (ranging from “very satisfied” to “dissatisfied”), usefulness of treatment (ranging from “very useful” to “not useful”), and level of overall improvement (ranging from “very much improved” to “much worse”).

Treatment Protocols

The 13 session CBT, COG, ACT, and RELAX conditions were conducted during 45 min meetings that were held once every 2 weeks (see Table 1). Two registered nurses with previous training and many years of experience in psychotherapy served as the interventionists. During the first 1.5 years of the study, each nurse implemented two of the interventions (either CBT and RELAX or ACT and COG). At the mid point in the study, re-training occurred, and each nurse was assigned the two interventions that she did not conduct during the first 1.5 years. In this way, each therapist over the course of the study implemented all four treatment modalities. Each of the interventions was individualized, and the exact dose was somewhat different for different members. While interventions were individualized for different participants, these variations were not quantified or documented.

Cognitive Behavior Therapy (CBT)

The CBT treatment regimen was developed in collaboration with Vincent Deary, who has worked for many years with the team that completed a successful controlled clinical trial of CBT in CFS (Deale et al., 1997). This treatment was collaborative, educative, and negotiated with participants based on a comprehensive cognitive–behavioral emphasis. Specifically, participants were asked to evaluate the effect of gradual and consistent increases in activity and utilize strategies other than avoidance. The aim was to show participants that activity levels could be increased steadily and safely without exacerbating symptoms. The 13-session protocol is summarized below.

Sessions 1–3. The first three sessions involved engaging participants in therapy and offering them a detailed treatment rationale. A careful assessment of presenting problems was made, including an analysis of the initial in vivo assessment of participant activity, stress, mood, and fatigue.

Sessions 4–7. During session four, a schedule of planned, graded activity was developed in collaboration with the participant. Initial activity targets were modest, and small enough to be sustained despite fluctuations in

Table 1 Shared and distinct activities among treatment groups

	CBT	COG	ACT	RELAX
<i>Common activities</i>				
Nurse therapist	Yes	Yes	Yes	Yes
13 bi-weekly sessions	Yes	Yes	Yes	Yes
Activity homework	Yes	Yes	Yes	Yes
Future implementation of treatment strategies	Yes	Yes	Yes	Yes
<i>Activities CBT</i>				
Utilize strategies other than avoidance	Yes	Yes	No	No
Activity level increase	Yes	No	Yes	No
Stabilize activity and rest	Yes	Yes	No	No
Schedule of planned, graded activity	Yes	No	No	No
Assertiveness training	Yes	Yes	No	No
Anxiety management	Yes	No	No	No
Stress management	Yes	No	No	Yes
Assessment of activity, stress, mood, and fatigue	Yes	No	No	No
Identify and record NATs homework	Yes	No	No	No
Activity and rest pre-planned, not symptom driven	Yes	No	No	No
Cognitive strategies	Yes	Yes	No	No
Record unhelpful/bad thoughts	Yes	No	No	No
Sleep routine established	Yes	No	No	No
<i>Activities COG</i>				
Activity pacing	No	Yes	No	No
Identify and resolve anger	No	Yes	No	No
Improve frustration tolerance	No	Yes	No	No
Eliminate performance-based self-esteem	No	Yes	No	No
Memory assistance	No	Yes	No	No
Affirmations	No	Yes	No	No
Strategies for preventing and coping with setbacks	Yes	Yes	Yes	No
Teaching coping and stress reduction skills	Yes	Yes	No	No
Rapport building	No	Yes	No	No
Personal illness account	No	Yes	No	No
Relaxation exercises	No	Yes	No	Yes
Cue-controlled relaxation	No	Yes	No	No
Cognitive coping statements	Yes	Yes	No	No
Record daily stress and fatigue	No	Yes	No	Yes
Imagery technique of pleasant mood induction	No	Yes	No	Yes
Discussion of the quality of social support	No	Yes	No	No
<i>Activities ACT</i>				
Measure changes in flexibility and strength	No	No	Yes	No
Complete a daily exercise diary	No	No	Yes	No
Set specific goals	Yes	No	Yes	No
Exercise diary	No	No	Yes	No
Energy system and exercise education	No	No	Yes	No
Prescribing appropriate anaerobic exercise	No	No	Yes	No
Monitoring/maintaining functional gains	No	No	Yes	No
Identify problems with anaerobic exercise compliance	No	No	Yes	No
<i>Activities RELAX</i>				
Progressive muscle relaxation	No	No	No	Yes
Relaxation records	No	No	No	Yes

Table 1 continued

	CBT	COG	ACT	RELAX
Autogenic training	No	No	No	Yes
Breathing focus techniques	No	No	No	Yes
Relaxation in stressful situations	No	No	No	Yes
Yoga	No	No	No	Yes

symptoms. Activity was not always increased immediately. Instead, activity and rest were pre-planned and time-contingent rather than symptom-driven. Activity and rest were divided into small, manageable portions spread across the day. For example, three 5-min walks daily would be scheduled, rather than a 45-min walk once a week. Participants were encouraged to persevere in their predetermined goals. Henceforth, they were instructed to try and avoid both reducing targets on “bad” days, and exceeding them on “good” days. A discussion of negative automatic thoughts (NATs) emphasized their relationship to feelings and behavior (e.g., I always need the approval of others. I can never tolerate being hurt). In addition to activity homework, assignments intended to identify and record NATs were also provided to participants.

Sessions 8–13. NATs were discussed in relation to difficulties with planned activities. After thoughts regarding symptoms, rest, sleep, and high performance expectations were identified, cognitive strategies were then introduced. The aim was to develop new ways of thinking, which would effectively promote recovery. Participants continued to record any unhelpful or distressing thoughts. Furthermore, through discussions and homework, they were encouraged to practice generating less catastrophic and more helpful alternatives. These cognitive strategies focused on fears about symptoms and treatment as well as perfectionism, self-criticism, and unrealistic performance expectations. Once a structured schedule was established and tolerance began to develop, activity was gradually increased and rest was slowly reduced.

Specific daily targets that covered a range of activities (such as walking, reading, visiting friends or gardening) were also agreed upon. Furthermore, a sleep routine was established. This schedule included the cessation of daytime sleeping, the establishment of a set wake-up time every morning, and a general reduction of all time spent in bed. Sleep hygiene and stimulus control techniques for participants with insomnia were also incorporated. In the final sessions, strategies for dealing with setbacks were rehearsed. Participants created action plans and coping strategies to guide them through the coming months. The importance of maintaining the principles of therapy after termination were also reinforced.

Anaerobic Activity Therapy (ACT)

The ACT treatment focused on developing individualized, constructive and pleasurable activities accompanied by reinforcement of progress. Staci Stevens, an exercise physiologist, who has previously worked on similar interventions, supervised this condition.

In order to gain an assessment of flexibility and strength at both pre- and post-test, participants in all conditions completed the shoulder flexibility test, which measures the flexibility in the right and left shoulders. All participants also completed the sit and reach test, which is the most widely used measure of flexibility and a primary component of most physical fitness tests. The test is designed to measure the extensibility of the hamstring muscles and the lower back articulations by evaluating the maximal reach an individual can make in a seated position. This test has excellent test–retest and intra-rater reliability (Gabbe, Bennell, Wajswelner, & Finch, 2004). Finally, all participants completed the hand dynamometer, which measures a person’s grip strength and is a good measure of loss of work capacity (Chengalur, Smith, Nelson, & Sadoff, 1990). It is fast, easy to perform, and produces a reliable report that is simple to record (Innes, 1999). Information from these tests were helpful in guiding the therapists’ 13-session protocol, which is summarized below.

Sessions 1–3. The first three sessions involved engaging participants in therapy and offering them a detailed treatment rationale. The intervention was described to participants as involving activity scheduling and progress assessments. The treatment plan involved three phases: engagement and education, exercise prescription and monitoring, and maintaining functional gains. Behavioral goals for the program were explained to the participants and included energy system education, redefining exercise, prescribing appropriate exercise, increasing selected daily physical activities, and improving quality of life. The participants were assisted in translating these principles to certain physical activities employed in daily living. Participants were shown the principle of specificity in training for achieving functional gains and educated about its integral role within the exercise prescription.

After learning to acknowledge the reality of their symptoms, participants received an explanation regarding

the benefits of the pragmatic rehabilitative approach as well as the exercise model. Exercise progression was also described at this time. Participants were informed about the importance of gradually increasing anaerobic activity levels, and were asked to complete a daily exercise diary. Participants were requested to identify any goals and/or problems that they were experiencing with regards to exercise compliance.

Sessions 4–7. The self-monitoring diaries were reviewed and the rationale for treatment was evaluated. The aim was for behavioral homework to reinforce gradual, consistent increases in selected physical activity and discourage rapid fluctuations in activity. Preliminary targets were set at a safe, achievable level to maximize the likelihood of success. Each individual was given an exercise program that included both pictures and descriptions. Additionally, flexibility and exercise program guidelines were provided along with an exercise diary that detailed each program. This diary had to be attended to daily, and the exercise frequency was fixed at three times per week. The participants were informed that some amount of muscle soreness should be expected as a result of the exercise activity. Participants were also taught the difference between muscle soreness that may be a result of the exercise program and muscle pain. Participants were urged not to progress too quickly by adding their own exercises or excessively increasing intensity levels within normal daily activities. The goal was to reinforce gradual increases in activity rather than to promote sudden amplifications. As an example of stretching and strengthening, the participant would start with one set of four repetitions for each exercise. If the patient was successful with this assignment and felt no physical repercussions or delayed recovery response, they would then be encouraged to gradually progress until there was one set of eight repetitions was reached. Next, the participant would increase to two sets, starting at two sets of four repetitions.

Session 8–13. Homework was reviewed, problems were identified and dealt with, and targets were set for the following week. Preparations were continued for the maintenance of functional gains. New targets were established only after habituation was achieved to existing ones or if the participant consistently achieved his or her goals for a period of two weeks. The therapist conveyed a positive outlook, and all achievements were warmly reinforced. In depth analyses of in vivo activity and symptom records confirmed behavioral progress and identified potential and actual behavioral setbacks. As a result, new behavioral prescriptions with scheduling modifications were developed. In these final sessions, strategies for preventing and dealing with setbacks and relapses were rehearsed. The importance of maintaining the principles of therapy after termination were also reinforced.

Cognitive Therapy Treatment (COG)

This condition, formulated and supervised by Fred Friedberg, a clinical psychologist, incorporated a broad-based cognitive approach that focused on developing cognitive strategies to better tolerate and reduce stress and symptoms, and to lessen self-criticism. Cognitive changes were linked, in principle, to achieving a healthy balance between activity, rest, and leisure.

COG training was focused on treating maladaptive beliefs associated with illness-related depression, anxiety, and anger. It is a credible condition because it involves actively listening to participant's complaints, as well as teaching coping and stress reduction skills. In comparison to CBT and ACT, the COG condition does not include structured schedules of increasing activity or exercise (Deale et al., 1997; Fulcher & White, 1997; Sharpe et al., 1996). Rather, this approach emphasizes pacing activities, which involves trying to remain as active as possible while avoiding over-exertion. Low effort activities that are not associated with symptom flare-ups are selectively increased while symptom-producing activities are decreased or managed more effectively. For instance, activity pacing was applied to completing job or household tasks in energy-conserving small steps that were less likely to produce symptom flare-ups. In a more narrowly focused early version of this protocol (Friedberg & Krupp, 1994), a trend toward reduced depression scores and significant reductions in maladaptive illness beliefs were found. However, there were no changes in functional status. The 13-session COG protocol is summarized below.

Sessions 1–3. During the initial session, the therapist explained the purpose and goals of the intervention. Because of numerous encounters with physicians and others who have treated patients with CFS with condescension and even ridicule (McKenzie, Dechene, Friedberg, & Fontanetta, 1995), rapport building was a critical aspect of the treatment regimen (Deale et al., 1997). As an initial intervention, the participant's personal account of his/her illness, including CFS symptoms and their effects on vocational functioning, marital satisfaction, social relationships, and physical exercise was placed in the context of the four stage progressive model of chronic illness (Fennell, 1995). The model serves as a coping tool that allows the participant to view his/her reactions to the illness as understandable adjustments to an unpredictable, disabling condition. It also allowed the therapist to better target and individualize the coping techniques presented below.

Sessions 4–8. These sessions focused on stress reduction techniques for intrusive illness symptoms and limitations, as well as emotional distress. Initially, relaxation exercises were demonstrated and rehearsed in session. They were

later prescribed for home use with audiocassette tapes. Cue-controlled relaxation was then introduced to create an association between the self-instructed relaxation and the feeling state of being relaxed. Specific relaxation benefits were addressed to the participant so that active use of relaxation as a coping skill (Ost, 1987) was clearly explained. In addition, cognitive coping statements were formulated and prescribed to counteract (1) catastrophic thinking about illness limitations and its vocational and social consequences; (2) symptom-exacerbating self-demands for high achievement; and (3) intolerance of illness symptoms. To encourage practice of these coping skills, daily stress and fatigue records were reviewed to identify stress/symptom associations and then to prescribe relaxation and cognitive coping techniques to ameliorate these symptoms.

Sessions 9–13. As participants incorporated stress management and cognitive coping strategies into their daily routine, the imagery technique of pleasant mood induction was introduced as a method of alleviating depressed mood and uplifting mood in general. Pleasant mood induction involved visualizing enjoyable activities and events that could be performed by the participant, given the limitations of his or her illness. If the imagery exercises succeeded in elevating mood, they were incorporated into daily relaxation practice. The quality of social support was discussed in order to identify maladaptive beliefs that were detrimental to marital, family, and other significant relationships. Once identified, these maladaptive beliefs were used to generate cognitive coping statements that were intended to ameliorate relationship-damaging beliefs. These individually constructed coping statements were assigned as daily homework and were designed to counteract maladaptive thinking about relationships. Such sessions were devoted to the identification of specific cognitive difficulties and exposure to memory compensation and cognitive retraining techniques. For instance, to reduce debilitating feelings of cognitive overload, the participant was encouraged to (1) allow extra time to complete activities, (2) minimize distractions, and (3) watch for signs of increased mental fatigue and take necessary rest breaks. During the final session, the therapist and participant reviewed the course of therapy, including specific coping techniques that were learned and utilized. Improvements were also assessed in light of the four stage progressive model of CFS. Finally, a plan was developed to maintain the effective coping skills gained.

Relaxation Treatment (RELAX)

This condition was based on several prior studies in the area of chronic illness that showed relaxation training to be

an effective means of improving coping skills, reducing sleep disturbances and anxiety, and increasing general well-being and tolerance to illness. Dr. Fred Friedberg also supervised this arm of the study. Several types of relaxation were demonstrated to participants along with expectations for skills practice over a 13-session period.

Sessions 1–3. During the first session, the participant's history was obtained and the rationale for using relaxation techniques to treat CFS was explained. Participants were asked to keep a stress/fatigue diary. During session two, the stress diary was reviewed and the participants were provided an introduction to relaxation. They were shown how to engage in progressive muscle relaxation, and were asked to engage in this relaxation technique twice daily for the next two weeks. During session three, the results of the practice were discussed, and participants were provided more coaching to allow them to effectively practice this technique on their own.

Sessions 4–8. During session four, participants' relaxation records were reviewed as a means to assess the effectiveness of the progressive muscle relaxation techniques. Autogenic training was introduced, and practice sessions were devoted to this relaxation technique. Homework assignments were given to the participants, and they were encouraged to record their efforts to engage in this relaxation response. Breathing focus techniques were also introduced, and participants were asked to practice these techniques at home.

Sessions 9–13. During session 9, breathing focus homework was reviewed for compliance and effectiveness. Yoga form stretching was next introduced and offered in session and debriefed. Thematic imagery relaxation was subsequently demonstrated, and participants were asked to practice this relaxation technique at home. Participants were also shown how to use relaxation during stressful situations. For the last session, there was a review of the most helpful relaxation techniques that had been covered in the prior sessions. Progress made in therapy was reviewed, and a post-treatment relaxation program was developed in collaboration with the participant.

Participation

Participants attended an average of 10 sessions out of a possible 13 sessions, with a range from 1 to 13. There were no significant differences between the conditions in regards to how many sessions were attended. The average dropout rate was 25%, but it was not significantly different per condition. Dropouts were conservatively defined as attending four or fewer sessions or stopping therapy prior to satisfactory completion of therapy (as rated by the therapist, Project Director and Principal Investigator).

This definition has been used by others and is very conservative. These dropout rates are comparable to other clinical trials with CFS (Whiting et al., 2001). For example, among CBT and ACT trials in patients with CFS, drop-out rates of 28% (Prins et al., 2001), 29% (Wearden et al., 1998), 34% (Ridsdale et al., 2001), 34% (Ridsdale et al., 2004), and 39% (Akagi, Klimes, & Bass, 2001) have been found. The only US based study of CFS among Gulf War Veterans using CBT and graded activity actually found that only 30% of participants adhered to the treatment (Donta et al., 2003).

Statistics

The Best Linear Unbiased Predictor is an estimator that follows from the Laird and Ware random effects model (Robinson, 1991). In other words, this value represents a slope of the raw data over time. Within each person, there will be in the current study up to four values (baseline, post-test, 6 and 12 month follow-up). The Best Linear Unbiased Predictor is the slope of those four values, but if there are only two or three values, a slope can still be determined for that case. What this allows is for a slope for every case with at least two data points. The Laird and Ware random effects model is well established in the statistical literature (Laird & Ware, 1982). The analyses here are modeled after those presented by Gould, Abramson, Galasko and Salmon (2001), who indicate that the Best Linear Unbiased Predictor is an unbiased estimator of the population mean and is a linear combination of the observations. It minimizes the mean squared error (MSE), where the mean is taken across all individuals in the population.

Results

Sample

There were 29 participants each in the CBT and ACT conditions and 28 in the COG and RELAX conditions. There were no statistically significant socio-demographic differences among these groups at baseline. Of the 114 participants, 16.7% were male and 83.3% were female. The average age at baseline was 43.8 years. Regarding ethnicity, 87.7% were Caucasian, 4.4% were African-American, 4.4% were Latino, and 3.5% were Asian-American. As for marital status, 49.1% were married/living with someone, 33.3% were single, and 17.6% were either divorced or separated. In terms of work status at the baseline, 24.6% were on disability, 23.7% were unemployed, 20.2% were working part-time, 19.3% were working full-time, 6.1% were retired, 4.4% were part-time students, .9% were full time students, and .9% were working part-time and on disability. In terms of education, 47.4% had earned a

standard college degree, 21.8% had a graduate or professional degree, 21.1% had partial college, and 9.7% had a high school/GED degree or less. In regard to psychiatric co-morbidity, 62.3% had a lifetime Axis I diagnosis, and 38.6% had a current Axis I diagnosis (depressive and anxiety disorders were most common).

Fidelity Ratings

In order to verify the distinctiveness of the behavioral treatments, a validation study was completed using a fidelity rating scale developed for this study. A random sample of audiotaped sessions were selected, and each session was rated to the degree that the therapists exhibited behaviors and introduced techniques that were unique to each of the four treatment conditions. Fidelity ratings were implemented in order to monitor the consistency of implementation of the different treatment conditions, as specified in each treatment manual, and to ensure that the treatment conditions were in fact distinct. Ratings were conducted by a licensed psychologist and a master's level psychologist, both of whom were familiar with CFS and who had training and experience in cognitive behavior therapy techniques.

First, inter-rater reliabilities were computed for 34 audio taped treatment sessions to ensure an acceptable level of inter-rater reliability. For these sessions, median inter-rater percent agreement for item reliability was .79, and these were at an acceptable level (Steve Hollon, personal communication reference, June 17, 1998).

Next, mean scores for 46 rated sessions indicated that the four treatment conditions were significantly differentiated by the questions tapping the corresponding categories (see Table 2). There was some overlap between the COG and CBT conditions, but that is because the COG condition includes CBT cognitive issues. *T*-tests indicated that the majority of the items that reflected the various cognitive-behavioral techniques in fact discriminated between the conditions at the $p < .05$ level. This suggested that the therapists implemented the treatment conditions as specified by the treatment manual. Further, high ratings on each set of items were in the expected direction for each treatment condition, when assessed by a clinical expert in cognitive-behavior therapy. Thus, our fidelity rating scale analyses indicated that the four treatments arms were distinct and were implemented as specified in the corresponding treatment manuals for each condition.

Outcome Data

The Best Linear Unbiased Predictors represent estimates of random effects, which are the within-person slopes.

Table 2 Fidelity ratings across four conditions

	CBT	COG	ACT	RELAX	F-value
<i>CBT questions</i>					
Did the therapist discuss a rationale for a graded activity technique(s)?	2.82 ^{abc}	1.00 ^a	1.00 ^b	1.36 ^c	5.47*
Did the therapist discuss initial assessment data in order to establish a consistent baseline routine?	2.55 ^{abc}	1.00 ^a	1.10 ^b	1.07 ^c	4.16*
Did the therapist discuss or assign a schedule of gradually increased activity?	2.64 ^{abc}	1.00 ^a	1.10 ^b	1.07 ^c	4.70*
Did the therapist identify beliefs related to the dangers of increasing activity such as the occurrence or intensification of symptoms?	1.36	1.00	1.20	1.07	1.33
Were new cognitive strategies to reduce fears about symptoms discussed or assigned?	1.18	1.00	1.00	1.00	1.07
How much did the therapist focus on maintaining activity assignments regardless of symptom fluctuations?	1.91	1.00	1.40	1.00	2.08
Mean for all CBT questions	2.07 ^{abc}	1.00 ^a	1.13 ^b	1.10 ^c	6.95**
<i>ACT questions</i>					
Did the therapist discuss a rationale for an anaerobic exercise(s)?	1.09 ^a	1.71 ^b	5.00 ^{abc}	1.00 ^c	31.55***
Did the therapist demonstrate in session or explain to the client how to do an anaerobic exercise?	1.00 ^a	1.00 ^b	4.40 ^{abc}	1.00 ^c	15.75***
To what extent did the therapist focus on individualizing an anaerobic exercise prescription for the client?	1.00 ^a	1.00 ^b	5.70 ^{abc}	1.00 ^c	75.40***
To what extent did the therapist troubleshoot client problems with anaerobic exercise?	1.00 ^a	1.00 ^b	5.50 ^{abc}	1.43 ^c	28.91***
Mean for all ACT questions	1.02 ^a	1.11 ^b	5.15 ^{abc}	1.10 ^c	53.57***
<i>COG questions</i>					
Did the therapist discuss a rationale for a coping skills technique(s)?	1.55 ^a	4.45 ^{abc}	1.00 ^b	1.00 ^c	19.78***
Did the therapist explore with the client a general belief that underlies many of the client's specific negative thoughts and beliefs?	3.45 ^{cd}	3.45 ^{ab}	1.20 ^{ac}	1.00 ^{bd}	6.71***
Did the therapist and client practice possible rational responses to the client's negative thoughts or beliefs?	1.82 ^a	2.91 ^{abc}	1.40 ^b	1.07 ^c	3.85*
Did the therapist explore with the client how the client's way of communicating affects her/his interpersonal relationships?	1.73 ^{abc}	1.18 ^a	1.00 ^b	1.14 ^c	3.00*
Did the therapist encourage the client to consider potential options for dealing with an interpersonal problem (or role expectation issue within a relationship)?	2.91 ^{cd}	2.36 ^{ad}	1.00 ^{ac}	1.21 ^{bd}	4.11*
Did the therapist discuss or assign reductions in family, social, vocational, recreational, or exercise activities?	2.91 ^{ab}	2.18	1.40 ^a	1.36 ^b	2.96*
Did the therapist encourage the client to engage in activities (other than a relaxation exercise) which would be pleasurable?	3.27 ^a	2.91 ^b	1.10 ^{ab}	1.93	2.90*
Mean for all COG questions	2.52 ^{ad}	2.78 ^{bc}	1.16 ^{ab}	1.24 ^{cd}	12.83***
<i>RELAX questions</i>					
Did the therapist discuss the rationale for using a relaxation exercise?	2.00 ^a	2.55	1.00 ^b	4.14 ^{ab}	4.93**
Did the therapist administer a relaxation technique to the client during the session?	1.00 ^a	2.09 ^b	1.00 ^c	6.14 ^{abc}	26.69***
Did the therapist discuss or assign relaxation exercises as homework?	1.82 ^a	2.82 ^{bd}	1.00 ^{cd}	5.50 ^{abc}	11.88***
To what extent did the therapist troubleshoot client problems with a relaxation exercise?	1.18 ^a	1.91 ^b	1.00 ^c	5.07 ^{abc}	25.60***
Mean for all RELAX questions	1.50 ^a	2.34 ^{bd}	1.00 ^{cd}	5.21 ^{abc}	27.16***

Table 2 continued

	CBT	COG	ACT	RELAX	F-value
<i>General therapeutic skills</i>					
How much rapport was there between therapist and client (i.e., how well did the therapist and client get along)?	6.45	6.73	6.60	6.50	0.33
Did the therapist convey that she/he understood the client's problems and is able to help the client?	6.55	6.45	6.50	6.36	0.14
How interesting is the therapist's style of communication?	4.64	5.18	5.60	4.86	2.78
Did the therapist convey warmth?	6.64	6.55	6.10	6.50	1.12
Was the therapist empathic toward the client (i.e., did she/he convey an intimate understanding or sensitivity to the client's experiences and feelings)?	6.91	6.73	6.50	6.21	2.62
How much did the therapist talk?	3.89	4.00	4.70	4.21	2.32
How much did the therapist direct or guide the session in an explicit way?	4.91	4.73	4.90	5.36	1.25
How involved was the therapist?	6.82	7.00 ^a	7.00 ^b	6.64 ^{ab}	3.13*

In each row, cells with the same superscript are significantly different at the .05 level

* Significant at .05; ** Significant at .01; *** Significant at .001

Tables 3 and 5 provide the means of these slopes across all persons within conditions. The slope represents change per month, and statistical analyses were conducted on the slope values. Values with a negative sign indicate a decrease per month over time in the measure, whereas values with a positive sign indicate an increase per month over time in the measure (see notes at the bottom of the tables to see whether decreases or increases are considered positive for particular variables). Tables 4 and 6 provide the baseline and 12 month follow-up means and standard deviations. As an example, for physical functioning, the COG condition had a score of .82 in Table 3, which means that there was an average of .82 change for each of 18 months of the study, or an average change of 14.76 (.82 × 18) on the physical functioning scale for that condition over the 18 month period of the study. The difference score on the COG physical functioning variable based on Table 4 would result in a slightly different value (15.91), and this is because a difference score based on two numbers (baseline versus 12 month follow up) differs from a slope value that has four data points (baseline, post-test, 6 and 12 month follow up). Similar calculations from Tables 4 and 6 would result in values that differ slightly from Tables 3 and 5 because Tables 4 and 6 use only two data points whereas Tables 3 and 5 use four data points. Significant ANOVAS (at the .05, .01, and .001 levels) across conditions are indicated, and six Tukey pairwise comparisons were conducted if significant treatment effects were found. The only overall significant difference at baseline for the treatment conditions was the self-efficacy scale $F(3,108) = 4.697$, $p < .01$, and post hoc analyses indicated that both the CBT and ACT groups had significantly higher scores on this scale than the RELAX group. Because there were 25 measures in this study, one significant difference would be expected to occur by chance.

Among the dependent measures in Table 3, significant overall differential treatment condition effects were found for the SF-36 Physical Functioning subscale, the Beck Depression and Anxiety Inventories, Self-Efficacy and the BPI severity index. In addition, Table 5 shows that significant effects were found for the following Fukuda et al. (1994) symptoms: sore throat, tender lymph nodes, muscle pain, pain in multiple joints, impaired memory and concentration, post-exertional malaise, and headaches. For each of these measures, with the exception of physical functioning and self-efficacy, lower scores (i.e., more negative slopes) mean change in a more favorable direction. For those variables that were significant, the COG condition had significantly more favorable slope scores on six variables relative to one or more other conditions (physical functioning and depression in Table 3, and in Table 5, the following symptoms: sore throat, pain in multiple joints, impaired memory or concentration, and

Table 3 Summary statistics on Best Linear Unbiased Predictors for non-symptom outcomes

Variables	CBT			COG			ACT			RELAX			<i>F</i> -value
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	
Physical functioning ^B	23	0.67 ^a	0.05	24	0.82 ^b	0.03	23	0.22 ^{ab}	0.18	25	0.43	0.14	5.03**
Fatigue ^A	24	-0.03	0.01	24	-0.02	0.01	25	-0.03	0.01	25	-0.02	0.01	0.47
Depression ^A	23	-0.11 ^{ab}	0.02	24	-0.38 ^{acd}	0.02	21	-0.24 ^{bc}	0.01	24	-0.19 ^d	0.03	19.60***
Anxiety ^A	23	-0.02 ^a	0.04	24	-0.11	0.003	21	-0.03	0.04	24	-0.19 ^a	0.07	3.22*
Self-efficacy ^B	23	-0.004	0.03	24	0.047	0.02	20	-0.04 ^a	0.02	24	0.05 ^a	0.02	3.38*
Stress ^A	23	-0.10	0.03	24	-0.15	0.01	23	-0.06	0.03	25	-0.13	0.04	2.18
Pain severity ^A	23	-0.04 ^a	0.0004	24	-0.03 ^b	0.001	20	-0.02 ^c	0.009	23	0.02 ^{abc}	0.007	20.27***
Pain interference ^A	22	-0.05	0.01	24	-0.03	0.002	20	-0.02	0.03	23	0.01	0.02	1.75
Quality of life ^B	23	0.10	0.07	23	0.15	0.04	21	0.06	0.10	23	0.25	0.17	0.61
6 min walk ^B	20	10.90	6.27	20	6.89	1.80	15	2.40	1.33	18	6.20	0.16	0.88

^A Lower scores indicate better outcome

^B Higher scores indicate better outcome

In each row, cells with the same superscript are significantly different at the .05 level

* Significant at .05; ** Significant at .01; *** Significant at .001

post-exertional malaise). By comparison, the RELAX condition had the highest slope change scores on three variables relative to one or more other conditions (anxiety, muscle pain, and headaches). The CBT condition only had the highest slope change score on pain severity, and there was no variable demonstrating highest change for the ACT condition (although this condition had the second best scores on depression, sore throat, and headaches).

In addition, while there were no significant differences among conditions for a number of the variables in Tables 3 and 5, for the following variables, there was overall significant positive change over time: Fatigue Severity Scale, Perceived Stress Scale, 6 min walk, and severity ratings for unrefreshing sleep. In general, the participants across the conditions evidenced positive change over time.

For the physical functioning variable, the COG and CBT change scores were significantly higher than the ACT condition. For the BDI-II, the COG change scores were significantly better than the other three conditions, and the ACT was significantly better than the CBT. For the BAI, the RELAX condition was significantly better than the CBT. For self-efficacy, the RELAX condition was significantly better than the ACT condition. For pain severity, the CBT, COG, and ACT conditions did significantly better than the RELAX condition.

When examining the Fukuda symptom data, the COG condition had significantly more improvement in sore throat severity than the CBT condition. For tender lymph nodes, there were no significant differences between conditions. For muscle pain, the RELAX condition did significantly better than the three other conditions, and the COG did significantly better than the ACT condition. For pain in multiple joints, the COG condition did significantly

better than the three other conditions, and the CBT and ACT conditions did significantly better than the RELAX condition. For impaired memory, the COG and CBT conditions had significantly more improvement than the RELAX condition. For post-exertional malaise, the COG and CBT conditions did significantly better than the ACT condition. Finally for headaches, the RELAX and ACT conditions had significantly more improvement than the CBT condition.

Employment Changes

Because employment data were dichotomous, a GENMOD procedure was employed using SAS to analyze these data. No significant interaction effects were found, although those in the CBT condition reported directionally more change over time (percent employed increased from 45% at baseline to 62% at the 12 month follow-up) than those in the other three conditions (COG percent employed went from 50% to 56%; ACT from 41% to 33%; and RELAX from 46% to 43%).

Clinical Significance

White, Sharpe, Chalder, DeCesare, and Walwyn (2007) have recommended using the Physical Functioning subscale of the Medical Outcomes Survey-SF-36 as a primary outcome measure for CFS trials. In addition, Ferguson, Robinson, and Splaine (2002) have recommended using the Reliable Change Index (RCI), which evaluates the magnitude of change scores necessary for a measure to be

Table 4 Means (and SD) for baseline and 12-month follow-up for non-symptom outcomes

Variables	CBT		COG		ACT		RELAX	
	Baseline	12 Month	Baseline	12 Month	Baseline	12 Month	Baseline	12 Month
Physical functioning ^b	M (SD) 46.36 (27.44)	58.64 (30.44)	45.65 (23.71)	61.09 (23.74)	39.17 (15.65)	39.72 (27.63)	53.77 (26.66)	61.20 (27.70)
Fatigue ^a	M (SD) 6.05 (0.60)	5.37 (1.19)	6.25 (0.60)	5.87 (1.01)	6.23 (0.85)	5.77 (1.43)	5.82 (0.74)	5.62 (1.06)
Depression ^a	M (SD) 17.00 (11.30)	13.95 (13.08)	19.04 (9.36)	11.86 (7.36)	21.11 (11.22)	16.94 (11.82)	17.45 (6.97)	13.50 (9.97)
Anxiety ^a	M (SD) 12.09 (7.55)	11.45 (10.22)	10.78 (7.34)	8.96 (6.87)	12.50 (7.79)	12.11 (10.08)	14.95 (8.94)	11.41 (10.06)
Self-efficacy ^b	M (SD) 18.50 (2.35)	18.91 (4.37)	17.13 (2.91)	18.00 (3.84)	18.77 (1.52)	19.77 (2.93)	17.14 (2.19)	17.76 (4.15)
Stress ^a	M (SD) 8.96 (1.73)	6.80 (4.30)	8.91 (2.28)	5.91 (3.15)	9.40 (1.46)	8.06 (4.11)	8.45 (1.30)	6.23 (3.21)
Pain severity ^a	M (SD) 4.21 (2.59)	3.56 (2.57)	3.85 (1.94)	3.12 (1.96)	3.97 (2.29)	3.63 (2.72)	4.28 (2.48)	4.60 (2.10)
Pain interference ^a	M (SD) 5.02 (2.90)	4.10 (3.36)	4.02 (2.82)	3.36 (2.74)	3.77 (3.19)	3.75 (3.14)	4.47 (2.76)	4.44 (2.79)
Quality of life ^b	M (SD) 66.14 (15.01)	69.10 (18.99)	70.24 (14.69)	72.52 (10.84)	60.82 (16.43)	63.00 (13.86)	65.75 (19.32)	72.00 (19.70)
6 min walk ^b	M (SD) 1346.35 (296.76)	1542.60 (634.11)	1389.50 (385.51)	1513.50 (270.95)	1335.27 (280.99)	1378.40 (208.92)	1317.78 (296.55)	1429.33 (286.19)

^a Lower scores indicate better outcome

^b Higher scores indicate better outcome

considered statistically reliable. To determine clinical significance of the Physical Functioning subscale, the baseline minus 12-month follow-up change scores need to exceed the age adjusted RCI and the 12-month follow-up scores must fall within the normative value (defined for this study as being within one standard deviation of the mean). Using these two criteria, the CBT, COG, ACT, and RELAX groups achieved clinically significant improvements for physical functioning in 18.2%, 30.4%, 11.1%, and 21.7% of participants, but there were no significant differences among conditions [$\chi^2(3, N = 86) = 2.41, p = .49$].

Participant and Clinician Improvement Ratings

At the 12-month follow-up, participants and clinicians rated participant improvement. As is evident from Table 7, there were few significant changes, although in general the CBT and COG conditions had directionally higher ratings on two of the four participant ratings. The only significant difference, using chi-square analyses, was between participant ratings for level of improvement [$\chi^2(3, N = 83) = 11.11, p = .011$], with the CBT condition yielding significantly higher ratings than the ACT [$\chi^2(1, N = 42) = 9.81, p = .002$] or RELAX [$\chi^2(1, N = 41) = 7.16, p = .007$] conditions. Based on the physician’s diagnosis, the majority of participants continued to have a CFS diagnosis at 12-month follow-up (only four participants from the CBT condition, four from the COG, two from the ACT, and 0 from the RELAX condition no longer met CFS criteria).

Discussion

The present study found few differential results among the non-pharmacologic interventions, although the COG condition appeared to have more positive change than the other conditions. On only three variables was one intervention clearly and significantly different from all of the other three conditions (depression and pain in joints for COG, and muscle pain for RELAX). For the 25 variables examined in this study, when one treatment condition evidenced significant positive change over at least one other condition, seven of these occurrences were for the COG condition, five for the CBT condition, four for the ACT condition, and three for the RELAX condition. In other words, significant change occurred for 28%, 20%, 16%, and 12% of the variables for the COG, CBT, ACT, and RELAX conditions respectively. When examining clinical significance on the Physical Functioning subscale, somewhat similar findings occurred, with 30.4%, 18.2%, 11.1%, and 21.7% of individuals for the COG, CBT, ACT, and RELAX improving.

Table 5 Summary statistics on Best Linear Unbiased Predictors for symptom outcomes^A

Variables	CBT			COG			ACT			RELAX			<i>F</i> -value
	<i>N</i>	Mean	SE	<i>N</i>	Mean	SE	<i>N</i>	Mean	SE	<i>N</i>	Mean	SE	
Sore throat	22	0.22 ^a	0.14	23	-0.64 ^a	0.24	20	-0.17	0.06	22	-0.16	0.07	5.47**
Tender lymph nodes	22	0.06	0.13	24	-0.29	0.12	21	-0.23	0.08	21	0.108	0.09	3.43*
Muscle pain	23	-0.41 ^a	0.07	24	-0.61 ^{bc}	0.02	21	-0.20 ^{bd}	0.14	23	-1.01 ^{acd}	0.11	13.26***
Pain joints	22	-0.52 ^{ab}	0.09	24	-0.97 ^{acd}	0.05	21	-0.31 ^{cc}	0.06	22	0.27 ^{bde}	0.02	77.83***
Impaired memory	23	-0.60 ^a	0.18	24	-0.72 ^b	0.16	21	-0.28	0.24	22	0.09 ^{ab}	0.05	4.66**
Unrefreshing sleep	23	-0.32	0.04	24	-0.53	0.13	21	-0.33	0.27	23	-0.88	0.16	2.60
Post-exertional malaise	23	-1.39 ^a	0.04	22	-1.51 ^b	0.25	21	-0.43 ^{ab}	0.12	22	-1.02	0.25	6.25***
Headaches	23	-0.11 ^{ab}	0.27	24	-0.25	0.21	21	-0.91 ^a	0.12	23	-0.93 ^b	0.05	5.35**

^A Lower scores are better, i.e., a decrease in symptoms over time

In each row, cells with the same superscript are significantly different at the .05 level

* Significant at .05; ** Significant at .01; *** Significant at .001

Table 6 Means (and SD) for baseline and 12-month follow-up symptom outcomes^a

Variables		CBT		COG		ACT		RELAX	
		Baseline	12 Month	Baseline	12 Month	Baseline	12 Month	Baseline	12 Month
Sore throat	M (SD)	24.76 (26.39)	26.43 (33.21)	17.96 (23.49)	10.00 (21.53)	17.78 (19.80)	13.61 (19.08)	23.43 (25.23)	20.95 (25.72)
Tender lymph nodes	M (SD)	33.25 (28.25)	32.00 (35.00)	19.13 (26.27)	16.09 (21.95)	25.79 (34.29)	20.79 (27.50)	18.13 (24.93)	19.75 (27.84)
Muscle pain	M (SD)	63.75 (27.14)	57.50 (32.34)	53.61 (33.18)	40.83 (27.92)	56.71 (36.40)	54.11 (35.50)	60.52 (26.09)	41.36 (33.85)
Pain joints	M (SD)	55.13 (39.46)	45.53 (42.62)	51.87 (31.04)	31.52 (30.47)	45.92 (38.16)	39.74 (41.18)	37.62 (37.57)	41.91 (34.73)
Impaired memory	M (SD)	64.73 (25.07)	53.86 (27.03)	67.83 (24.35)	56.96 (26.27)	64.05 (21.82)	58.47 (29.84)	58.57 (25.11)	59.24 (26.37)
Unrefreshing sleep	M (SD)	82.08 (22.51)	72.95 (27.11)	81.73 (17.24)	69.50 (27.98)	73.05 (27.49)	68.37 (30.86)	79.21 (14.09)	64.09 (31.50)
Post-exertional malaise	M (SD)	77.50 (24.19)	50.68 (31.67)	77.50 (16.47)	49.14 (38.68)	78.42 (15.19)	69.26 (24.63)	67.88 (14.08)	47.25 (36.11)
Headaches	M (SD)	53.18 (33.69)	50.00 (37.26)	41.14 (32.88)	38.36 (39.26)	54.89 (34.23)	37.72 (36.33)	56.93 (31.87)	38.64 (31.86)

^a Lower scores indicate better outcome

It should be mentioned that the changes in the present trial were relatively modest and few participants experienced remission of illness. At the follow-up, there were no significant changes across conditions in the number of participants who were no longer classified as having CFS. These results are consistent with conclusions from other investigators, particularly those that have collected longer term follow-up data. For example, when Deale, Husain, Chalder, and Wessely (2001) conducted a five-year follow-up, only 23% of those provided with CBT said they had completely recovered. Similar erosion occurred in the Sharpe et al. (1996) investigation. In addition, in Van Hoof's (2004) critique of the Prins et al. (2001) CBT trial, the treatment effects were no longer present after three years.

Comparison of our findings with those of earlier studies should not overlook differences in the samples. The current

sample was about 10 years older in age than the other samples of patients with CFS in prominent clinical trials that have reported relatively strong outcomes (Deale et al., 1997; Powell et al., 2001; Prins et al., 2001; Sharpe et al., 1996). In addition, the illness duration of our sample is about 5 years longer than the others. Our sample also had more people working and fewer people on disability than the others. We also have fewer current comorbid psychological diagnoses in our sample than the samples in the Sharpe et al. (1996) and Deale et al. (1997) articles. Our sample had a higher mean Physical Functioning score at baseline than the Powell et al. (2001) and Deale et al. (1997) samples. It is possible that one of the reasons the findings of the present study differ from some of the earlier outcome studies of non-pharmacologic interventions is due to the current sample at baseline being less physically impaired, more likely to be in the work force, and having

Table 7 12-Month follow-up participant and clinician ratings

	CBT (%)	COG (%)	ACT (%)	RELAX (%)
<i>Participant ratings</i>				
I feel—Satisfied by the treatment				
Satisfied—very satisfied	86	86	84	74
Dissatisfied	14	14	16	26
I found the treatment I received				
Useful—very useful	91	86	84	72
Not useful	9	14	16	28
Treatment made me feel				
Better—much improved	78	64	48	42
Worse—unchanged	22	36	52	58
Level of Improvement*				
Improved—much improved—very much improved	86 ^{ab}	64	40 ^a	47 ^b
Much worse—worse—no change	14	36	60	53
<i>Clinician ratings</i>				
Patients improvement in overall functioning has				
Improved—much improved—very much improved	67	68	35	41
Very much worse—much worse—worse—no change	33	32	65	59

* $p < .05$

In each row, cells with the same superscript differ significantly at the .01 level

less psychiatric co-occurring disorders. If they were healthier at the beginning of the study, and less likely to be out of the workforce and on disability, it is possible that some were over-extending themselves energy wise, and thus they might have been more likely to benefit from actually reducing their overall activities than increasing them.

With regards to illness duration, Van der Werf, de Vree, Alberts, van der Meer, and Bleijenberg (2002) found that CFS patients with duration less than 15 months had a more favorable outcome than those with a longer duration. Although the average duration of the other non-pharmacologic studies exceeded 15 months, the average duration in our study was still much longer. Along with work status, this might be an important factor to consider when comparing our results to the other studies.

This study along with others suggests that some modest improvements appear to occur over time for participants with CFS provided non-pharmacologic interventions. A model that helps explain why so many different types of non-pharmacologic interventions could be somewhat helpful to patients with CFS has been proposed by Miller and Cohen (2001). They state that when individuals perceive a stressful experience as a significant threat and as exceeding available coping resources, they have negative emotional responses. These negative emotional responses can cause patients to engage in behaviors (e.g., altering sleep patterns, alcohol and tobacco use, decreasing physical activity), which conceivably modify immune responses. In addition, negative emotional states might activate the sympathetic division, whose fibers (descending from the

brain to lymphoid tissues such as bone marrow, thymus, spleen, etc.) could release substances that influence immune responses. Distress also can activate the HPA axis and hormonal products from these systems can dysregulate the immune system. What might be common to the effective non-pharmacologic interventions, whether they involve cognitive, behavioral or relaxation interventions, is that they help patients reduce stress or allow patients to better deal with stressors.

In addition, while CBT interventions have emphasized cognitive and behavioral factors in the etiology and maintenance of CFS (Vercoulen et al., 1998), the stereotype of patients with CFS being perfectionistic and having negative attitudes toward psychiatry has not been supported (Wood & Wessely, 1999). Several investigators have suggested that the central problem with patients experiencing CFS is a psychosomatic preoccupation with one's fatigue (Vercoulen et al., 1998), but Song and Jason's (2005) empirical investigation could not find support for this model. Other approaches to psychotherapy, including Cognitive Coping Skills Therapy (Friedberg & Krupp, 1994), Envelope Theory (Jason et al., 1999), a consumer driven rehabilitation program (Taylor, Jason, Shiraishi, Schoeny, & Keller, 2006), pacing (Goudsmit, 2001), and pacing plus graded exercise (Wallman, Morton, Goodman, Grove, & Guilfoyle, 2004) do not challenge or question patients' beliefs in regards to the cause of CFS, as occurs within some CBT interventions. Instead, these treatments espouse a biopsychosocial approach, which acknowledge biological, psychological, and psychosocial contributions to the expression of the illness.

Given the general positive effects of all the conditions in the present trial, there seems to be considerable merit in further studying approaches that tend to be better accepted by patient groups. These types of non-pharmacologic interventions deal with cognitive restructuring, coping skills, provision of psychological support, and illness education. Results from this study fit well with the latter model of non-pharmacologic interventions as tools to enhance illness management, as this investigation found few rates of full recovery. Other investigations have found somewhat similar non-pharmacologic treatment techniques can assist with illness management of diseases such as breast cancer and HIV/AIDS, and these types of interventions may also affect immunological status (Antoni et al., 2006; McGregor et al., 2004). Thus, these non-pharmacologic therapies might be considered an important management tool that can be utilized as part of a comprehensive plan of medical and psychological treatment for patients with CFS.

While all of the treatments were found to be of modest benefit for individuals with CFS, the COG condition exhibited the most beneficial changes for depression and pain in joints, when compared to the other three treatment conditions. The study results suggest that cognitive therapies, which focus on modifying unhelpful or negativistic illness cognitions and facilitate the use of active, constructive coping skills, might be most effective for treating depression and pain in joints. In addition, this condition had more favorable change when compared to at least one other condition for the following outcomes: physical functioning, pain severity, sore throats, muscle pain, pain in joints, impaired memory, and post-exertional malaise (although for pain severity and impaired memory, these findings were due to comparing the COG to the RELAX condition which evidenced worsening over time). There were several important differences between the CBT and COG therapies in that the COG intervention placed more emphasis on pacing of activities when compared to the CBT treatment. Indeed in the COG therapy, individuals were not instructed to engage in regular amounts of activity, and were not encouraged to engage in regular or sustained physical activity. It is possible that pacing of activity, which puts a strong emphasis on becoming aware of total available energy, managing energy, and not going beyond one's energy limits, may lead to the higher improvements seen in the post-exertional malaise and, ultimately, to better overall physical functioning.

When the authors had initially designed the study, it was hypothesized that the RELAX condition would actually serve as the control condition. However, in an effort to insure that patients attended an equivalent number of sessions as the other conditions, RELAX was considerably strengthened with a variety of activities, and in the end,

became an independent treatment rather than a control condition. Surprisingly, the RELAX group showed stronger relative improvements in anxiety when compared to the CBT group. It might have been anticipated that the cognitive restructuring component of the CBT group would more effectively address negative mood. However, the RELAX group included relaxation techniques that decreased muscle tension, improved bodily awareness, and encouraged mild stretching. It might be that addressing anxiety through active relaxation techniques are an effective behavioral intervention for addressing anxious mood in people with CFS. It is also of interest that the largest gains in self-efficacy occurred for the RELAX condition, particularly when compared to the ACT condition. The RELAX group also had the greatest reductions in muscle pain than any of the other conditions. Regarding headaches, both the RELAX group and the ACT group had more significant overall positive change in headache severity compared to the CBT condition. It might be expected that relaxation could reduce muscle pain. In addition, relaxation and anaerobic physical activities might have decreased headache severity, as headaches sometimes are caused by muscle tension or by negative emotional mood, which were also affected in these two conditions. It should be noted that for the RELAX condition, negative change over time did occur for pain severity, tender lymph nodes, pain in joints, and impaired memory. It is a bit unclear why RELAX would have been effective for the muscle pain and headache symptoms but not in other areas where pain is felt. Still, besides these measures, when inspecting change scores for the RELAX condition, on most measures the changes were in positive directions.

Data from employment status and satisfaction were generally similar to the findings above. There were few significant differences for employment or the participant and clinician ratings among the four conditions at the 12-month follow-up. In general, participants in all four conditions were generally satisfied with the non-pharmacologic treatments and found them to be useful (with ratings in the 70–90%). While participants seemed to have been satisfied with the treatments and found them to be useful, individuals were less likely to indicate that these treatments made them feel better; and clinician ratings of improvements were also generally lower than the treatment satisfaction ratings. Regarding differential effects, significantly higher ratings of level of improvement were found for the CBT condition than the ACT or RELAX conditions. The CBT condition also had directionally more changes in employment than the other conditions. This may be because the CBT intervention incorporated a range of cognitive and behavioral/activity interventions; and exposure to a wider array of treatment techniques might have been perceived as more acceptable and more helpful to individuals in this group.

Previous findings from participant questionnaires and some non-pharmacologic clinical trials regarding the acceptability of non-pharmacologic treatments have produced mixed results. For example, a survey of 3,228 respondents (Preliminary Report, 2001) and a separate survey sponsored by the ME Association (Cooper, 2001) found that graded exercise was felt to be the type of treatment that made more people with CFS worse than any other. Edmonds et al. (2004) reviewed randomized controlled trials of using exercise, and concluded that these treatments are less acceptable to patients than other approaches such as rest and pacing. Recent findings suggest that there might be some patients who are particularly sensitive to exercise exertion, particularly of the aerobic type, and it was for this reason that the present study selected an anaerobic type of exercise. While in healthy controls, exercise increases pain threshold by releasing endogenous opioids and growth factors, individuals with CFS have reductions in pain threshold after modest exercise (Whiteside, Hansen, & Chaudhuri, 2004). Peckerman et al. (2003) have suggested that there might be left ventricular dysfunction in the heart of some patients with CFS, and lower cardiac output could make it difficult for patients to exercise. Black, O'Connor, and McCully (2005) found that 28% on average increases in daily physical activity for a 4-week period among a sample of people with CFS resulted in worsening overall mood, muscle pain intensity, and time spent each day with fatigue. Black and McCully (2005) concluded that patients with CFS developed exercise intolerance as demonstrated by reduced total activity after 4–10 days. Clearly, clinicians and investigators need to closely monitor potentially iatrogenic effects of interventions, and such assessments might help researchers better determine which non-pharmacologic interventions are best delivered to patients with CFS.

Limitations and Summary

There were several limitations in the present study. The sample size for each condition was relatively small, and it is important to attempt to replicate the findings with larger samples. In addition, because there were a large number of measures, some of the significant contrasts could have occurred by chance. Also, individuals with CFS comprise a heterogeneous group. Indeed, subgrouping of individuals with CFS has been recommended in recent research. Unfortunately, due to the small sample size of each treatment condition, subgrouping of individuals based on their particular cluster of symptoms was not possible. In addition, future studies need to collect data concerning whether the treatments and suggested behavior change actually occur outside of the sessions.

Furthermore, our current study provides just data from the post-testing, 6- and 12-month follow-up. Clearly, longer-term follow-up studies are needed before we can draw any firm conclusions on the effectiveness of these non-pharmacologic interventions (Chambers, Bagnall, Hempel, & Forbes, 2006). The absence of a control group also makes it more difficult to know whether changes over time might have occurred in the absence of any interventions. In addition, it is possible that getting the attention of being in the present study might have been therapeutic in itself. However, Cho, Hotopf, and Wessely (2005) reviewed all controlled trials with patients with CFS, and found a pooled placebo response of 19.6%, which is a relatively low placebo response. Relaxation or standard medical care had a low placebo response (14%), oral placebos had a medium placebo response (16.5%), and injected placebos had a high placebo response (24%). These data suggest that patients with CFS have a low rate of spontaneous remission.

In summary, these findings suggest mixed results for these treatment strategies. Modest treatment effects were found for each treatment conditions, and no one treatment strategy was clearly superior to another treatment strategy in all areas. Commonalities across the conditions may have tended to outweigh or mute the impact of differences across conditions. Specifically, the “general therapeutic skills” in Table 2 appear to have been shared across all conditions. In addition, the overlap between the CBT and COG conditions as reflected in the COG questions in Table 2 may have also reduced differences between these conditions. Further, there was low recovery from the illness, and this is in contrast to results from efficacy trials of cognitive behavioral therapies for CFS. Instead, the results suggest that these different treatment techniques may have modest, differential effects on the symptoms of CFS and individualizing a person’s treatment might make sense. For example, individuals whose symptoms include depression might benefit from a cognitive coping skills therapy, whereas individuals with high levels of headaches might benefit most from relaxation techniques. However, more research should be done in order to validate the utility of these specific recommendations for treatment of patients with CFS with different symptom presentations.

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