

# How relevant are exercise capacity measures for evaluating treatment effects in chronic fatigue syndrome? Results from a prospective, multidisciplinary outcome study

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**Objective:** To evaluate the outcome of a multidisciplinary treatment programme for patients with chronic fatigue syndrome, including health-related quality of life (HRQoL) and psychosocial variables, and exercise capacity measures.

**Design:** A six-month prospective outcome study.

**Setting:** University outpatient rehabilitation clinic; group setting.

**Subjects:** One hundred and sixteen women fulfilling chronic fatigue syndrome criteria.

**Interventions:** Cognitive behaviourally and graded exercise-based strategies; emphasis on adaptive lifestyle changes.

**Measures:** Short Form General Health Survey (SF-36); Symptom Checklist (SCL-90); Causal Attribution List (CAL); Self-Efficacy Scale (SE); maximum progressive bicycle ergometer test with respiratory gas analysis; and isokinetic leg strength test, before and after treatment.

**Results:** The total group significantly improved on nearly all reported HRQoL/psychosocial variables. Changes in exercise capacity measures were rather modest and did not correlate or only weakly correlated with HRQoL/psychosocial variables. Subgroup analyses indicated that less fit patients improved significantly more on exercise capacity measures than their more fit counterparts. Patients who were fitter at baseline scored better on pretreatment HRQoL/psychosocial variables, but both subgroups improved similarly on these variables.

**Conclusions:** Health-related quality of life and psychosocial functioning in patients with chronic fatigue syndrome improves after a six-month cognitive behaviourally and graded exercise-based multidisciplinary treatment programme. Increase in exercise capacity measures is not a necessary condition for reported improvements, except for less fit patients.

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## Introduction

Chronic fatigue syndrome is a distressing and often debilitating condition characterized by persistent, medically unexplained fatigue, in combination with muscular and articular pains, headaches, sleep disturbances, sore throat, tender cervical or axillary lymph nodes, concentration and memory difficulties and postexertional malaise.<sup>1</sup> Although several explanations for the syndrome have been proposed, a clear aetiopathogenesis is not established.<sup>2</sup>

Follow-up studies indicate that complete recovery is uncommon.<sup>3</sup> So far, pharmacological treatment strategies have proven to be largely unsuccessful in chronic fatigue syndrome. On the other hand, many patients with chronic fatigue syndrome may benefit from behaviourally oriented treatments, such as cognitive behavioural therapy, and graded exercise therapy.<sup>4</sup>

Cognitive behavioural therapy aims at correcting illness-perpetuating factors (such as rigid somatic attributions, catastrophizing thoughts and maladaptive activity patterns), which may help patients with chronic fatigue syndrome to better cope with their functional limitations and ameliorate their quality of life. Although several cognitive behavioural therapy studies have reported positive results in chronic fatigue syndrome, these studies have also been criticized for using too broad chronic fatigue syndrome criteria, and including only highly motivated and relatively active patients, while excluding those with concomitant psychiatric problems, taking antidepressants, or involved in medico-legal procedures. Thus, according to some, the clinical validity as well as the generalization of these studies to the broader chronic fatigue syndrome population may be questionable.<sup>5,6</sup> It should also be noted that the possibilities for individual cognitive behavioural therapy are limited in most countries, given the lack of trained therapists and the time-consuming character of this type of intervention. Group cognitive behavioural therapy would be more feasible and economic, but evidence for the effects of this therapeutic format is much weaker.<sup>7</sup>

The purpose of graded exercise therapy is to increase the patient's physical condition by gradually building up aerobic activities such as walking or cycling. Randomized controlled trials of graded

exercise training found varying degrees of improvement in fatigue and disability in patients with chronic fatigue syndrome,<sup>8-13</sup> but the rationale of this therapeutic strategy has been criticized as well. Some authors are convinced that physical deconditioning may generally play a maintaining role in chronic fatigue syndrome,<sup>2,14,15</sup> but this has not always been confirmed.<sup>16</sup> Moreover, it has been demonstrated that most patients with chronic fatigue syndrome do not show activity avoidance<sup>17</sup> and may already function near to maximum levels of activity.<sup>5,6</sup> In the same vein, some have stated that the primary pathophysiological process of chronic fatigue syndrome may be unresponsive to, or may even be worsened by graded exercise training, particularly when the programme is not sufficiently individualized.<sup>5,6,18</sup>

Research on the effects of multidisciplinary outpatient treatment in chronic fatigue syndrome – individual as well as group-based – has been inconclusive,<sup>19</sup> frankly positive,<sup>20</sup> or only positive in a postinfectious subgroup.<sup>21</sup> Preliminary evidence for the efficacy of multidisciplinary inpatient programmes has also been reported.<sup>22</sup>

Given these rather disparate data, we intended to study the outcome of a structured, multidisciplinary group programme for a large, relatively unselected group of patients with chronic fatigue syndrome in a naturalistic outpatient rehabilitation setting. The programme mainly consisted of cognitive behaviourally and graded exercise-based strategies, with a strong emphasis on adaptive lifestyle changes. We expected positive post-treatment changes in reported health-related quality of life (HRQoL) and psychosocial variables, as well as improved effort tolerance reflected by increases in exercise capacity measures.

## Methods

### Subjects

Between May 2002 and January 2004, 135 patients (116 female and 19 male) attended a six-month multidisciplinary outpatient treatment programme at the chronic fatigue syndrome reference centre of the University Hospital of Pellenberg (KU Leuven). To obtain a more homogeneous sample and because the number of men was rather small, the present analysis is confined to the data of the women.

### Diagnostic screening

Each patient entered the programme via a general practitioner. Patients were first thoroughly screened by a specialist in internal medicine for any somatic dysfunction, and by a psychiatrist to exclude primary psychopathology which could better account for the patient's symptoms. Those fulfilling Centers for Disease Control (CDC) criteria for chronic fatigue syndrome<sup>1</sup> completed a further investigation, including a functional musculoskeletal and neurological examination, a psychosocial interview and several questionnaires (see below). Fibromyalgia was additionally diagnosed when diffuse musculoskeletal pain (> three months duration) and at least 11 tender points were present.<sup>23</sup>

In a final advice interview, the patient was informed about the negative results of the diagnostic screening and, subsequently, a working hypothesis with regard to her condition was proposed in the following terms: 'You are suffering from physical and mental effort intolerance because of a loss of resilience of your stress system'. It was further explained that an active therapeutic approach would not only facilitate symptom control but also optimize chances of recovery. When the patient showed sufficient motivation for this approach, she gave written consent and entered the programme. No other selection criterion was used, except the impossibility of attending an outpatient setting (e.g. because of geographical reasons).

### Evaluation of health-related quality of life/ psychosocial variables

The following questionnaires (in Dutch) were completed before and after treatment. The Short Form General Health Survey (SF-36)<sup>24</sup> assesses the patient's own health perception and can be considered a HRQoL index. Eight subscales are distinguished: physical and social functioning, role limitations attributed to physical and emotional problems, mental health, vitality (energy/fatigue), pain, and general health perception. For all subscales a higher score reflects a more positive experience.

The Symptom Checklist 90 (SCL-90)<sup>25</sup> is an indicator of psychopathology. Ninety physical and psychological symptoms are questioned, divided into eight clinical items. For the purpose of the present study, only the total score was considered.

A higher score is associated with a higher degree of psychopathology.

The Causal Attribution List (CAL)<sup>26</sup> assesses whether the patient is likely to attribute complaints to physical or non-physical causes. A higher score indicates a stronger conviction.

The Self-Efficacy Scale (SE)<sup>26</sup> evaluates the extent to which the patient feels in control of her symptoms. A higher score means more control.

### Evaluation of exercise capacity

Before and after treatment, all patients performed progressive bicycle ergometry until volitional exhaustion (20+10 W/min). Heart rate was measured continuously by the electrocardiogram and expired gases were analysed breath-by-breath by a computerized standard open-circuit technique (Sensormedics Vmax 29; Sensormedics, Yorba Linda, CA, USA). The flowmeter and gas analysers were calibrated each morning. Peak oxygen uptake ( $\dot{V}O_2$ ) and peak respiratory gas exchange ratio are the highest 30 s values at the end of the exercise test. The highest workload achieved (peak workload) and exercise duration were also recorded.

Leg muscle strength was assessed by isokinetic dynamometry (Cybex Norm; Lumenex, Ronkonkoma, NY, USA). Peak torque of hamstrings and quadriceps was measured at a speed of 60°/s, normalized for body weight, and expressed as a percentage. The values of right and left hamstrings and quadriceps were averaged for the analyses.

### Therapeutic intervention

The treatment lasted six months. It took two days a week (4 h a day) during the first month, and was then gradually reduced to one day in a month. Each visit consisted of a cognitive behavioural therapy group session and a graded exercise training group session. Gradually, psycho-educational and supportive group discussions (one in the presence of the patient's family), relaxation and breathing exercises, and (on demand) psychiatric and/or medical consultations were added to the programme.

In line with our working hypothesis, the cognitive behavioural therapist encouraged patients to pace their activities and respect their physical and mental limitations, emphasizing at the same time

the importance of progressively building up their physical condition.<sup>27</sup> It was explained to the patients that by combining these two strategies they could regain physical and mental resilience, and restore a new physical and mental equilibrium which could eventually lead to symptomatic improvements and long-term recovery.

Graded exercise training consisted of one-hour sessions, structured as follows: warming-up – cycling – stretching – individual discussion of problems or progression. An electromagnetically braked ergometer was used for cycling, with continuous heart rate registration (Polar Electro Inc., Lake Success, NY, USA). Initial exercise duration was 10 min and progressively increased to 30 min (each two weeks +2 min). Initial training intensity corresponded to the workload at 60% of the heart rate reserve (Karvonen's formula; calculated on the basis of the maximal exercise test).

The main goal of graded exercise training during the first two weeks was to familiarize the patient with cycling and to titrate the training programme. Starting from week 3, all participants were asked to exercise three times a week. Thus, during weeks 3 and 4, the patients cycled twice a week at the centre and once at home; during months 2 and 3, once a week at the centre and twice at home; and from the fourth month on, three times a week at home, and once each month at the centre. The training programme was adjusted to a slower pace when deemed necessary, after discussion with the patient.

### Statistical analysis

Data are presented as means  $\pm$  standard deviations ( $X \pm SD$ ) or as otherwise indicated. After the data were checked for normality, paired Student's *t*-tests were used to assess changes between pre- and postrehabilitation (exercise test, strength test, questionnaires). After testing for linearity Pearson's correlation coefficients were calculated to determine the relationship of (the change in) peak  $\dot{V}O_2$  with general characteristics, physical and HRQoL/psychosocial variables. Statistica software (StatSoft Inc., Tulsa, OK, USA) was used for all analyses; the level of significance was set at  $P < 0.05$ .

## Results

Three out of 119 patients were excluded from the analysis because they withdrew prematurely from the therapy: one subject had other priorities (relational problems), for one patient the physical demand of the training programme was too high, and the third was unable to combine the therapy with professional occupations.

The patients' general, demographic and clinical characteristics at baseline are presented in Table 1. Pre- and post-treatment data concerning self-report questionnaires and the exercise/strength measurements are presented in Table 2.

### Health-related quality of life/psychosocial variables

Mean scores of the SF-36 questionnaire showed significant improvements on all subscales, except role limitations attributed to emotional problems (increments calculated on the basis of the range of the raw data; Table 2): physical functioning (+5%), social functioning (+6%), role limitations

**Table 1** General demographic and clinical characteristics of the subjects ( $n = 116$ )

General	
Age (years)	38.75 $\pm$ 8.16
Height (m)	1.65 $\pm$ 0.063
Weight (kg)	65.38 $\pm$ 11.01
Pain	
Tender points (N)	9.19 $\pm$ 5.49
Additional diagnosis fibromyalgia N (%)	54 (48)
Employment	
Unemployed N (%)	85 (73)
Duration unemployment (months)	15.79
Part-time employment N (%)	19 (16)
Full-time employment N (%)	12 (10)
Without help in householding N (%)	41 (36)
Day schedule	
Sleeptime (h)	9.36 $\pm$ 2.94
Downtime (h)	12.17 $\pm$ 3.04
Uptime (h)	11.86 $\pm$ 3.18
Activity time (h)	6.87 $\pm$ 3.76
Medical history	
Pre-existing fatigue (months)	58.06 $\pm$ 55.61
Involved in medico-legal procedure N (%)	9 (8)

Data are presented as  $X \pm SD$  unless indicated as N (%) (number of subjects (percentage)).

**Table 2** Data of questionnaires pre- and post-treatment, bicycle ergometry and strength tests

		Pre	Post
SF-36	Physical functioning (range 10–30)	18.17±4.13	19.06±4.43***
	Social functioning (range 2–10)	4.85±1.71	5.32±1.81*
	Limitations (phys) (range 4–8)	4.19±0.61	4.64±1.13***
	Limitations (emo) (range 3–6)	4.70±1.38	4.92±1.32
	Mental health (range 5–30)	19.57±4.77	20.66±4.65*
	Vitality (range 4–24)	9.66±2.87	11.15±3.65***
	Pain (range 2–12)	4.95±1.78	5.39±1.83**
	General health (range 5–25)	12.13±2.45	13.89±0.61***
SCL-90	Total score (range 90–450)	190±47.22	185.73±45.65
CAL	Non-physical (range 5–20)	10.78±2.86	11.72±2.94***
	Physical (range 5–20)	13.86±4.01	13.53±2.97
SE	Self-efficacy (range 5–24)	14.22±4.90	15.68±4.45**
Bicycle test	Peak $\dot{V}O_2$ /kg (mL/min/kg)	15.38±5.04	15.84±5.59
	Peak $\dot{V}O_2$ (mL/min)	992.35±346.56	1013.95±344.92
	Duration (min)	7.15±3.24	8.11±3.31***
	Peak W (W)	87.34±33.63	97.21±35.71***
	Peak RER	1.08±0.12	1.11±0.11*
	HR rest (sl/min)	85.34±15.19	85.12±14.40
	Peak HR (sl/min)	142.21±26.69	143.36±24.67
Strength test	Hamstrings (%BW)	54.81±29.41	60.65±32.37**
	Quadriceps (%BW)	121.28±54.49	125.3±56.87

Data are presented as  $X \pm SD$ ; SF-36, Short Form 36; SCL-90, Symptom Checklist 90; phys, attributed to physical problems; emo, attributed to emotional problems; CAL, Causal Attribution List; Peak  $\dot{V}O_2$ , peak oxygen uptake; Duration, time cycled; Peak W, highest achieved workload; Peak RER, highest respiratory gas exchange ratio; HR rest, heart rate at rest; Peak HR, highest heart rate recorded; BW, body weight.

\* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .

attributed to physical problems (+11%), mental health (+4%), vitality (+7%), pain (+4%), general health (+9%).

Also mean scores on the Causal Attribution List non-physical causes (+6%) as well as the Self-Efficacy Scale (+8%) improved significantly. The decrease of the mean total SCL-90 scores was not statistical significant.

### Exercise capacity measures

Statistically significant improvements were noted for mean exercise duration (+30%), peak workload (+18%), peak respiratory gas exchange ratio (+3%) and hamstring strength (+29%). On the other hand, changes in peak  $\dot{V}O_2$  were not significant (pre- and post-training peak  $\dot{V}O_2$  only amounted to 57% and 59%, respectively, of a normal sedentary population – reference values according to Wasserman).<sup>28</sup>

An analysis of the ergometer and isokinetic data of the 19 male patients yielded very comparable results: mean exercise capacity measures were equally low at baseline and only little improvements were found after six months of therapy (data not shown).

### Further analyses

Correlation analyses indicated that (changes in) peak  $\dot{V}O_2$  did not correlate, or only weakly correlated with (changes in) HRQoL/psychosocial variables (Table 3).

To assess which patients would derive most benefit from the therapeutic programme, the total group was split in two subgroups, according to the patients' initial fitness level. After peak  $\dot{V}O_2$  was corrected for age, height and weight (Wasserman's formula), patients were assigned to either the group with the highest or the lowest initial peak

**Table 3** Significant Pearson correlation coefficients (*r*) of peak  $\dot{V}O_2$  with HRQoL/psychosocial variables ( $P < 0.05$ )

Relation of peak $\dot{V}O_2$ (pre) with HRQoL/psychosocial (pre) variables		Relation of peak $\dot{V}O_2$ (post) with HRQoL/psychosocial (post) variables		Relation of $\Delta$ peak $\dot{V}O_2$ with HRQoL/psychosocial ( $\Delta$ ) variables	
Variables	<i>r</i>	Variables	<i>r</i>	Variables	<i>r</i>
SCL-90 total score	-0.27	SCL-90 total score	-0.21	SCL-90 total score	ns
Physical functioning	0.45	Physical functioning	0.38	Physical functioning	ns
Social functioning	ns	Social functioning	ns	Social functioning	-0.26
Limitations (emo)	0.22	Limitations (emo)	ns	Limitations (emo)	ns
Mental health	0.22	Mental health	0.21	Mental health	ns
Vitality	0.25	Vitality	ns	Vitality	-0.25
Pain	0.20	Pain	0.23	Pain	-0.22
Self-Efficacy	0.34	Self-Efficacy	0.38	Self-Efficacy	ns

Peak  $\dot{V}O_2$ , peak oxygen uptake (mL/min/kg);  $\Delta$ , change, post-pre; ns, not significant ( $P > 0.05$ ). SCL-90, Symptom Checklist 90; Limitations (emo), role limitations attributed to emotional problems.

$V_{O_2}$  (i.e. above or below the median value, respectively).

Post-treatment, the *less fit* subgroup showed a significant increase of their exercise capacity, either expressed as peak workload achieved, peak  $V_{O_2}$  or exercise duration, but not in terms of hamstrings or quadriceps strength; in contrast, the *more fit* subgroup did not change significantly (Figure 1). Furthermore, with regard to the HRQoL/psychosocial variables, both subgroups showed generally similar post-treatment changes (Table 4).

## Discussion

### Reported improvements

After six months of multidisciplinary treatment, significant improvements were noted in most HRQoL/psychosocial variables (i.e. an increase in nearly all SF-36 subscales, as well as an increase in non-physical causal attributions and self-efficacy), pointing to the fact that patients reported better physical and psychosocial functioning, and engaged in more active coping with all aspects of their ailment.

Thus, these findings suggest that patients with chronic fatigue syndrome may substantially benefit from therapeutic strategies that help them accept current functional limitations, carefully manage energy, reduce emotional stress and overburden-

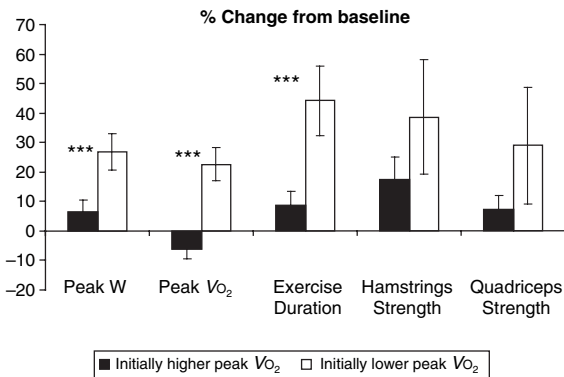
ing, adjust maladaptive lifestyle patterns (e.g. not engage in periodic ‘bursts’ of activity) and reset long-term goals and priorities, while at the same time trying to ameliorate their physical condition as much as possible.<sup>5,6,29</sup> Although it seems plausible that such adaptive changes may in the long-term favour an increase of physical and mental effort tolerance, due to the recovery of neurobiological (e.g. hypothalamic–pituitary–adrenal axis) imbalances and/or perceptual disturbances underlying the syndrome,<sup>29–34</sup> definite proof for this assumption is still lacking.<sup>35</sup>

### Measured exercise capacity

At the end of the programme, changes in exercise capacity measures were found to be rather modest. For example, mean increase of peak  $V_{O_2}$  was only 9% in our patients, which is somewhat lower than the results of earlier studies.<sup>8,9</sup> Moreover, exercise capacity measures did not correlate, or only weakly correlated to (changes in) HRQoL/psychosocial variables. Interestingly, less fit patients with chronic fatigue syndrome seemed to improve most on exercise capacity measures, while reaching similar HRQoL/psychosocial improvements as their more fit counterparts.

These findings suggest that an increase in exercise capacity (or aerobic fitness) may not be a necessary condition to obtain a significant amelioration of health-related quality of life and psychosocial functioning in patients with chronic fatigue syndrome. This is in accordance with the results of other graded exercise therapy studies,<sup>13,15</sup> and implies that reported improvements may be more determined by psychosocial changes such as a reduction in symptom focus<sup>13</sup> and/or lifestyle adaptations such as avoiding stress-exacerbating activities.<sup>36,37</sup> In the same vein, some authors found that exercise capacity only weakly correlated with activity limitations/participation restrictions.<sup>38</sup>

Consequently, exercise capacity (as measured by a maximal progressive bicycle ergometer test) should *not* be considered a primary outcome tool for evaluating therapeutic success in patients with chronic fatigue syndrome – contrary to what is often expected by social security and medico-legal authorities wanting to assess the patient’s ability to return to gainful employment.



**Figure 1** Effects of a six-month multidisciplinary treatment programme on the different aspects of exercise capacity in patients with lower versus higher initial peak  $V_{O_2}$ . Data are presented as means  $\pm$  SEM. \*\*\* =  $P < 0.001$ , % change from baseline of the patients with initially the highest peak  $V_{O_2}$  compared with the patients who were less fit. Peak W, peak workload; peak  $V_{O_2}$ , peak oxygen uptake.

**Table 4** Data of questionnaires pre- and post-treatment in patients with higher (HIGH) versus lower (LOW) initial fitness level

		HIGH			LOW		
		Pre	Post	Delta	Pre	Post	Delta
SF-36	Physical functioning (range 10–30)	18.8	19.7	+0.8	17.0*	18.1	+1.4
	Social functioning (range 2–10)	4.7	5.2	+0.6	4.8	5.3	+0.5
	Limitations (phys) (range 4–8)	4.2	4.6	+0.5	4.2	4.6	+0.5
	Limitations (emo) (range 3–6)	4.9	5.0	+0.1	4.4	4.7	+0.3
	Mental health (range 5–30)	20.6	21.0	+0.2	18.5*	20.1	+1.6
	Vitality (range 4–24)	10.1	11.2	+1.5	9.0	10.8	+2.0
	Pain (range 2–12)	5.1	5.4	+0.5	4.8	5.3	+0.7
	General health (range 5–25)	11.9	13.8	+1.9	12.2	14.0	+1.8
SCL-90	Total score (range 90–450)	179	181	–2	206**	194	–14
CAL	Non-physical (range 5–20)	10.4	11.8	+1.6	11.2	11.6	+0.6
	Physical (range 5–20)	14.5	14.3	–0.6	12.7**	13.0*	–0.6
SE	Self-Efficacy (range 5–24)	14.6	16.4	+2.0	13.2	14.7	+1.2

Data are means (without SD); SF-36, Short Form 36; phys, attributed to physical problems; emo, attributed to emotional problems; SCL-90, Symptom Checklist 90; CAL, Causal Attribution List.

\* $P < 0.05$ , \*\* $P < 0.01$ .

Finally, our findings suggest that patients with chronic fatigue syndrome who are severely physically deconditioned (e.g. as a result of excessive rest, activity avoidance or persistent sleep disturbances<sup>15,39–41</sup>) may derive most benefit from graded exercise therapy. However, from a methodological point of view, this conclusion should be regarded with caution (see below).

### Methodological considerations

First, in the absence of a control group, we cannot exclude that our findings may be influenced by non-specific therapeutic factors. Second, since we studied a multimodal treatment, we cannot rule out that 'pure' graded exercise therapy or 'pure' cognitive behavioural therapy might have resulted in a different outcome. Third, it is possible that the cognitive behavioural part of our treatment, when carried out in an individual (instead of a group) setting, could have led to better overall results.

On the other hand, the clinical validity of our study may be high, for several reasons. First, we investigated a large sample of strictly defined patients with chronic fatigue syndrome who were relatively unselected, implying that many of them had concomitant psychosocial and/or psychiatric

problems – as is frequently the case in these patients.<sup>2,29</sup> Furthermore, our study took place in a naturalistic setting, using treatment strategies that are commonly used in routine clinical practice. Finally, the drop-out rate in our study was remarkably low compared with that in other

### Clinical messages

- A multidisciplinary outpatient group treatment, mainly based on cognitive behavioural and graded exercise therapy, may significantly improve the health-related quality of life and psychosocial functioning of patients with chronic fatigue syndrome.
- Exercise capacity measurement by a maximal progressive bicycle ergometer test is not an adequate tool for evaluating therapeutic success in chronic fatigue syndrome.
- Less fit patients with chronic fatigue syndrome may need a different therapeutic approach from more fit patients with chronic fatigue syndrome.

studies (see e.g. ref. 13), which also adds to its clinical validity.

## Conclusions

A multidisciplinary group treatment for patients with chronic fatigue syndrome, mainly based on cognitive behavioural and graded exercise therapy, and carried out in an outpatient rehabilitation setting, may lead to significant benefits with regard to health-related quality of life and psychosocial functioning, *without* pronounced changes in exercise capacity – as measured by a maximal progressive bicycle ergometer test. However, for less fit patients with chronic fatigue syndrome an increase of exercise capacity appears to be necessary to attain benefits similar to those in their more fit counterparts.

These results add to the uncertainties and discussions about the role of physical deconditioning in the aetiopathogenesis and treatment of chronic fatigue syndrome,<sup>5,6,16,42</sup> and suggest that the perceived physical and mental exertion of patients with chronic fatigue syndrome may be primarily due to a central problem of impaired effort tolerance.<sup>27–32,43</sup>

Although there are no doubts about the potential usefulness of graded exercise therapy in chronic fatigue syndrome,<sup>44,45</sup> further controlled research should investigate which patients with chronic fatigue syndrome would need such therapy, and which would not.

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