A Randomized Controlled Graded Exercise Trial for Chronic Fatigue Syndrome: Outcomes and Mechanisms of Change

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Abstract

The aim of this study was to investigate the potential mechanisms underlying the efficacy of graded exercise therapy for chronic fatigue syndrome (CFS). Forty-nine CFS patients were randomized to a 12-week graded exercise programme or to standard medical care. At the end of treatment the exercise group rated themselves as significantly more improved and less fatigued than the control group. A decrease in symptom focusing rather than an increase in fitness mediated the treatment effect. Graded exercise appears to be an effective treatment for CFS and it operates in part by reducing the degree to which patients focus on their symptoms.

Keywords

chronic fatigue syndrome (CFS), cognitive behavioural model, deconditioning, graded exercise therapy, illness perceptions, randomized controlled trial, symptom focusing

CHRONIC fatigue syndrome (CFS) is characterized by ongoing, debilitating fatigue, and a range of other symptoms such as headaches, sleep disturbance, neuropsychiatric difficulties and muscle pain (Fukuda et al., 1994). The illness has a serious impact on the everyday functioning of patients and results in high levels of medical consumption and problems with work. Data collected from tertiary care settings suggest that left untreated, less than 10 per cent of adults with CFS return to pre-morbid levels of functioning, and most patients remain functionally impaired.

To date, the aetiology of CFS remains unclear. Factors such as viruses, immune system and hypothalamic pituitary axis dysfunction have been implicated in the disorder, but no consistent evidence has been produced for a single biological cause (Moss-Morris & Petrie, 2000). In recent years cognitive behavioural models have been proposed which hypothesize that an interaction between cognitive and behavioural factors perpetuates fatigue and disability in CFS (Surawy, Hackmann, Hawton, & Sharpe, 1995; Wessely, Butler, Chalder, & David, 1991). These models propose that in the recovery period following a physiological stressor such as a virus, people may experience symptoms of inactivity or deconditioning such as fatigue and muscle aches as they begin to return to normal levels of activity. People who go on to develop CFS have a tendency to interpret these symptoms as signs of ongoing illness, and in response reduce activity further, resulting in a downward spiral of bursts of activity followed by periods of symptom induced inactivity. Over time these patients develop the belief that they have an ongoing, serious and uncontrollable illness. They believe that too much activity is harmful for symptoms and that the only way to manage their illness is to accommodate to the condition.

Support for this model comes from a recent systematic review of treatments for CFS, which concluded that the most promising findings have been from studies that provided cognitive and/or behavioural interventions. High quality randomized controlled trials of cognitive behavioural therapy (CBT) have shown beneficial results for patients which are sustained over time (Deale, Chalder, Marks, & Wessely, 1997; Prins et al., 2001; Sharpe et al., 1996). However, CBT requires skilled therapist attention, which reduces its feasibility in many health settings.

Graded exercise therapy, a behaviourally based intervention, has also been shown to be effective. Graded exercise relies less on the availability of skilled therapists, making it a more accessible and possibly cost-effective option. The aim of this therapy is to encourage the patient gradually to increase exercise with the emphasis placed on consistency. Initial exercise intensity and duration are prescribed at a level that is determined to be safe and unlikely to exacerbate symptoms in the patient. In turn, the patient is encouraged to decrease the degree to which he or she monitors symptoms to determine activity levels (Fulcher & White, 1998).

To date three published randomized controlled trials conducted in the United Kingdom (UK), have shown benefits for graded exercise as a treatment for CFS (Fulcher & White, 1997; Powell, Bentall, Nye, & Edwards, 2001; Wearden et al., 1998). A Manchester-based study showed that exercise was effective in reducing fatigue six months after the intervention, but showed no effect on disability scores and had a relatively high drop-out rate (Wearden et al., 1998). A London-based study showed that exercise was effective in reducing both fatigue and physical disability, but CFS patients with clinically significant levels of anxiety and depression were excluded from the study. As around 25–40 per cent of CFS patients can be expected to have a comorbid anxiety or depressive condition, it is difficult to generalize these results to the wider CFS population. The most recent study of exercise therapy conducted in Liverpool had particularly convincing results. At one-year follow-up, CFS patients receiving the graded exercise treatment showed significant improvements in fatigue, mood, sleep and disability. However, this exercise trial included a substantial cognitive and educational component so it is difficult to evaluate the effectiveness of the exercise on its own.

Although we now have good evidence to suggest that graded exercise is an effective intervention for at least some CFS patients, the mechanisms behind its efficacy remain unclear. One possibility is that graded exercise improves physical fitness, thus reducing symptoms of deconditioning and preventing the ongoing downward spiral of symptom monitoring and activity reduction. There is certainly evidence that CFS patients show a decreased exercise

capacity when compared to sedentary controls (de Becker, Rocykens, Reynders, McGregor, & de Mierleir, 2000; Fulcher & White, 2000) and that decreased fitness in CFS patients is related to fatigue and physical impairment (Bazelmans, Bleijenberg, van der Meer, & Folgering, 2001). However, this hypothesis may be overly simplistic, as Fulcher and White (1997) found that self-reported improvement following exercise therapy was not related to improvements in physical fitness or strength.

An alternative hypothesis is that gradual increases in exercise help to alter patients' beliefs about their symptoms and illness. A number of studies have shown that CFS patients' negative perceptions of their illness, their tendency to focus excessively on their symptoms and their beliefs that decreasing activity is the way to control symptoms are related to increased fatigue and disability (Heijmans, 1998; Moss-Morris & Petrie, 2001; Moss-Morris, Petrie & Weinman, 1996; Ray, Jefferies, & Weir, 1997; Silver et al., 2002). Graduated exercise may enable patients to be reassured that activity is not harmful and does not exacerbate symptoms. It may also help to alter control beliefs, thereby increasing their confidence to undertake other daily activities and reducing their levels of fatigue and disability.

The principal aim of the current study was to investigate the potential mechanisms or mediators of the efficacy of graded exercise in CFS in a randomized controlled trial. There were two, not necessarily mutually exclusive hypotheses. The first was that graded exercise would lead to a reduction in fatigue and disability through an increase in physiological fitness. The second was that graded exercise would lead to a reduction in fatigue and disability through decreasing patients' tendencies to focus on their symptoms, by increasing their beliefs that exercise can help to control symptoms and by decreasing their illness identity or the number of symptoms they ascribe to their CFS. We also wanted to investigate the effectiveness of a graded exercise intervention in a New Zealand sample of CFS patients. To date all the graded exercise trials have been conducted in the UK. To determine the generalizability of the findings, patients with and without comorbid psychopathology were included.

Method

Participants

Participants were recruited from a specialist CFS private general practice in Auckland, New Zealand. The general practice advertised the fact that the University of Auckland was running a graded exercise study. Patients who were interested in participating contacted the investigators directly. For this reason a response rate could not be obtained.

Patients were eligible if they met the US Centers for Disease Control and Prevention criteria for CFS (Fukuda et al., 1994) and if they were between 18 and 65 years of age. Patients who were unable to undergo exercise testing for medical reasons or who were already performing a consistent and regular exercise programme were excluded from the study. Patients with a concurrent anxiety and depressive disorder were included. Anxiety and depression levels were assessed at baseline using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983).

Our power analysis to determine the number of participants was based on an effect size of .76 calculated from Fulcher and White's (2000) graded exercise study. With power = .80 and alpha = .05, we needed 27 patients in each group.

Fifty-one patients volunteered to participate in the study. All of these patients met CDC criteria for CFS as assessed by the specialist general practitioner and labelled themselves as such. Two of these patients were excluded from the trial, one because she was already exercising three times a week for 30 minutes or more and another because he was obese and deemed a medical risk for exercise testing. Of the 49 patients eligible to participate, 70.9 per cent were female, and 22.4 per cent were unemployed and unable to work due to disability. Ages ranged from 19 to 60 years (mean age 40.9 years). The median duration of illness was 3.08 years, ranging from 6 months to 45 years.

Outcome measures

Global rating of improvement The primary outcome measure was the participants' self-ratings of improvement, based on a measure of overall change. This measure has been used in previous studies examining the effects of a

graded exercise intervention for people with CFS (Fulcher & White, 1997; Powell, 2001). Participants are asked to respond to the question 'how would you rate the change in your CFS in the last three months?' by indicating their response from seven possible scores ranging from 'very much worse' to 'very much better'. In accordance with Fulcher and White (1997) responses were recoded into two variables where responses of 'very much better' or 'much better' were rated as being indicative of clinical improvement and all other responses as showing no improvement.

CFS-related impairment The 14-item Fatigue Scale was selected to assess improvements in CFS-related fatigue. The Fatigue Scale was designed specifically for use with CFS patients, and assesses both mental and physical fatigue. It has been used in all the previous studies examining the efficacy of exercise programmes for CFS (Fulcher & White, 1997; Powell et al., 2001; Wearden et al., 1998) and has good reliability and validity (Chalder et al., 1993). The 0, 1, 2, 3 scoring system was used in the current study.

The physical functioning subscale of the Short Form Health Questionnaire (SF-36) was used to measure physical functioning. The SF-36 has been validated on the New Zealand population and has good internal reliability and stability (Scott, Tobias, Safarti, & Haslett, 1999).

Mediating variables

Physiological assessments In order to assess physical fitness, each participant underwent incremental exercise testing to determine maximum aerobic capacity (VO_2 peak) on a motorized treadmill. Testing was conducted by a research assistant blind to treatment condition. Following a brief warm-up on the treadmill, the walking protocol began at an initial intensity of 4 metabolic equivalents (METS; 1 MET equalling resting energy expenditure) and increased 1 MET every 2 minutes until maximal effort was achieved. Using METS meant that exercise could be adjusted with reference to the participant's weight while maintaining a steady increase. Throughout the test, expired gas was analysed for percentages of oxygen and carbon dioxide, and minute ventilation to give the peak oxygen consumption (L/min) using a Schiller CS100 metabolic analyser. Participants wore a polar heart rate monitor during the test, and HR was recorded every 30 seconds. Due to the fact that few subjects were capable of achieving their age-predicted maximal heart rate or a plateau in oxygen consumption at peak workload, we were unable to achieve a true physiological VO_2 max. Instead VO_2 peak, which measures the highest single oxygen consumption measurement, was used in the present study. While this measurement underestimates the subject's physiological maximum, it does represent the highest level of activity they are able to achieve.

The modified Borg scale was used to measure the rates of participants' perceived exertion (RPE) throughout the exercise test. Participants were asked to rate their perception of effort required on a 10-point scale at 2-minute intervals throughout the test until maximal perceived effort (10) was reached.

Illness beliefs The Illness Perceptions Questionnaire-Revised (IPQ-R) (Moss-Morris et al., 2002) was used to ascertain whether change in patients' beliefs about their CFS mediates the relationships between exercise therapy and outcome. The subscales of the IPQ and IPQ-R (Moss-Morris, 1997; Moss-Morris & Chalder, 2003; Moss-Morris et al., 1996) have been shown to be associated with both fatigue and disability in CFS. Three of the subscales that were hypothesized to change following graded exercise therapy were included. The *identity* section assesses the degree to which patients identify symptoms they experience as being related to their illness. *Treatment control* assesses the degree to which patients believe their treatment helps to control their symptoms while *personal control* measures how much control patients feel they themselves have over the illness.

Symptom focusing This potential mediator was measured using the focusing on symptoms subscale of the Illness Management Questionnaire (Ray, Weir, Stewart, Miller, & Hyde, 1993). The questionnaire was designed specifically for CFS patients and has been shown to have good psychometric properties. Examples of items include, 'I think a great deal about my symptoms', 'I pay close attention to how well or badly I am feeling' and 'you have to realize you are helpless in the face of this illness'. Previous

research has indicated that symptom focusing is related to fatigue levels in CFS (Ray, Jefferies, & Weir, 1995).

Procedure

The Auckland Ethics Committee granted ethical approval for the study. Once patients provided informed consent, they were randomized into either the treatment or control conditions by means of a sequence of computer generated random numbers placed in sealed, opaque envelopes by an independent administrator. Patients in the control group received standard medical care from their CFS specialist physician, while patients in the treatment group received 12 weeks of graded exercise therapy. Three of the 25 patients dropped out of treatment and 3 of the 24 control patients did not return follow-up questionnaires at 12 weeks. Of the patients who dropped out of treatment, one patient stated she was doing well in the programme but had unexpectedly to return home to the United States. Another injured his calf and decided not to continue while the third could not be contacted at the time of follow-up.

Consequently, 88 per cent of both groups completed the fitness assessment and self-report questionnaires at baseline and at 12 weeks (the end of the treatment period). Patients were also sent a 6-month follow-up self-report questionnaire (42 weeks after the baseline assessment). Sixteen exercise patients (73 per cent of completers) returned this questionnaire and 17 (81%) of the controls.

Following the completion of the baseline assessments, patients in the intervention group met with one of the researchers (CS or RT) for an initial one-hour interview. The rationale behind the graded exercise programme was explained using an adapted version of the cognitive behavioural model of CFS. The model focused on the downward spiral of activity reduction, physical deconditioning and symptoms. An individual plan for starting the exercise programme was then developed. The target heart rate for each participant was initially set at 40 per cent of VO_2max (approximately 50 per cent max HR) attained on the treadmill test, to be maintained for 10–15 minutes 4 to 5 times a week.

Exercise goals were set collaboratively between the researcher and participant. Initial exercise intensity and duration were set at a level that had been identified during exercise testing as achievable and unlikely to exacerbate symptoms in the patient. The importance of consistently meeting but not exceeding exercise targets was emphasized so that the amount of exercise undertaken each day was not dependent on symptoms. Participants were issued with a polar heart rate monitor to assess heart rate during exercise sessions. The heart rate monitor served two purposes. It assisted participants to meet but not exceed the prescribed intensity levels, and also provided external monitoring which reduced the likelihood of focusing on, and adjusting exercise intensity in response to bodily symptoms.

Researchers and participants met weekly over a period of 12 weeks to assess progress, provide encouragement and set new exercise goals. During the first six weeks increases focused on duration of exercise rather than intensity. Increases generally involved duration increases of three to five minutes per week. After six weeks, intensity of exercise was gradually increased, aiming for heart rate increases of approximately five beats/minute per week. This gradual increase in intensity was selected to improve subject compliance and confidence, based on the fact that large or sudden increases in exercise intensity induced anxiety and breathlessness in many subjects during baseline testing. The final goal was for each participant to be exercising for approximately 30 minutes for 5 days per week at an intensity level relating to 80 per cent of their expected maximum heart rate (70 per cent of VO_2max).

Both the exercise and the control groups received standard medical care. All patients consulted with the same specialist general practitioner for their CFS. This practitioner offers both individual consultation on an ‘as needed basis’ and education sessions on how to manage issues such as diet, stress and CFS symptoms.

Data analysis

All data analyses were conducted on SPSS version 10. Differences between the groups at time one were tested using independent samples *t*-tests, Mann Whitney U and chi-squared analysis depending on the nature of the data. Differences between the groups on the key binary outcome, self-rated improvement, were

assessed using chi-square analysis. The number needed to treat (NNT) calculation was based on the risk difference of self-rated improved versus not improved participants in each of the groups. Analysis of the outcome data included a completer analysis as well as an analysis on an intention-to-treat basis. Because the key aim of this research was to test mediation, both main effects for group at the completion of treatment and mediation effects were tested using multiple linear regression. Possible baseline differences between the two groups were controlled for by entering baseline variables into the regression analyses. Repeated measures analysis was used to determine whether changes were maintained at the six-month follow-up point.

Results

Testing for group equivalence on the demographic characteristics

Before testing the study's hypotheses, comparisons were made to determine whether the two groups were equivalent with regards to their demographic and psychological characteristics. Table 1 shows that the exercise group were significantly younger on average than the control group. Age was also significantly correlated with three of the four outcome variables with $r = .41$ ($p < .01$) for physical fatigue, $r = .43$ ($p < .01$) for mental fatigue and $r = –.34$ ($p < .01$) for the SF-36 physical functioning subscale. Consequently age was controlled for in the regression analyses testing for group differences on the outcome variables and for mediation effects.

Although there were no statistically significant differences between the groups with regards to length of illness, level of education and gender the data presented in Table 1 show that the control group appeared to have been ill for somewhat longer than the exercise group and that there were more women in this group. However, gender and length of illness were not deemed to be potential confounding factors as there were no significant correlations ($r < .10$) between gender, length of illness and any of the outcome variables.

We also compared the groups on their levels of anxiety and depression. Table1 shows that there were no statistically significant differences between the groups on either the anxiety or depression subscales of the HADS. Using the recommended cut-off (Zigmond & Snaith, 1983) our data showed that 56 per cent of the total sample were either possible or probable cases of psychiatric disorder. With regards to depression, eight participants (three exercise and five controls) fell into the possible depressive disorder category and six (two exercise and four controls) fell into the probable depressive disorder category. This suggests that 30 per cent of the total sample were either possible or probable cases of depression, with probable cases making up 13 per cent. With regards to anxiety, thirteen (eight exercise and five controls) participants fell into the possible anxiety disorder category and six (two exercise and four controls) into the probable anxiety disorder category. This suggests that as many as 42 per cent of the sample were either possible or probable cases of anxiety disorder, with probable cases making up 13 per cent.

Treatment outcome

Our main outcome was the dichotomized self-rated clinical global impression scale. Twelve of the 22 (54.5%) patients who completed the exercise programme rated themselves as 'much' or 'very much' better compared with 5 (23.8%) of the controls. Cross-tabulation using chi-squared

Table 1. Comparison of the demographic characteristics of the exercise and standard care control groups

	Exercise group (n = 25)	*Control group (n = 24)*	*Statistical comparison*
Age (*M*, SD)	36.72 (11.83)	45.48 (10.45)	$t = –2.71$ ($p = .009$)
Length of illness (median, range)	2.67 (.60–20.00)	5.00 (.50–45.00)	$Z = –1.61$ ($p = .11$)
Education (*M*, SD)	4.32 (1.6)	4.26 (1.45)	$t = .13$ ($p = .89$)
Gender (female)	15	19	$\chi^2 = 2.96$ ($p = .09$)
Anxiety (*M*, SD)	6.72 (3.44)	7.17 (3.43)	$t = –.44$ ($p = .67$)
Depression (*M*, SD)	5.70 (2.69)	6.70 (.67)	$t = –1.127$ ($p = .27$)

showed that this difference was statistically significant $\chi^2 = 4.25$ ($p = .04$); NNT = 1/(.55–.24) = 3.2.

We were also interested in determining the acceptability of the graded exercise therapy to the CFS patients. At the end of treatment 68 per cent of the exercise patients rated their exercise therapy as 'effective' or 'highly effective' and the same number rated their exercise treatment as 'better' or 'very much better' than any other treatment they had received to date.

The group means before and after the 12-week exercise period for fatigue and physical functioning are presented in Table 2. Four separate multiple linear regression analyses were used to ascertain whether there were any statistically significant main effects for group on outcome. The outcome or criterion variables were physical and mental fatigue, total fatigue and the SF-36 physical functioning score. The predictor variables entered into all of these analyses were group (dummy coded as 0 for exercise and 1 for controls), age and the baseline score for the particular criterion variable. After controlling for age and possible baseline differences between the two groups, group was a significant predicator in three out of the four regression analyses (see the group standardized beta-weights from these analyses in Table 2). The exercise group scored significantly lower on physical, mental and total fatigue than the control group after the 12-week exercise period. There was no statistically significant effect for group on physical functioning although the exercise group did report higher levels of physical functioning after treatment than did the controls.

Comparability of the current data with previous exercise trials

The graded exercise protocol used in our study was based on Fulcher and White's (1997) protocol. Consequently, we used the outcome data from their completers to ascertain the comparability of our treatment effect. Table 3 demonstrates that both our study and the Fulcher and White study reported that 55 per cent of patients rated themselves as significantly better at the end of the graded exercise treatment. Single samples *t*-tests demonstrated that the sample from our study was significantly less

Table 2. Means and standard deviations for the outcome variables at baseline and after completing treatment. β values provide the group effect on outcome from the regression analyses

	Baseline		*After the 12-week treatment period*		
	Exercise group (n = 25)	*Control group (n = 24)*	*Exercise group (n = 22)*	*Control group (n = 21)*	*β value*
Physical fatigue	14.55 (5.40)	14.61 (4.86)	7.91 (7.06)	14.27 (5.75)	.34 ($p = .02$)
Mental fatigue	9.90 (3.74)	10.74 (3.90)	6.00 (4.06)	10.14 (4.27)	.32 ($p = .03$)
Total fatigue score	24.45 (8.79)	25.35 (8.05)	13.91 (10.88)	24.41(9.69)	.34 ($p = .02$)
SF-36 Physical functioning	53.10 (18.39)	45.65 (21.07)	69.05 (21.94)	55.00 (22.94)	–.10 ($p = .49$)

Table 3. Outcome variables after 12 weeks of treatment for the current study compared to the Fulcher and White (1997) study. *P* values are based on single samples *t*-tests

	After 12 weeks of treatment		
	Exercise group current study (n = 22)	*Exercise group Fulcher and White (1997) study (n = 29)*	*P value*
Self-rated global change score (% improved)	54.5%	55%	
Total fatigue score (*M*, SD)	13.91 (10.88)	20.50 (8.90)	.01
SF-36 Physical functioning (*M*, SD)	69.05 (21.94)	69.00 (18.50)	.99

fatigued at the end of treatment than the Fulcher and White sample but the samples were equivalent on their SF-36 physical functioning scores.

Intention-to-treat analysis

To determine whether drop-outs affected the treatment effects, we completed an intention-to-treat analysis. Patients with missing data were counted as non-improvers on the clinical global impression change score. Time two scores on the other outcome measures were obtained by substituting the missing data with the scores obtained at time one.

Intention-to-treat analysis showed that there was still a statistically significant effect for group on the global impression change score (χ^2 = 4.25; p = .05) with 48 per cent of the exercise group rating themselves as 'much' or 'very much better' compared to 21 per cent of controls. Multiple regression analyses showed that group remained a statistically significant predictor of physical fatigue at time two (β = .30; p = .03). There was also a strong trend for the effect of group on mental fatigue (β = .27; p = .06). The effect for group on physical functioning remained non-significant (β = –.04; p = .76).

Six-month follow-up data

Six-month follow-up questionnaires were returned by 77 per cent of the completers (67 per cent of the people who initially entered the study). At this time point 54 per cent of the exercise group rated themselves as 'much' or 'very much' better compared with 28 per cent of the controls. Figure 1 presents the data for the other outcome measures at the three time points. The Figure shows that the exercise group maintained the gains they had made at the end of treatment. A 2 (group) × 3 (time) repeated measures ANOVA showed that the group by time interaction for physical fatigue was statistically significant suggesting that the exercise group were still less physically fatigued at six months follow-up than controls (F = 3.06; p < .05). However, the group by time interactions for mental fatigue (F = 1.43; p < .25) and physical functioning were not statistically significant (F = 1.08; p < .35).

The effect of exercise treatment on the potential mediators

Multiple regression analysis was used to determine whether exercise treatment had an effect on the proposed cognitive and physiological mediators included in the study. In these analyses, group, age and the relevant baseline variable were entered as predictors and the time two variable was used as the criterion. Table 4 shows the means for these variables across the groups at baseline and after the 12-week treatment period, and the standardized beta weights for the group effect in each of the regressions. The exercise group was significantly less likely to focus on their symptoms after treatment than were the controls. However, group had no effect on patients' control beliefs or their illness identity.

There were also no statistically significant group effects for the physiological variables,

Table 4. Means and standard deviations for the potential cognitive and physiological mechanisms at baseline and after completing treatment. β values provide the group effect on potential mediators from the regression analyses

	Baseline		*After the 12-week treatment period*		
	Exercise group (n = 25)	*Control group (n = 24)*	*Exercise group (n = 22)*	*Control group (n = 21)*	*β Value*
Symptom focus	29.51 (7.59)	29.87 (7.42)	26.15 (5.83)	29.81 (6.91)	.28 (p = .03)
Treatment control	17.64 (3.47)	16.15 (3.33)	18.29 (2.73)	16.81 (2.58)	–.05 (p = .68)
Personal control	23.12 (3.03)	21.48 (4.65)	23.19 2.47	22.57 3.78	.02 (p = .88)
Illness identity	20.80 (4.08)	21.49 (4.79)	20.43 (5.73)	20.91 (5.23)	–.06 (p = .63)
Maximum HR* achieved	166.79 (5.74)	164.72 (6.47)	168.29 (6.50)	156 (7.34)	–.20 (p = .15)
% predicted* maximum HR	93.03 (2.97)	93.30 (3.35)	93.82 (3.47)	87.80 (3.92)	–.24 (p = .13)
VO_2 peak (ml/kg/min)*	31.99 (19.94)	31.02 (21.37)	27.21 (5.53)	25.80 (3.95)	.16 (p = .39)

* n = 14 (exercise group) n = 12 (control group)

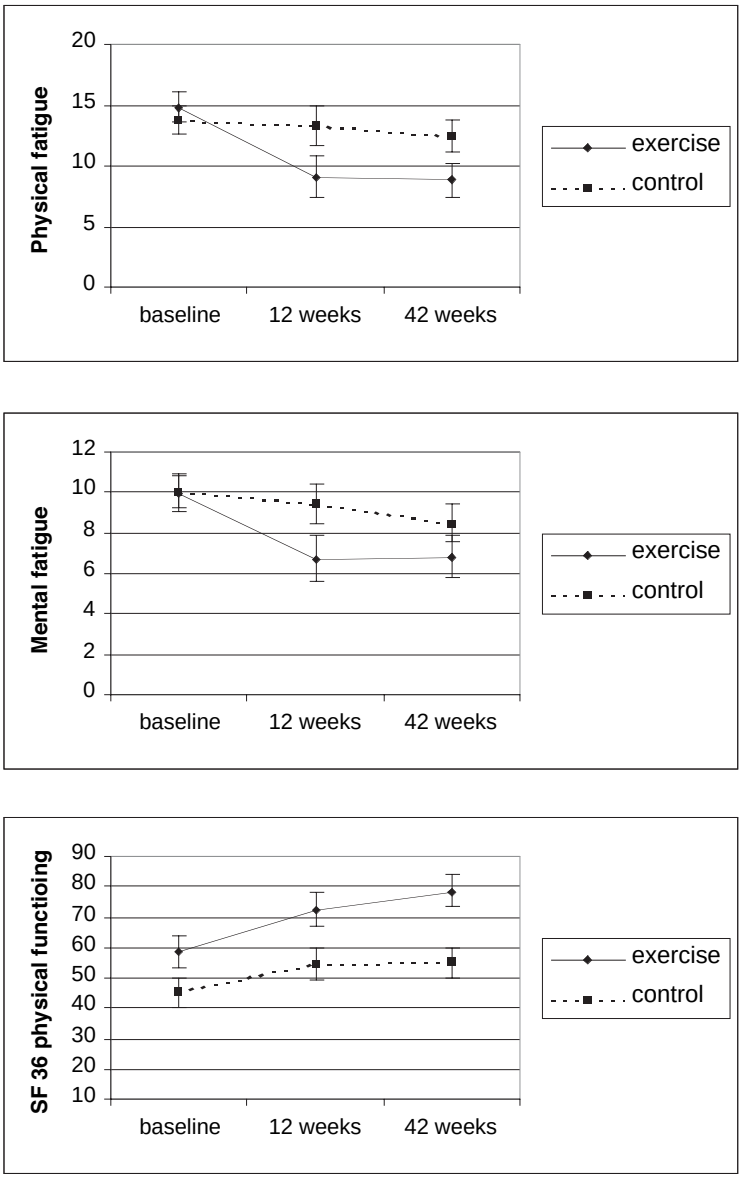

Figure 1. Physical and mental fatigue and physical functionimg across groups at baseline, 12 weeks and 42 weeks.

including the maximum heart rate achieved, the percentage of the predicted maximum heart rate and VO_2 peak. However, the physiological data need to be treated with caution, as complete data were only available for just over half of the sample. This was due to the fact that ten patients refused to have a second test as they believed the initial test was harmful to them, five failed to continue until they perceived themselves to have reached maximal effort, making their data invalid and the data from two patients could not be used due to equipment failure.

One way of dealing with the lack of power owing to missing data is to compute the effect

size of group on the physiological variables. We computed a partial Eta square for each of the physiological outcomes. The effect size for VO_2 peak was .03, for heart rate achieved .09 and for heart rate predicted .11. The effect of group on symptom focusing which was found to be significant was also .11. The conventional cut-offs for small, medium and large values for partial Eta square are .01, .06 and .14, respectively. Consequently, the effect size for heart rate predicted was considered to be large enough to include in the mediation analysis.

Taken together these data suggest that the only variables that could be tested for mediation were symptom focusing and heart rate as a requirement for testing mediation is the existence of a significant relationship between the independent variable (in this case group) and the mediator (symptom focusing and heart rate) (Baron & Kenny, 1986).

Testing mediation effects

Mediation was tested according to the guidelines published by Baron and Kenny (1996). These guidelines specify that the dependent variable (DV) (fatigue) needs to be regressed on the independent variable (IV) (group) and the mediating variable (MV) (symptom focusing) in two separate linear regressions. If both the IV and the MV are significant in these separate regressions, mediation can be tested in a third regression whereby both the IV and the MV compete for the variance in the DV. If the effect of the IV is no longer significant but the MV retains its significance, mediation is deemed to have occurred.

The data from the series of regressions conducted for change in heart rate and then change in symptom focusing on physical fatigue are presented in Table 5. With regards to symptom focusing, both group and change in symptom focusing were independent predictors of physical fatigue in the first two linear regressions. Examination of the beta weights in the third regression showed that both variables remained statistically significant, although the effect for symptom focusing was greater than the effect for group. This suggests that partial mediation occurred, but that exercise treatment and a decrease in symptom focusing both have an independent effect on physical fatigue.

A similar pattern was found for change in heart rate, with the beta weights in the final regression showing a significant effect for change in heart rate but not for group, suggesting a stronger mediation effect. The beta weights for heart rate were in a negative direction suggesting that an increase in heart rate on

Table 5. Series of linear regressions investigating change in percentage heart rate predicted and change in symptom focus as mediators of the relationship between treatment group and physical fatigue outcome

	Change in heart rate (n = 26)			*Change in symptom focus (n = 43)*		
Variables in the regressions	*β*	*Adj. R^2*	*F*	*β*	*Adj. R^2*	*F*
Regression 1 (IV on DV)						
Criterion: physical fatigue at time two						
1. Age	.31*			.31*		
2. Physical fatigue at time one	.27*			.27*		
3. Group	.35**	.30	7.23**	.35**	.30	7.23**
Regression 2 (MV on DV)						
Criterion: physical fatigue at time two						
1. Age	.32			.29*		
2. Physical fatigue at time one	.16			.38**		
3. Change in mediator	–.59***	.48	8.06***	.49***	.41	11.02***
Regression 3 (IV + MV on DV)						
Criterion: physical fatigue at time two						
1. Age	.26			.22		
2. Physical fatigue at time one	.16			.36**		
3. Group	.25			.25*		
4. Change in mediator	–.52**	.51	7.11***	.43**	.46	9.99***

*$p < .05$; **$p < .01$; ***$p < .001$

the second treadmill test was the mediator of change. At first glance this finding appears to be somewhat contradictory. Usually increased fitness is associated with a decrease in maximal heart rate not an increase. The fact that heart rate increased in the exercise group suggests that the change in heart rate was a psychological rather than a physiological response. It may be that patients altered their perceptions in the second test and were able to push themselves to a greater extent.

Table 6 shows true mediation effects for both the mediators on mental fatigue. Group, change in symptom focusing and change in heart rate were independent predictors of mental fatigue in the first two series of linear regressions. In the final linear regressions a decrease in symptom focusing and an increase in heart rate across the programme remained statistically significant but group was no longer significant.

If patients change their illness beliefs and get fitter, do they get greater benefit from the exercise therapy?

Although the intervention did not have a significant effect on fitness or illness beliefs, we were interested to determine whether change in these variables could still predict a better outcome. In other words if patients in the exercise group did alter their beliefs or get fitter did they do better than those who did not?

In order to answer this question, we computed change scores by subtracting baseline scores from the scores obtained at the end of treatment for the cognitive and physiological variables as well as for the fatigue variables and physical functioning. We then computed correlations between change in the proposed mediators and change in outcome for the exercise group. Table 7 shows that decreasing symptom focusing and increasing beliefs in treatment control were significantly correlated with decreased mental and physical fatigue, increased physical functioning and a higher global rating of change. Increasing personal control beliefs was significantly correlated with a decrease in both mental and physical fatigue. Change in illness identity was not significantly related to change in outcome but there was a strong trend suggesting that patients who changed their perceptions about the number of symptoms associated with their condition also decreased their fatigue scores and rated themselves as significantly better after treatment.

With regards to the physiological data, an increase in fitness was non-significantly related to an improvement in both mental and physical

Table 6. Series of linear regressions investigating change in heart rate predicted and change in symptom focus as mediators of the relationship between treatment group and physical fatigue outcome

	Change in heart rate (n = 26)			*Change in symptom focus (n = 43)*		
Variables in the regressions	*β*	*Adj. R^2*	*F*	*β*	*Adj. R^2*	*F*
Regression 1 (IV on DV)						
Criterion: mental fatigue at time two						
1. Age	.32*			.32*		
2. Mental fatigue at time one	.32*			.32*		
3. Group	.23	.30	6.99	.23	.30	6.99
Regression 2 (MV on DV)						
Criterion: mental fatigue at time two						
1. Age	.26			.31*		
2. Mental fatigue at time one	.05			.37*		
3. Change in mediator	–.55	.32	4.60**	.46***	.40	10.42***
Regression 3 (IV + MV on DV)						
Criterion: mental fatigue at time two						
1. Age	.22			.25*		
2. Mental fatigue at time one	.04			.33**		
3. Group	.14			.21		
4. Change in mediator	–.51**	.30	3.51*	.40**	.42	8.88***

*$p < .05$; **$p < .01$; ***$p < .001$

Table 7. Relationships between change in outcome and change in the proposed cognitive and physiological mechanisms across the 12 weeks for the exercise group (n = 22)

	Global change score	*Change in physical fatigue*	*Change in mental fatigue*	*Change in physical functioning*
Change in symptom focus	.61***	.59**	.62***	–.42*
Change in treatment control	–.48**	–.50**	–.52**	.41*
Change in personal control	–.21	–.39*	–.38*	.32
Change in illness identity	.33	–.33	–.31	–.13
Change in maximum HR achieved	–.42	–.54*	–.47*	.54*
Change in % of maximum HR predicted	–.42	–.54*	–.48*	.54*
Change in VO_2 peak (ml/kg/min)	–.12	–.37	–.37	.51*

*$p < .05$; **$p < .01$; ***$p < .001$

fatigue and significantly associated with improvement in physical functioning. In accordance with the mediation data, patients whose maximal heart rate and percentage of predicted maximal heart rate increased at the follow-up assessment showed a significantly greater reduction in fatigue and improvement in physical functioning.

Discussion

The results from this study suggest that a simple graded exercise intervention is a more effective treatment for CFS than standard medical care on its own. Between 50 to 55 per cent of CFS patients reported that they were much or very much better after the 12 weeks of exercise therapy compared to 24 per cent of controls. The intervention produced a statistically significant reduction in patients' physical and mental fatigue and these gains were maintained six months post-treatment. Patients in the intervention group also improved their levels of physical functioning, but not significantly more than the standard care control group. The lack of significant findings in this area may be related to the small sample size. Alternately, it may be that exercise therapy is a more effective treatment for fatigue rather than disability. Wearden et al. (1998) also reported changes in fatigue rather than disability in their CFS graded exercise trial.

Comparisons with Fulcher and White's (1997) data at the end of their 12-week treatment period suggests that the gains made in the current study were equivalent to those of this earlier study in relation to global ratings of improvement and physical disability. The improvements in fatigue appeared to be even greater in the current study. However, patients in the Fulcher and White (1997) study continued to improve over the six-month follow-up period, while the patients in the current study only maintained their improvements. The lack of continued improvement may be a ceiling effect in the current study in that the mean fatigue score at end of treatment was less than 14, the recommended cut-off for case level of fatigue. Alternatively, it maybe that around 40 per cent of patients in the current study had a probable comorbid anxiety or depressive disorder. Fulcher and White (1997) excluded patients with a concurrent depressive and anxiety disorder. Dysphoria measured by the HADS has been shown to predict poor outcome following exercise treatment (Bentall, Powell, Nye, & Edwards, 2002).

The results from this study also suggest that one of the key mechanisms of change during graded exercise therapy is a reduction in the extent to which patients focus on their symptoms. Patients in the exercise treatment significantly reduced the amount they focused on their symptoms, but there was no change on this variable in the control group. A reduction in symptom focusing was strongly associated with a reduction in mental and physical fatigue. It was also related to the self-rated global improvement score and to an increase in physical functioning. This finding is in accordance with a study on CBT for CFS, which showed that CBT was associated with a reduction in beliefs about the harmful effects of exercise and that this reduction was associated with improved outcome (Deale, Chalder, & Wessely, 1998).

Whereas CBT is geared towards directly identifying and challenging fear beliefs, the use

of heart rate monitors in exercise interventions may provide an alternative medium for altering symptom focusing and fear beliefs. In this trial, patients were instructed to use the heart rate monitor, rather than their symptoms, as an external cue to decide whether they were exercising within a safe range.

Graded exercise therapy appeared to be less effective in altering patients' control beliefs or their illness identity. However, if patients did alter these beliefs they did substantially better. Increasing the perception that the illness can be controlled was associated with a statistically significant change in fatigue and disability. There was also a trend suggesting that patients who decreased the number of symptoms associated with their CFS also decreased their fatigue levels and rated themselves as significantly better after treatment. These data suggest that including a cognitive element in the exercise therapy aimed at challenging control and identity beliefs may help to maximize the treatment effect. This idea is further supported by the findings from the Liverpool exercise trial, which reported particularly impressive improvements in their treatment group (Powell et al., 2001). This may be due to the inclusion of structured exercises that helped patients to challenge their negative beliefs about symptoms (Powell, 2001).

With regards to the physiological data, the lack of an increase in aerobic fitness following exercise therapy was unexpected. A similar training programme in CFS patients did manage to show an improvement in fitness (Fulcher & White, 1997). However, three things may help to explain this discrepancy. First, many patients terminated their VO_2 max test for reasons other than maximal effort. As a result less than 25 per cent of VO_2 max tests achieved a true maximum, as defined by physiological responses (Baldi et al., 2003). Consequently, we used VO_2 peak as our measure of fitness. Furthermore, many patients refused to repeat the max test after their intervention, resulting in a large percentage of missing data. Thus, our VO_2 peak data may not accurately reflect adaptations to the training protocol. Second, it was also noted that many subjects had an exaggerated heart rate response to the initial stages of the incremental exercise test, which plateaued during the later stages of the test. While the reasons for this are not known, the 'normal' response to incremental exercise is a linear increase in heart rate. As a result, prescribed exercise intensities, which were calculated as a percentage of maximum heart rate, may have represented a lower relative intensity than expected, which may explain a lack of improvement in aerobic fitness. Third, the first six weeks of our programme focused predominantly on consistency of exercise and it was only in the latter six weeks that intensity was increased. This gentle approach may be important in reducing exercise-related fears in that only 12 per cent of patients dropped out of the treatment. However, it may mean that exercise programmes should be extended a further 6 weeks so that patients have a 12-week period where they work on upgrading their intensity of exercise.

Although there was not an overall effect for fitness, a proportion of patients did get fitter and there was some evidence that this was associated with greater reductions in fatigue and improvements in physical functioning. The strongest association was with physical functioning. This finding was also reported by Fulcher and White (2000) suggesting that physical fitness may be more important in terms of increasing physical capacity than decreasing fatigue.

The physiological change variable that appeared to be most important in terms of treatment response in this study was heart rate. An increase in percentage predicted maximal heart rate after the intervention was found to mediate the group effect on fatigue, particularly mental fatigue. Patients who achieved a higher maximal heart rate on the second test also showed statistically significant improvements in functioning and rated themselves as much improved. This suggests that improvement may be related to an increased ability to exert themselves on the second test. The fact that many patients failed to reach true maximum suggests that fear of exertion may be a problem. Reducing this fear through graded exercise may be reflected in an increase in the maximal heart rate achieved.

Certain limitations of the study should be noted. The sample size was smaller than anticipated which could have affected our power to detect significant differences and to test for mediation. Recruitment was severely handicapped by the appearance of an Australian

article in the lay CFS literature suggesting that exercise therapy for CFS patients was harmful and should be avoided. As all the patients were volunteers, they may reflect a small proportion of patients who are prepared to engage in the therapy. The exercise testing proved to be particularly difficult with this population suggesting that future studies may be better to rely on submaximal tests to collect more complete and accurate fitness data.

Despite these limitations, this study adds to the growing body of literature suggesting that graded exercise therapy is an effective treatment for CFS. It appears to have a particularly significant impact on fatigue and global ratings of improvement and less impact on physical functioning. The key mechanism for improvement appears to be psychological rather than physiological. A reduction in symptom focusing and an increased ability to exert oneself were significant mediators of the treatment effect. Using heart rate monitors may help to facilitate this process. Improving aerobic fitness appears to be less important as treatments gains were made independently of improvements in aerobic fitness. However, if patients do get fitter, they appear to make significant improvements in their physical functioning.

References

Baldi, J. C., McFarlane, K., Oxenham, H. C., Whalley, G. A., Walsh, H. J., & Doughty, R. N. (2003). Left ventricular diastolic filling and systolic function of young and older trained and untrained men. *Journal of Applied Physiology*, *95*, 2570–2575.

Baron, R. M., & Kenny, D. A. (1986). The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology*, *51*, 1173–1182.

Bazelmans, E., Bleijenberg, G., van der Meer, J. W. M., & Folgering, H. (2001). Is physical deconditioning a perpetuating factor in chronic fatigue syndrome? A controlled study on maximal exercise performance and relations with fatigue, impairment and physical activity. *Psychological Medicine*, *31*, 107–114.

Bentall, R. P., Powell, P., Nye, F., & Edwards, R. H. T. (2002). Predictors of response to treatment for chronic fatigue syndrome. *British Journal of Psychiatry*, *183*, 248–252.

Borg, G. A. V. (1982). Psychophysical bases of perceived exertion. *Medical Science of Sports and Exercise*, *14*, 377–381.

Chalder, T., Berelowitz, G., Pawlikowska, T., Watts, L., Wessely, S., Wright, D., & Wallace, P. (1993). The development of a Fatigue Scale. *Journal of Psychosomatic Research*, *37*, 147–153.

Deale, A., Chalder, T., Marks, I., & Wessely, S. (1997). Cognitive behavior therapy for chronic fatigue syndrome: A randomized controlled trial. *American Journal of Psychiatry*, *154*(3), 408–414.

Deale, A., Chalder, T., & Wessely, S. (1998). Illness beliefs and treatment outcome in chronic fatigue syndrome. *Journal of Psychosomatic Research*, *45*, 77–83.

De Becker, P., Rocykens, J., Reynders, M., McGregor, N., & de Mierleir, K. (2000). Exercise capacity in chronic fatigue syndrome. *Archives of Internal Medicine*, *160*, 3270–3277.

Fukuda, K., Straus, S. E., Hickie, I., Sharpe, M. C., Dobbins, J. G., & Komaroff, A. (1994). The chronic fatigue syndrome: A comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Annals of Internal Medicine*, *121*(12), 953–959.

Fulcher, K. Y., & White, P. D. (1997). Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. *British Medical Journal*, *314*(7095), 1647–1652.

Fulcher, K. Y., & White, P. D. (1998). Chronic fatigue syndrome: A description of graded exercise treatment. *Physiotherapy*, *84*, 223–226.

Fulcher, K. Y., & White, P. D. (2000). Strength and physiological response to exercise in patients with chronic fatigue syndrome. *Journal of Neurology, Neurosurgery and Psychiatry*, *69*, 302–307.

Heijmans, M. J. (1998). Coping and adaptive outcome in chronic fatigue syndrome: Importance of illness cognitions. *Journal of Psychosomatic Research*, *45*, 39–51.

Moss-Morris, R. (1997). The role of illness cognitions and coping in the aetiology and maintenance of the chronic fatigue syndrome. In K. J. Petrie & J. Weinman (Eds.), *Perceptions of health and illness: Current research and applications* (pp. 411–439). London: Harwood Academic Publishers.

Moss-Morris, R., & Chalder, T. (2003). Illness perceptions and levels of disability in patients with chronic fatigue syndrome and rheumatoid arthritis. *Journal of Psychosomatic Research*, *55*, 305–308.

Moss-Morris, R., & Petrie, K. J. (2000). *Chronic fatigue syndrome*. London: Routledge.

Moss-Morris, R., & Petrie, K. J. (2001). Discriminating between chronic fatigue syndrome and depression: A cognitive analysis. *Psychological Medicine*, *31*, 469–479.

Moss-Morris, R., Petrie, K. J., & Weinman, J. (1996). Functioning in chronic fatigue syndrome: Do illness perceptions play a regulatory role? *British Journal of Health Psychology*, *1*, 15–25.

Moss-Morris, R., Weinman, J., Petrie, K. J., Horne, R., Cameron, L. D., & Buick, D. (2002). The Revised Illness Perception Questionnaire (IPQ-R). *Psychology and Health*, *17*, 1–6.

Powell, P. (2001). *An educational intervention treatment using physiological explanation of symptoms to encourage graded exercise in chronic fatigue syndrome*. Liverpool: Liverpool University.

Powell, P., Bentall, R. P., Nye, F. J., & Edwards, R. H. (2001). Randomised controlled trial of patient education to encourage graded exercise in chronic fatigue syndrome. *British Medical Journal*, *322*(7283), 387–390.

Prins, J. B., Bleijenberg, G., Bazelmans, E., Elving, L. D., Boo, T. M., Severens, J. L., van der Wilt, G. J., Spinhoven, P., & van der Meer, J. W. M. (2001). Cognitive behaviour therapy for chronic fatigue syndrome: A multicenter randomised controlled trial. *The Lancet*, *357*, 841–847.

Ray, C., Jefferies, S., & Weir, W. R. C. (1995). Coping with chronic fatigue syndrome: Illness responses and their relationship with fatigue, functional impairment and emotional status. *Psychological Medicine*, *25*(5), 937–945.

Ray, C., Jefferies, S., & Weir, W. R. (1997). Coping and other predictors of outcome in chronic fatigue syndrome: A 1-year follow-up. *Journal of Psychosomatic Research*, *43*(4), 405–415.

Ray, C., Weir, W., Stewart, D., Miller, P., & Hyde, G. (1993). Ways of coping with chronic fatigue syndrome: Development of an illness management questionnaire. *Social Science and Medicine*, *37*(3), 385–391.

Scott, K. M., Tobias, M., Safarti, D., & Haslett, S. J. (1999). SF-36 health survey, reliability, validity and norms for New Zealand. *Australian and New Zealand Journal of Public Health*, *23*, 401–406.

Sharpe, M., Hawton, K., Simkin, S., Surawy, C., Hackmann, A., Klimes, I., Peto, T., Warrell, D., & Seagroatt, V. (1996). Cognitive behaviour therapy for the chronic fatigue syndrome: A randomized controlled trial. *British Medical Journal*, *312*(7022), 22–26.

Silver, A., Haeney, M., Vijayadurai, P., Wilks, D., Pattrick, M., & Main, C. J. (2002). The role of fear of physical movement and activity in chronic fatigue syndrome. *Journal of Psychosomatic Research*, *52*(6), 485–493.

Surawy, C., Hackmann, A., Hawton, K., & Sharpe, M. (1995). Chronic fatigue syndrome: A cognitive approach. *Behaviour Research and Therapy*, *33*(5), 535–544.

Wearden, A. J., Morriss, R. K., Mullis, R., Strickland, P. L., Pearson, D. J., Appleby, L., Campbell, I. T., & Morris, J. A. (1998). Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. *British Journal of Psychiatry*, *172*, 485–490.

Wessely, S., Butler, S., Chalder, T., & David, A. (1991). The cognitive behavioural management of the post-viral fatigue syndrome. In R. Jenkins & J. Mowbray (Eds.), *Postviral fatigue syndrome* (pp. 305–334). Chichester: John Wiley & Sons.

Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavia*, *67*, 361–370.