

# Health-related quality of life in patients with chronic fatigue syndrome: group cognitive behavioural therapy and graded exercise versus usual treatment. A randomised controlled trial with 1 year of follow-up

Montserrat Núñez · Joaquim Fernández-Solà ·  
Esther Nuñez · José-Manuel Fernández-Huerta ·  
Teresa Godás-Sieso · Esther Gomez-Gil

Received: 11 March 2010 / Revised: 20 December 2010 / Accepted: 23 December 2010  
© Clinical Rheumatology 2011

**Abstract** Chronic fatigue syndrome (CFS) produces physical and neurocognitive disability that significantly affects health-related quality of life (HRQL). Multidisciplinary treatment combining graded exercise therapy (GET) cognitive behavioural therapy (CBT) and pharmacological treatment has shown only short-term improvements. To compare the effects on HRQL of (1) multidisciplinary

treatment combining CBT, GET, and pharmacological treatment, and (2) usual treatment (exercise counselling and pharmacological treatment) at 12 months of follow-up. Prospective, randomized controlled trial with a follow-up of 12 months after the end of treatment. Patients consecutively diagnosed with CFS (Fukuda criteria) were randomly assigned to intervention ( $n=60$ ) or usual treatment ( $n=60$ ) groups. HRQL was assessed at baseline and 12 months by the Medical Outcomes Study Short-Form questionnaire (SF-36). Secondary outcomes included functional capacity for activities of daily living measured by the Stanford Health Assessment Questionnaire (HAQ) and comorbidities. At baseline, the two groups were similar, except for lower SF-36 emotional role scores in the intervention group. At 12 months, the intervention did not improve HRQL scores, with worse SF-36 physical function and bodily pain scores in the intervention group. Multidisciplinary treatment was not superior to usual treatment at 12 months in terms of HRQL. The possible benefits of GET as part of multidisciplinary treatment for CFS should be assessed on an individual patient basis.

M. Núñez

Rheumatology Service, Functional Readaptation Unit,  
Hospital Clinic,  
Barcelona, Spain

J. Fernández-Solà · J.-M. Fernández-Huerta

Department of Internal Medicine, Chronic Alcohol Unit,  
Hospital Clinic, Barcelona. CIBEROBN, Carlos III Health Institute,  
Majadahonda, Madrid, Spain

E. Nuñez

Health Services, Catalan Health Institute,  
SAP Diagnostic and Treatment Support,  
Barcelona, Spain

T. Godás-Sieso

Department of Psychology, Chronic Alcohol Unit,  
Hospital Clinic,  
Barcelona, Spain

E. Gomez-Gil

Department of Psychiatry, Chronic Alcohol Unit, Hospital Clinic,  
Barcelona, Spain

M. Núñez (✉)

Department of Rheumatology, Hospital Clinic,  
Villarroel 170, 08036 Barcelona, Spain  
e-mail: mnunez@clinic.ub.es

**Keywords** Chronic fatigue syndrome ·  
Cognitive behavioural therapy · Graded exercise therapy ·  
Health-related quality of life · Outcomes

## Introduction

Chronic fatigue syndrome (CFS) is a disorder of unknown origin whose symptoms include persistent physical fatigue

with low activity and neurocognitive impairment, post-exertional malaise, muscle and joint pain, headache, sleep disturbances, fever, sore throat, and enlarged cervical nodes [1]. The prevalence of CFS varies from 0.2% to 2.2% among adults in community samples, with a preponderance of females over males [1, 2]. The wide range may reflect different criteria and assessment methods [3]. CFS produces marked functional impairment involving both physical and neurocognitive areas and has significant occupational, family and personal repercussions [4].

Evaluation of health-related quality of life (HRQL) dimensions is a means of measuring functional impairment, activity limitations, and participation restrictions of patients with CFS [5]. Validated HRQL measures include generic instruments such as the Medical Outcomes Study Short-Form questionnaire (SF-36) or disease-specific measures such as the Stanford Health Assessment questionnaire (HAQ) [6–8]. Studies have found that HRQL is markedly more affected in CFS than in other chronic disabling rheumatic diseases. A study which compared HRQL (SF-36 and HAQ) in patients affected by CFS and rheumatoid arthritis found that CFS patients had markedly worse HRQL [9].

There is no effective treatment that returns CFS patients to normal function, and recovery without treatment is infrequent [3, 10, 11], with no pharmacological treatment alone demonstrating significant improvement. Various treatments are proposed for CFS. While animal models in mice have found that some anxiolytic or antidepressant drugs have a protective effect and might be used in chronic fatigue-like conditions, [12], other trials have found that specific drugs (ondansetron) have no efficacy [13]. A systematic review by Edmonds et al. of the effect of exercise treatment in CFS found that the five studies included (out of nine considered) showed that exercise seemed a promising therapy although higher-quality studies measuring outcomes such as quality of life and cost-effectiveness were needed [14].

A Cochrane review of randomised trials of cognitive behaviour therapy (CBT) in CFS concluded that although CBT is effective in reducing the symptoms of fatigue at post-treatment compared with usual care, and may be more effective in reducing fatigue symptoms compared with other psychological therapies, the evidence base is limited [15]. A meta-analysis of the efficacy of CBT in treating CFS and control conditions using wider inclusion criteria and measuring effect sizes rather than direct comparisons found that CBT tends to be moderately efficacious. This review included two studies with a 12-month follow-up [3].

Multidisciplinary treatment combining supervised, graded exercise therapy (GET) with cognitive behavioural therapy (CBT), and pharmacological symptomatic treatment has been shown to improve CFS symptoms in the short-term results (3–

6 months) [16, 17]. However, it is not clear whether this beneficial effect is maintained in the long-term (1 year or more) [15, 18]. Although there are some reports of improvement with CBT at 12 months follow-up [3], recommendations from the Cochrane meta-analysis suggest evaluating the long-term effects of CBT [15].

In the review by Price et al., therapy was individual in ten studies and in groups in five [15]. Likewise, the meta-analysis by Malouff et al., included only two studies based on group CBT therapy [3]. However, some authors state that equivalence between individual and group treatment is commonly found in psychotherapy research [19].

We hypothesized that a relatively intensive course of multidisciplinary treatment using group therapy could improve outcomes in CFS patients.

Therefore, the aim of this study was to compare the HRQL of CFS patients receiving group CBT plus GET and conventional pharmacological treatment with that of patients receiving usual treatment with exercise counselling and conventional pharmacological treatment at 12 months of follow-up.

## Methods

### Study design

We carried out a prospective, randomized controlled trial with a follow-up of 12 months. Study reporting was made according to CONSORT guidelines for non-pharmacologic interventions [20, 21].

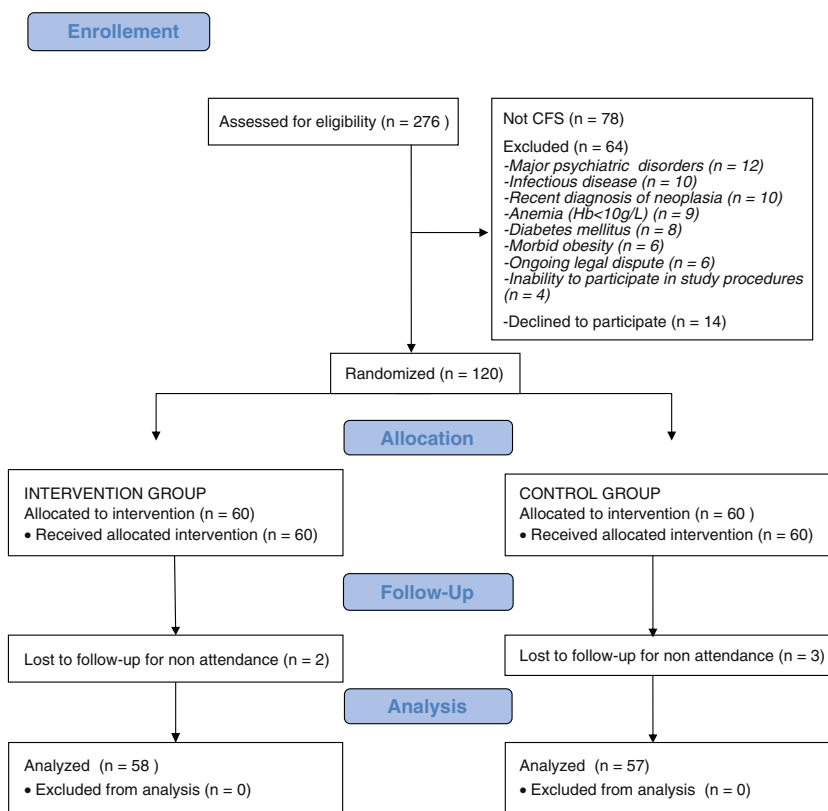
### Subjects and study setting

The study was carried out in the Chronic Fatigue Unit, Hospital Clinic of Barcelona (Spain), a public, tertiary, university hospital with a reference area of more than one million people.

### Participants

Between January and December 2006, 276 patients were referred to the CFS outpatient referral clinic by primary health care physicians due to prolonged, disabling fatigue of unknown origin of more than 6 months duration. All underwent the standard protocol according to the consensus document for CFS management in Catalonia [22]. This included a clinical history, physical exam, analytical tests (biochemical, hematological, hormonal, and immunological profile), chest X-ray, 12-lead electrocardiogram, and psychological evaluation. A total of 198 patients were finally diagnosed with CFS according to Fukuda criteria [23] (see flow-diagram Fig. 1) and were considered for inclusion.

**Fig. 1** Flow chart of participants



**Exclusion criteria**

Patients with any past or current diagnosis of a major depressive disorder with psychotic or melancholic features according to Fukuda criteria were excluded. Patients with physical diseases that could cause fatigue, including morbid obesity, hypothyroidism, Cushing syndrome, anemia (blood haemoglobin < 10 g/L), diabetes mellitus, active neoplastic or infectious disease, inflammatory rheumatic disease, and patients unable to participate fully in study procedures were also excluded. Patients involved in ongoing legal or occupational conflicts, such as disputes about work-loss due to CFS, that could have interfered with the evaluation were also excluded. All patients gave written informed consent before inclusion. The study was approved by the hospital Ethics Committee (ref # V2 19/12/06) and was performed in accordance with the ethical standards of the 1964 Helsinki Declaration.

**Intervention**

The intervention group received multidisciplinary treatment with group CBT, GET, and conventional pharmacological symptomatic treatment. CBT was carried out by one author (GS, T) a clinical psychologist with 7 years experience in CBT [16, 24, 25].

Patients received CBT and GET in groups of 16. The CBT program was composed of nine, twice-weekly, 90-min

sessions during a 2.5–3-month period. The main objective was to identify correct behavioural patterns and adaptive thought models and create a therapeutic link [15]. CBT contents included (1) psychoeducational interventions to explain the multi-factorial character of CFS, (2) progressive muscle relaxation procedures (Jacobsen) to identify muscle tension, (3) sleep hygiene patterns to enable entry into and maintenance of phase IV sleep, (4) detection and control of verbal and non-verbal pain-inducing attitudes, (5) cognitive restructuring to modify non-adapted and catastrophic thought patterns, (6) information about the relationship between vegetative and anxiety symptoms, (7) modification of type A behavioural patterns, (8) improvement in assertiveness, (9) patterns to increase attention and memory, (10) sensorial focalization for sexual inhibition, and (11) disease relapse prevention [16].

GET included thrice-weekly 1-h sessions carried out in intermittent periods of 10 min for 3 months, according to established protocols [26, 27]. Patients were informed that exercise was designed to restore their ability to do sustained physical exercise as far as possible. After a 1-week baseline assessment with a 10-min walking session, gradual increases in aerobic exercise at a rate of 5 min per session were introduced. Complementary activities such as flexibility exercise and relaxation therapy were also included. Total exercise load was maintained or increased to a maximum of 40 min per day, according to individual

tolerance. All GET sessions were personally supervised by a qualified physiotherapist, who is a registered nurse with a diploma in physiotherapy, and more than 20 years experience in general physiotherapy for neurological disease and 8 years experience in a third-level CFS and fibromyalgia (FM) reference unit. CBT and GET were administered in an integrated manner according to the previously mentioned Catalan protocol [22].

The control group received usual CFS therapy including exercise counselling and conventional pharmacological symptomatic treatment [19, 28]. Exercise counselling was performed by personal interview with the same physiotherapist. The objective was to provide activities that restored the patient's ability to do sustained physical exercise as far as possible. The program included three daily 10-min sessions, performed in separate periods, with adapted aerobic exercise, including walking and home-stretching exercises.

Symptomatic pharmacological treatment was equal in the two groups and included analgesia (paracetamol 1–3 g/day p.o.), ibuprofen (600–1800 mg/day p.o.) if subjects reported inflammation (fever, myalgia, enlarged cervical nodes), and zolpidem 10 mg/night p.o. if patients reported significant insomnia [19]. No other treatment was admitted during the study period. Verbal and written information on the general characteristics of CFS was provided to the two groups at baseline. Further verbal information was provided during the study and new written information at the end of study according to the previously mentioned Catalan protocol. [22].

## Outcomes

The main outcome variable was HRQL at 12 months after the end of treatment evaluated by the generic Medical Outcomes Study Short-Form (SF-36) questionnaire adapted to the Spanish population [6, 7]. The SF-36 is a self-administered questionnaire that measures HRQL according to individual self-reported health perceptions and includes two areas: physical function and emotional perception, in 36 items grouped in eight subscales with a point range of 0–100 (in each subscale), with higher values signifying better HRQL.

Secondary outcome measures included the functional capacity to perform the activities of daily living measured by the self-administered Stanford Health Assessment Questionnaire (HAQ) [8]. The HAQ is composed of 20 items that include eight functional categories with a score range of 0–3 (index), with higher scores indicating more disability (0=without any difficulties to 3=unable to perform activities of daily living). In addition, it includes a general evaluation of the global health status according to the patient's perspective and a measurement of pain intensity by means of two 10 cm visual analogical scales

(VAS), with a score of 0 (best) and 10 (worst). In this study, three closed questions were added to the 20 HAQ items to determine whether functional impairment was related to pain, limitation (joint impairment to movement), or muscle weakness, with a range of 0–20, with higher scores indicative of the main cause of disability [9].

We also evaluated the following comorbidities [29, 30]: FM, Sicca syndrome, endometriosis/dysmenorrhea, dysthymia, thyroid dysfunction, multiple chemical sensitivity, and irritable bowel syndrome. FM was evaluated by the American College of Rheumatology criteria [31], validated in Catalonia by an expert committee [22]. Sicca syndrome was defined as clinical dry mouth and dry-eye, with pathological Schirmer test [32]. Endometriosis was defined as persistent dysmenorrhea and echographic or laparoscopic evidence of extra-uterine endometrial tissue. Although significant psychiatric disease was an exclusion criteria, anxiety or depression was evaluated by the Hospital Anxiety and Depression Scale (HADS) at baseline [33]. Thyroid dysfunction was evaluated by blood thyroxin and thyroid stimulating hormone levels and antithyroid antibodies. Multiple chemical sensitivity was measured according to international consensus criteria [34]. Irritable bowel syndrome was defined according to the Rome Criteria [35]. Fatigue was measured in both groups at baseline and at 12 months according to the Fatigue Impact Scale questionnaire (FIS) score (0–160) [36].

## Clinical and epidemiologic data

Sociodemographic data collected included age, gender, occupational status, and disease duration (months) since diagnosis of CFS.

## Evaluations

Clinical, sociodemographic, and outcome measurements were performed at baseline. Outcome measurements, comorbidities, and FIS were determined at 12 months. All evaluations were made by an independent investigator, blinded to the group assignment.

## Sample size and randomization

Sample sizes were calculated according to preliminary data from previous studies and to the number of CFS patients reasonably expected to be seen during 1 year in our clinic. Patients were randomized in a two-step process. One author (N, E) drew up a random list of numbers using an ad hoc randomization generator specifically designed for this study. Another author (FS, J), who was blinded to the randomization, allocated one of the numbers generated to each patient, who was then assigned to the group indicated.

## Statistical analysis

Study variables were tabulated descriptively for the two groups. The mean and standard deviations (SD) were calculated for continuous variables and absolute and relative frequencies for categorical variables. As some variables presented a non-normal distribution, all comparisons were made using non-parametric statistics, allowing estimates to be made without considering the distribution of variables.

Final scores between groups were compared using the Mann–Whitney  $U$  test (or  $\chi^2$  test for categorical data), and within-group comparisons were made using the Wilcoxon matched pairs signed-ranks test (or McNemar test for categorical data). Ninety-five percent confidence intervals (CI) were calculated, and statistical significance was established as  $p=0.05$ .

## Results

### Patient selection

Of the 198 patients diagnosed with CFS, 64 were excluded (see Fig. 1) and 134 fulfilled inclusion criteria, of whom 14 declined to participate. Therefore, 120 patients were finally

randomized to the intervention ( $n=60$ ) and usual treatment groups. Five patients were lost to follow-up due to non-attendance, and therefore 58 patients from the intervention and 57 from the usual treatment groups completed the 12-month follow-up and were included in the final analysis (see Fig. 1). There were no significant differences in baseline epidemiological and clinical characteristics (Table 1). Both groups had high anxiety and depression scores in the HADS questionnaire.

The only significant differences at baseline in the SF-36 and HAQ scores was the SF-36 emotional role score, which was lower (worse) in the intervention group ( $28.07\pm 41.69$  vs.  $47.62\pm 48.77$ ,  $p=0.042$ ).

### Within-group differences

*Intervention group* Main and secondary outcome measures are compared in Table 2. At 12 months, there were significantly lower SF-36 physical function and bodily pain dimension scores compared to baseline ( $p=0.004$  and  $p=0.021$ , respectively).

Although the functional capacity to perform activities of daily living measured by the HAQ did not change significantly with respect to baseline, there were significant changes in bodily pain. Patients reported more impairment

**Table 1** Baseline characteristics of the intervention and control groups

Variables	Intervention group ( $n=58$ )	Control group ( $n=57$ )	Differences between groups $p$ value <sup>a</sup>
Age (years), mean $\pm$ SD	42.65 $\pm$ 9.60	44.27 $\pm$ 10.76	0.405
Gender, $n$ (%)			0.172
Women	53 (93)	48 (14.3)	
Men	4 (7)	8 (85.7)	
Work status, $n$ (%)			0.109
Active work	9 (16.4)	11 (19.6)	
Unemployed	5 (9.1)	2 (3.6)	
Temporary work disability	18 (30.9)	13 (23.2)	
Permanent work disability	19 (32.7)	25 (44.7)	
Retired	0	1 (1.8)	
Other	6 (10.9)	4 (7.1)	
Disease duration (months)	32 $\pm$ 2	33 $\pm$ 2	0.543
$N$ comorbidities, mean $\pm$ SD	1.60 $\pm$ 1.09	1.46 $\pm$ 1.13	0.537
Comorbidity, $n$ (%)	40 (70.2)	37 (66.1)	0.395
Fibromyalgia	43 (75.43)	35 (62.5)	0.099
Sicca syndrome	5 (8.8)	11 (19.6)	0.082
Dysthymia	20 (35.1)	13 (23.2)	0.119
Thyroid disturbances	7(12.3)	9 (16.1)	0.379
Dysmenorrhea/endometriosis	0	0	
Chemical sensitivity	3(5.3)	4 (7.1)	0.490
Other comorbidities	13 (22.8)	10 (17.9)	0.338
Anxiety, mean $\pm$ SD	11.4 $\pm$ 4.62	11.1 $\pm$ 4.03	0.865
Depression, mean $\pm$ SD	11.9 $\pm$ 3.20	10.7 $\pm$ 3.01	0.758

SD Standard deviation,  $n$  number

<sup>a</sup> Mann–Whitney  $U$  test

**Table 2** Outcome measures of SF-36 and HAQ questionnaires at 12 months

	Intervention group ( <i>n</i> =58)			Control group ( <i>n</i> =57)			Between-group differences (12 months) <i>p</i> value <sup>b</sup>
	0 months	12 months	<i>p</i> value <sup>a</sup>	0 months	12 months	<i>p</i> value <sup>a</sup>	
<b>SF-36</b>							
Physical function	39.69±22.80	32.63±22.52	0.004	40.04±22.09	38.28±22.73	0.975	0.147
Physical role	8.33±22.82	4.39±15.76	0.194	11.61±28.19	9.82±26.41	0.775	0.350
Bodily pain	27.09±24.22	21.81±21.43	0.021	27.41±19.04	29.34±21.58	0.236	0.040
General health	29.96±16.48	30.19±16.98	0.838	27.43±14.90	29.76±15.14	0.051	0.945
Vitality	16.14±14.76	15.00±15.06	0.385	17.05±15.37	18.66±16.11	0.197	0.198
Social function	34.21±25.61	30.92±24.90	0.402	34.82±24.85	37.72±26.27	0.395	0.160
Emotional role	28.07±41.69	35.67±43.12	0.345	47.62±48.77	46.43±47.85	0.734	0.286
Mental health	44.70±21.17	46.25±21.57	0.560	50.14±22.54	50.86±20.58	0.595	0.420
<b>HAQ</b>							
Functional capacity (index)	1.14±0.73	1.27±0.72	0.105	1.05±0.69	1.14±0.66	0.239	0.291
Patient global assessment (VAS)	6.93±2.23	7.27±1.88	0.200	7.21±1.96	6.83±2.09	0.325	0.316
Pain intensity (VAS)	6.51±2.63	6.91±2.28	0.191	6.55±2.33	6.28±2.40	0.366	0.133
<b>Causes of disability</b>							
Pain	6.87±6.76	8.35±6.62	0.012	5.17±4.94	6.21±6.25	0.082	0.075
Limitations	3.50±5.35	4.20±5.88	0.533	2.89±3.93	3.75±4.42	0.055	0.475
Weakness	6.31±6.07	8.61±6.58	0.002	6.98±6.39	6.47±6.18	0.844	0.102
Number of comorbidities	1.59±1.10	2.09±1.01	<0.001	1.47±1.12	2.09±1.03	<0.001	0.993

Results in mean±SD. Causes of disability with a score for each ranging from 0 [none] to 20 [main cause of disability]

SD standard deviation, *n* number, VAS visual analogue scale, SF-36 Medical Outcomes Study Short-Form-36 (scores ranging from 0 [worst] to 100 [best]), HAQ Stanford Health Assessment Questionnaire (index score ranging from 0 [normal functional capacity] to 3 [maximum disability])

<sup>a</sup> Wilcoxon signed matched pairs

<sup>b</sup> Mann–Whitney *U* test

due to pain and weakness in the HAQ ( $p=0.012$  and  $p=0.002$ , respectively). No changes in the global health status and pain intensity measured by VAS were detected. There was also a significant increase in comorbidities between baseline and 12 months ( $p<0.001$ ) (Table 2).

**Control group** No significant changes were detected in the main and secondary outcome measures at 12 months compared to baseline, with the exception of the number of comorbidities, which significantly increased at 12 months ( $p<0.001$ ) (Table 2).

#### Between-group differences

At 12-months, SF-36 pain dimension scores were significantly lower in the intervention group (21.81±21.43 vs. 29.34±21.58,  $p=0.040$ ) (Table 2). There were no significant differences in FIS scores, which were 137.3±9.6 and 135.7±10.5 at baseline and 139.2±8.3 and 137.4±10.1 at 12 months in the intervention and control groups, respectively. We also carried out a multivariate analysis adjusted by treatment group, the baseline value of each SF-36

dimension, age, gender, and number of comorbidities, to observe the effect of treatment on HRQL outcomes. The only significant result was that the treatment group was associated with the SF-36 bodily pain dimension, with mean scores significantly worse in the intervention group ( $B -7.44$ ; 95% CI  $-13.5$ – $1.4$ ).

#### Discussion

We compared HRQL at 12 months of follow-up in CFS patients receiving group CBT, GET, and conventional pharmacological treatment with those receiving only usual treatment and found no evidence that the intervention improved HRQL scores at 12 months. There were no significant differences between groups at baseline except for the SF-36 emotional role dimension, with the intervention group having worse scores than controls. Within-group comparisons between baseline and 12 months after treatment showed worse scores in the SF-36 physical function and bodily pain dimension scores and more difficulties due to pain and lack of strength measured by the HAQ in the intervention group at 12 months. Between-group analysis

showed that the intervention group had worse SF-36 bodily pain dimension scores at 12 months. We also observed a significant increase in comorbidities in both study groups at 12 months, in agreement with other reports, suggesting a marked role of comorbidities in CFS disability [29, 30].

The effectiveness of CBT and GET, in isolation or combined, in CFS remains controversial. O'Dowd et al. [19] found CBT did not significantly improve HRQL measured by the SF-36 at 12 months in CFS patients. A review of CBT in CFS by Price et al. found only three randomized trials of adequate quality. The results showed CBT to be beneficial for physical functioning in adult out-patients but not severely disabled patients or those treated in primary care. In addition, there was no evidence for the effectiveness of group CBT, and conclusive evidence on the effectiveness of CBT alone or in combination therapy compared with other treatments was lacking. They also found that the benefits of CBT in improving physical function and reducing depression, anxiety, and psychological distress are uncertain. Our results tend to confirm this analysis [15]. A meta-analysis by Malouff et al. of 13 studies and a total of 1,371 individuals with CFS or a similar disorder suggested that CBT tends to have substantial positive effects on CFS and similar disorders, but that there is considerable room for improvement in outcomes [3]. A review by Whiting et al. of all interventions used to treat or manage CFS, including 2,801 patients from 44 trials, found that CBT and GET showed promising results [11].

With respect to GET, the picture is more complex. Surveys conducted by the charity Action for Myalgic Encephalomyelitis (ME) found that half the patients receiving GET felt worse [37, 38] and that many patients might not have been treated by experienced therapists [39]. UK National Institute for Clinical Excellence (NICE) guidelines on the management of CFS/ME recommends offering CBT and/or GET to people with mild or moderate CFS but also warn that unstructured and poorly monitored or progressed exercise programs can cause significant symptom exacerbation and can arguably make CFS worse [40].

However, we believe that this is not the case in our study, as all sessions of GET were administered by a qualified physiotherapist working in a third-level research hospital. White et al. have provided evidence of abnormal metabolic and immunological reactions to exercise in subsets with CFS [41]. A letter by Nijs et al. summarizes recent findings on the clinical importance of observational findings on the biological nature of post-exertional malaise as a feature of CFS and suggests that clinicians using exercise therapy for patients with CFS should take the biological nature of post-exertional malaise into consideration [42].

However, a review of the CBT/GET model in 2009 by Twisk and Maes found that CBT/GET was not only hardly more effective than non-interventions or standard medical

care but that many patients report that the therapy had affected them adversely, the majority of them even reporting substantial deterioration [43]. In addition, the authors suggest that exertion, and thus GET may have a negative impact on many CFS patients due to post-exertional malaise as it may amplify pre-existing physiopathological abnormalities [43]. This is in line with studies, suggesting the physiopathological basis of this phenomenon may include increased oxidative stress and altered muscle excitability [44], combined with reduced cytokine and heat-shock protein responses when CFS patients are exposed to incremental strenuous exercise [45].

In our study, the therapeutic intervention did not result in improved results and was, in fact, slightly inferior to usual care alone, resulting in a similar between-group level of HRQL at 12 months. While it is not possible to distinguish between the components of the combined therapy, in the intervention group, SF-36 pain dimension scores were significantly worse at 12 months, while some scores relating to emotional and mental aspects improved slightly, but not significantly. This suggests that each type of treatment might have had different effects.

Between-study comparison in CFS is complicated due to methodological heterogeneity, including different case definitions, diversity in patient inclusion criteria, settings, the wide range of outcomes evaluated, group and individual interventions, and a wide range of rating methods [15]. Some authors, such as the Nijmegen group, suggest that the processes of therapeutic changes required in CFS patients are more facilitated by individual CBT than by a group approach [46–48]. However, a meta-analysis of CBT for CFS performed by Malouff et al. [3] included 15 different studies on CBT, 13 on an individual, and 2 on a group basis. When the authors performed a moderator analysis for effect sizes by treatment features and diagnosis, they found no significant differences between individual versus group therapy. These results suggest CBT may be similar in efficacy to individual CBT for CFS. These problems make it difficult to compare the impact of treatment interventions in patients with CFS until methods are standardized.

In our study, the total weekly combined time of CBT and GET was 6 h.

The duration of CBT was somewhat longer than usual for group CBT (3–10 h) but similar to the duration for individual treatment (10–16 h) [3]. However, the results show that this somewhat more intensive therapy was not beneficial.

Our study has various limitations. First, all patients came from one tertiary center, meaning the results are only applicable to this specific group and could vary in other CFS patients, such as those attended by primary care. Second, the 10:1 female/male ratio of our patients is higher than in other studies but reflects our clinical experience

over many years and does not differ greatly from other studies (Jason et al. included 83.3% of females) [2]. Third, except for comorbidities, emotional or social events occurring during the follow-up that might have modified the functional outcome were not recorded. Fourth, the size of the CBT and GET therapy groups (16 patients per group) may not have been optimal. Most trials of CBT include ten members per session. Fifth, although we did not use a specific treatment manual, we followed the recommendations of the Catalan protocol, which was agreed by expert consensus. Sixth, we did not directly measure fatigue, and no immediate post-treatment assessment was made. However, the HAQ evaluates weakness, which may be seen as a similar variable to fatigue and provide valuable information. The main strengths of the study include the randomized, prospective design comparing multidisciplinary versus usual treatment rather than using the waiting list and the use of blinded outcome assessors. In addition, fatigue is usually the primary outcome measure in studies of CFS patients, and there are relatively few studies that analyze health outcomes such as HRQL.

Recent publications suggest the need to optimize CFS treatment through individualized pacing strategies and customization of CBT and other types of psychotherapy [1, 47, 49] as well as carefully modulating GET by an individual pacing strategy [4, 50].

In summary, the addition of group CBT and GET to usual treatment in a cohort of patients with CFS was not superior to usual treatment alone at 12 months follow-up in terms of HRQL. Although some studies cautiously conclude that exercise therapy is a promising treatment for CFS [14], the results of our study tend to support the somewhat controversial findings of Twisk and Maes [43] that the combination of CBT and GET is ineffective and not evidence-based and may in fact be harmful in some patients, a view supported by various surveys carried out by patient advocate groups [41]. The use of GET should be analyzed regularly on an individual basis. The few and methodologically heterogeneous studies available in this field and the lack of standardized criteria for CFS evaluation and treatment make inter-study comparisons difficult and conclusions of doubtful relevance. Further activity to achieve scientific consensus on the standardization of methods and results in studies of CFS is essential.

The forthcoming PACE trial, which will compare CBT, GET, and adaptive pacing in terms of efficacy, cost-effectiveness, and adverse events may provide valuable information [41].

**Acknowledgments** We thank David Buss for his editorial advice.

**Funding** Joaquim Fernandez-Solà received grants from the Generalitat of Catalonia, SGR 2009-1158, and CIBEROBN, Carlos III Health Institute, Majadahonda, Madrid.

**Disclosures** None.

## References

1. Prins JB, van der Meer JWM, Bleijenberg G (2006) Chronic fatigue syndrome. *Lancet* 367(9507):346–355
2. Jason LA, Torres-Harding S, Friedberg F, Corradi K, Njoku MG, Donaleck J et al (2007) Non-pharmacologic interventions for CFS. A randomized trial. *J Clin Psychol Med Settings* 14:275–296
3. Malouff JM, Thorsteinsson EB, Rooke SE, Buhllar N, Schutte NS (2007) Efficacy of cognitive behavioural therapy for chronic fatigue syndrome: a meta-analysis. *Clin Psychol Rev* 28(5):736–745
4. Ross SD, Estok RP, Frame D, Stone LR, Ludensky V, Levine CB (2004) Disability and chronic fatigue syndrome: a focus on function. *Arch Inter Med* 164(10):1098–1107
5. Rakib A, White PD, Pinching AJ, Hedge B, Newbery N, Fakhoury WK et al (2005) Subjective quality of life in patients with chronic fatigue syndrome. *Qual Life Res* 14(1):11–19
6. Ware JE, Sherbourne CD (1992) The MOS-36 item short form health survey (SF-36). *Med Care* 30(6):473–483
7. Alonso J, Prieto L, Antó JM (1995) The Spanish version of the SF-36 Health Survey (the SF-36 health questionnaire): an instrument for measuring clinical results. *Med Clin (Barc)* 104(20):771–776
8. Esteve-Vives J, Batlle-Gualda E, Reig A (1993) Spanish version of the Health Assessment Questionnaire: reliability, validity and transcultural equivalency. Grupo para la Adaptación del HAQ a la Población Española. *J Rheumatol* 20(12):2116–2122
9. Núñez M, Núñez E, del Val JL, Fernandez-Huerta JM, Alegre C, Bonet M et al (2007) Health-related quality of life in chronic fatigue syndrome versus rheumatoid arthritis as control group. *Journal of Chronic Fatigue Syndrome* 14(2):31–43
10. Cairns R, Hotopf M (2005) A systematic review describing the prognosis of chronic fatigue syndrome. *Occup Med* 55(1):20–31
11. Whiting P, Bagnall AM, Sowden AJ, Cornell JE, Mulrow SD, Ramirez D (2001) Interventions for the treatment and management of chronic fatigue syndrome. A systematic review. *JAMA* 286:1360–1368
12. Kumar A, Garg R (2009) Protective effects of antidepressants against chronic fatigue syndrome-induced behavioral changes and biochemical alterations. *Fundam Clin Pharmacol* 23(1):89–95
13. The GK, Bleijenberg G, Buitelaar JK, van der Meer JW (2010) The effect of ondansetron, a 5-HT<sub>3</sub> receptor antagonist, in chronic fatigue syndrome: a randomized controlled trial. *J Clin Psychiatry* 71(5):528–533
14. Edmonds M, McGuire H, Price J (2004) Exercise therapy for chronic fatigue syndrome. *Cochrane Database Syst Rev* (3):CD003200 (Review)
15. Price JR, Mitchell E, Tidy E, Hunot V (2008) Cognitive behaviour therapy for chronic fatigue syndrome in adults. *Cochrane Database Syst Rev* (3):CD001027
16. Godás Sieso T, Gómez-Gil E, Fernández-Solà J, Fernández-Huertas JM (2005) Significant increase of functional status and decrease of fatigue in patients with chronic fatigue syndrome after completing cognitive behavioural group therapy. *Med Clin (Barc)* 22 125(14):556–559
17. Torenbeek M, Mes CA, van Liere MJ, Schreurs KM, ter Meer R, Kortleven GC, Warmerdam CG (2006) Favourable results of a rehabilitation program with cognitive behavioural therapy and graded physical activity in patients with chronic fatigue syndrome. *Ned Tijdschr Geneesk* 150(38):2088–2094
18. Deale A, Husain K, Chalder T, Wessely S (2001) Long-term outcome of cognitive behaviour therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study. *Am J Psychiatry* 158(12):2038–2042



19. O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A (2006) Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme. *Health Technol Assess* 10(37) iii–iv, ix–x, 1–121
20. Schulz KF, Altman DG, Moher D, for the CONSORT Group (2010) CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 340:c332
21. Boutron I, Moher D, Altman DG, Schulz K, Ravaud P, for the CONSORT group (2008) Extending the CONSORT Statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med* 8:295–309
22. Nou Model d'atenció a la Fibromiàlgia i la síndrome de Fatiga Crònica. Catalunya 2006 Available at [http://www.gencat.cat/salut/depsalut/pdf/fm\\_sfccat.pdf](http://www.gencat.cat/salut/depsalut/pdf/fm_sfccat.pdf)
23. Fukuda K, Strauss SE, Hickie I, Sharp CM, Dobbins JG, Komaroff A (1994) The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med* 12:953–959
24. Godás T, Marcos T, Corominas J, Nuñez M, Salamero Baró M (2007) Study of the efficacy and risk factors of cognitive behaviour therapy for smoking in pregnancy. *Medicina Clinica* 129(16):607–611 (FI: 1.258/1.317; article in Spanish)
25. Marcos T, Godás T, Corominas J (2004) Nicotine replacement therapy versus gradual smoking withdrawal in smoking cessation. *Med Clin (Barc)* 123(4):127–130
26. Fulcher KY, White PD (1997) Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. *BMJ* 314(7095):1647–1652
27. Wallman K, Morton A, Goodman C, Grove R (2005) Exercise prescriptions for individuals with chronic fatigue syndrome. *Med J Aust* 183(3):142–143
28. Alijotas J, Alegre J, Fernández-Solà J, Cots JM, Panisello J, Peri JM et al (2002) Consensus report on the diagnosis and treatment of chronic fatigue syndrome in Catalonia. *Med Clin (Barc)* 118(2):73–76
29. Aaron LA, Burke MM, Buchwald D (2000) Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. *Arch Intern Med* 160(2):221–227
30. Ciccone DS, Natelson BH (2003) Comorbid illness in women with chronic fatigue syndrome: a test of the single syndrome hypothesis. *Psychosom Med* 65(2):268–275
31. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL et al (1990) The American College of Rheumatology 2009 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 33(2):160–172
32. Ramos-Casals M, Brito-Zerón P, Perez-De-Lis M, Jimenez I, Blanco MJ, Bove A et al (2009) Sjögren syndrome or Sjögren disease? The histological and immunological bias caused by the 2002 criteria. *Clin Rev Allergy Immunol* 38(2–3):178–185
33. Herrero MJ, Blanch J, Peri JM, De Pablo J, Pintor L, Bulbena A (2003) A validation study of the hospital anxiety and depression scale (HADS) in a Spanish population. *Gen Hosp Psychiatry* 25:277–283
34. Bartha J, Baumzweiger W, Buscher DS, Callender T, Dahl KA, Davidoff A et al (1999) Multiple chemical sensitivity: a 1999 consensus. *Arch Environ Health* 54(3):147–149
35. Coffin B (2009) Diagnosis of irritable bowel syndrome. *Gastroenterol Clin Biol* 33(Suppl 1):S9–S16
36. Meads DM, Doward LC, McKenna SP, Fisk J, Twiss J, Eckert B (2009) The development and validation of the Unidimensional Fatigue Impact Scale (U-FIS). *Mult Scler* 10:1228–1238
37. Clark LV, White PD (2008) Chronic fatigue syndrome: 1. prevention of symptom exacerbations in chronic fatigue syndrome. *J Rehabil Med* 40:882–883
38. Action for ME (AFME) (2001) Severely neglected ME in the UK. Action for ME, London. Available at <http://www.afme.org.uk/res/img/resources/Severely%20Neglected.pdf>. Accessed 12 August 2009
39. Action for ME (AFME) Members Survey—Conducted Spring 2003. 4. ME Essential Spring edition. ME, Gawcott. Available at <http://www.afme.org.uk/res/img/resources/afme%20members%20survey.pdf>. Accessed 12 August 2009
40. National Institute for Health and Clinical Excellence (2007) Clinical guideline CG53. Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management. NICE, London. Available at <http://guidance.nice.org.uk/CG53>
41. White PD, Nye KE, Pinching AJ, Yap TM, Power N, Vleck V et al (2004) Immunological changes after both exercise and activity in chronic fatigue syndrome: a pilot study. *J Chronic Fatigue Syndrome* 12:51–66
42. Nijs J, Paul L, Wallman K (2010) Response 2 to letter to the editor by Kindlon & Goudsmit: new insights in post-exertional malaise in patients with myalgic encephalomyelitis/chronic fatigue syndrome. *J Rehabil Med* 42:185–186
43. Twisk FN, Maes M (2009) A review on cognitive behavioral therapy (CBT) and graded exercise therapy (GET) in myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS): CBT/GET is not only ineffective and not evidence-based, but also potentially harmful for many patients with ME/CFS. *Neuro Endocrinol Lett* 30(3):284–311
44. Jammes Y, Steinberg JG, Mambrini O, Brégeon F, Delliaux S (2005) Chronic fatigue syndrome: assessment of increased oxidative stress and altered muscle excitability in response to incremental exercise. *J Intern Med* 257(3):299–310
45. Jammes Y, Steinberg JG, Delliaux S, Brégeon F (2009) Chronic fatigue syndrome combines increased exercise-induced oxidative stress and reduced cytokine and Hsp responses. *J Intern Med* 266(2):196–206
46. Nijs J, Paul L, Wallman K (2008) Chronic fatigue syndrome: an approach combining self-management with graded exercise to avoid exacerbations. *J Rehabil Med* 40(4):241–247
47. Nijs J, van Eupen I, Vandecauter J, Agustinus E, Bleyen G, Mororkens G, Meeus M (2009) Can pacing self-management alter physical behaviour and symptom severity in chronic fatigue syndrome? A case series. *J Rehabil Res Dev* 46(7):985–986
48. Tummers M, Knoop H, Bleijenberg G (2010) Effectiveness of stepped care for chronic fatigue syndrome: a randomized noninferiority trial. *J Consult Clin Psychol* 78(5):724–731
49. Bjørkum T, Wang CE, Waterloo K (2009) Patients' experience with treatment of chronic fatigue syndrome. *Tidsskr nor Lægeforen* 129(12):1214–1216
50. Van Houdenhove B, Luyten P (2010) Chronic fatigue syndrome reflects loss of adaptability. *J Intern Med* 268(3):249–251