

Effects of a Self-regulation Based Physical Activity Program (The “4-STEPS”) for Unexplained Chronic Fatigue: a Randomized Controlled Trial

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Abstract

Background This study aimed at assessing the effects of a self-regulation-based brief physical activity program for patients suffering from unexplained chronic fatigue, the “4-STEPS to control your fatigue program”.

Method A 12-week randomized controlled trial was conducted. Adult patients meeting the CDC criteria for idiopathic chronic fatigue were randomized to either the control condition (standard care) or the intervention condition (4-STEPS). The 4-STEPS was based on self-regulation principles and consisted of motivational interviewing and self-regulation skills training. All patients were assessed at baseline and post-treatment (12 weeks) for fatigue severity (primary outcome) and impact, physical activity (leisure time physical activity, number of daily steps and personal activity goal progress), health-related quality of life, somatic distress and psychological distress (depression and anxiety).

Results Ninety-one patients (45 intervention and 46 control patients) received the allocated intervention. At post-treatment, statistical analysis revealed a significant difference for subjective experience of fatigue (4.73 points; $g=0.51$) in favour of the intervention group. Mixed design ANCOVAs showed a significant effect of the 4-STEPS on fatigue severity, leisure time physical activity, personal activity goal progress and health-related quality of life. No significant effects were found for number of daily steps and somatic and psychological distress.

Conclusion The 4-STEPS program has significant beneficial effects at post-treatment. This brief self-regulation-based intervention looks promising for the management of unexplained chronic fatigue.

Trial Registration: ISRCTN70763996

Keywords Chronic fatigue · Randomized controlled trial · Physical activity · Self-regulation

Introduction

Unexplained or idiopathic chronic fatigue (ICF) is a condition characterized by the presence of severe and persistent fatigue (lasting for at least 6 months) that cannot be explained by an organic disease. According to the Centres for Disease Control and Prevention (CDC), persistent fatigue is diagnosed as chronic fatigue syndrome (CFS), a condition that a minimum number of additional somatic symptoms are present [1]. CFS is a serious medical condition in which the patient's functioning is significantly impaired leading to disability and lower health-related quality of life (HRQoL) [2]. One of the major symptoms is the presence of post-exertional malaise, which is characterized by severe exhaustion following physical activity. Patients' perceptions and expectations related to symptom exacerbation as a consequence of exercise can lead to fear of physical exercise and can, therefore, explain the reduced levels of physical activity found in these patients [3, 4]. In addition, several studies emphasize the fact that the lack of physical activity and excessive resting found in these patients can result in physical deconditioning and, as a consequence, perpetuate fatigue severity and physical disability [4–6]. Therefore, (balanced) physical activity has been considered to be an important behaviour in managing chronic fatigue [7].

Graded exercise therapy (GET), a behavioural intervention targeting a gradual increase in aerobic exercise (in order to avoid overexertion), has been shown to have beneficial effects

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on fatigue severity in CFS patients [8]. Cognitive behavioural therapy (CBT), which usually incorporates changes in physical activity (and rest) behaviour, has also demonstrated to be effective in reducing fatigue symptoms in CFS patients [9]. A recent meta-analysis compared the effectiveness of GET and CBT [10]. Both were moderately effective in reducing fatigue and functional impairment. Still, results were heterogeneous.

Both CBT and GET interventions are usually resource-intensive requiring a considerable number of contact hours and sessions (in general between 8 and 16 sessions) with patients [10, 11]. Recently, two randomized controlled trials that tried to overcome this limitation by conducting minimal contact CBT interventions based on self-guided instruction manuals and regular email contacts showed promising results [12, 13]. Another intervention study (pragmatic rehabilitation) targeting physical activity for chronic fatigue patients, comparing treatment conditions that differ in intensity, found that the minimum intervention conditions (two face-to-face sessions with or without seven brief telephone contacts) were as successful as a more extensive version of the program (nine face-to-face sessions) [14].

Adopting a health behaviour change framework, such as self-regulation (SR) theory, e.g. [15] can be useful for promoting physical activity in chronic fatigue patients [16, 17]. SR-based interventions have demonstrated to be effective in promoting health behaviour change in chronic disease populations [17–20]. According to SR theory, behaviour is a goal guidance process [16]. This process consists of a goal selection/goal setting or motivational phase, an active goal pursuit or action phase and a goal attainment or maintenance phase. Several SR cognitions and skills are guiding this process, such as autonomous regulation of behaviour (and goal ownership), self-efficacy, goal setting, planning, self-monitoring, feedback, emotional and attention regulation and relapse prevention strategies [16].

An important form of intervention that incorporates SR principles is motivational interviewing (MI), which is a “collaborative conversation style for strengthening a person’s own motivation and commitment to change” ([21] p. 12). In MI, the patient’s own motivation for change is evoked and self-efficacy is strengthened. MI was found to be effective in promoting health behaviour change, especially in helping patients move from ambivalence toward behaviour change during a motivational phase [21, 22]. While MI mainly focuses on SR cognitions, SR skills are equally important, especially during the active goal pursuit and maintenance phase [16].

From this perspective, we developed a brief SR-based intervention, combining MI and SR skills training to target physical activity among patients with unexplained chronic fatigue (the “4-STEPS to control your fatigue” program). This study aimed at evaluating the effects of the 4-STEPS program upon fatigue severity and impact, physical activity, health-related quality of life, somatic distress and psychological distress.

Method

The rationale and details of the trial design were given in detail elsewhere [23] and will thus only be briefly summarized here.

Trial Design

This was a 12-week parallel group, multicentre randomized controlled trial, with equal randomization (1:1) to either the intervention condition (4-STEPS program) or the control condition. Randomization sequence was stratified by sample (health-care centres and patient association) and within the first sample also by centre. Randomization was conducted using computer-generated allocation numbers under the supervision of a member of the research team, who did not take part in the subsequent phases of the trial. Group allocation was known to subjects, therapist and assessors. Patients were recruited from consecutive referrals. Patients were assessed at baseline (T1) and 12 weeks later (post-treatment, T2). The primary outcome was a subjective experience of fatigue, and secondary outcomes were fatigue severity, fatigue impact, physical activity, HRQoL (physical and psychological functioning), somatic distress and psychological distress (depression and anxiety). Approval was obtained from the Portuguese Medical Ethics Committee of the North Regional Health Administration and from the medical board of each participating health-care centre. The trial was conducted between January 2011 and December 2012.

Participants and Procedure

Adult patients meeting the CDC criteria for idiopathic chronic fatigue (i.e. presenting a main complaint of unexplained fatigue of at least 6 months duration) were eligible to participate in the study [1]. Additional inclusion criteria were to fully understand and speak Portuguese and to have the capacity to provide an informed consent. Patients presenting a concurrent somatic condition and/or a severe psychiatric disorder that could explain fatigue symptoms (according to the CDC criteria for exclusionary medical and psychiatric conditions [1]) were excluded.

The study was conducted in several Portuguese health-care institutions (four public primary care centres and one private practice) and in the Portuguese Fibromyalgia and Chronic Fatigue Syndrome Patient Association. Based on the inclusion and exclusion criteria, patients from the health-care centres were referred by their medical doctor. All patients were informed of the trial content and invited for an individual interview in the health-care centre (baseline assessment). Patients from the patient association who met the criteria (i.e. clinical diagnosis of unexplained chronic fatigue) and previously indicated their willingness to participate in research received an institutional letter containing the details of the trial. Patients who wished to participate returned the written informed consent form and were invited for the baseline assessment. For

both samples, the inclusion and exclusion criteria were checked by the research team using self-report measures based on the CDC criteria. In addition to standard medical care, patients assigned to the control condition received a flyer with information about the general health benefits of physical activity and current physical activity guidelines for adults [24] and set a personal physical activity goal for the upcoming months. Participants assigned to the intervention condition additionally received the 4-STEPS program.

4-STEPS to Control Your Fatigue

The 4-STEPS program consisted of a brief SR-based intervention to promote physical activity in chronic fatigue patients. The intervention was delivered by one trained health psychologist (with motivational interviewing training) to individual patients. The intervention was structured around the SR phases of goal pursuit (goal selection and setting, active goal pursuit and goal attainment, maintenance and disengagement) [17]. Firstly, participants received two 1-h face-to-face individual motivational interviewing sessions (weeks 1 and 3) aimed at (a) exploring important health and life goals to which a physical activity goal could be related, (b) increasing participants' motivation and confidence to be physically active and (c) setting a specific personal physical activity goal. This personal and flexible physical activity goal, which took into consideration the need to avoid overexertion, was set by each patient during the second MI session. Patients also formed action plans regarding their goal (i.e. which physical activities would be done and when, where, for how long and with whom each would take place). Secondly, participants received an informational booklet (available from the first author) containing information regarding (a) the diagnosis of CF(S), (b) factors contributing to a better or worse prognosis and (c) the link between CF(S) symptoms and physical (in-)activity and the boom-bust pattern (i.e. erratic pattern of rest and activity) commonly found in these patients. Thirdly, a SR-based workbook (available from the first author) was given to patients. The SR workbook was divided in four steps, each one focusing on specific SR cognitions and skills: step 1—"Am I ready to start?" (focusing on self-efficacy, motivation and control over competing goals), step 2—"My physical activity goal" (focusing on goal setting, action planning and self-monitoring), step 3—"Overcoming obstacles" (focusing on coping efficacy and planning, feedback and attention and emotion regulation, i.e. control of distracting stimuli and negative emotions to maintain a focus on goal pursuit) and step 4—"I am physically active...and I want to keep it this way" (focusing on relapse prevention, including coping efficacy and planning and goal reformulation). Fourthly, patients received two brief SR-based telephone counselling sessions (weeks 5 and 9). This telephone support aimed at reviewing the participants' physical activity goal and providing relapse prevention strategies. Fifthly, patients received a pedometer to

register steps taken on a daily basis during the 12-week intervention period. Finally, patients received a leaflet for their partner or significant other with relevant information on chronic fatigue, the objective of which was to increase social support.

Outcomes

Patient Characteristics Socio-demographic characteristics included age, gender, education and employment status. Clinical information was gathered using the following indicators: (1) presence of persistent fatigue, (2) duration of fatigue symptoms, (3) impact of fatigue on daily activities (4) whether fatigue was alleviated by rest, (5) number of medical consultations and (6) a CDC-based symptom checklist for CFS [25]. The checklist presents 19 major and minor symptoms of CFS, as defined by the CDC criteria [1]. Respondents are asked to rate if they experienced each of the symptoms for the last 6 months. For the purpose of this study, a dichotomous scale (yes/no) was used. A major symptom score is calculated by adding up the number of major symptoms presented (ranging from 1 to 8). To be diagnosed with CFS, patients need to have a complaint of persistent unexplained fatigue (at least 6 months) that leads to a significant disability and to have at least four of the major CFS symptoms listed by the CDC. Patients not fulfilling the full criteria were classified as ICF patients. The self-reported measures also included a question regarding the presence of chronic disease and/or psychiatric disease, as well as name and duration if any.

Fatigue Severity It was assessed at T1 and T2 by means of the Portuguese adaptation of the Checklist of Individual Strength (CIS20-P) [26], which is a well-validated and reliable measure for assessing fatigue severity in chronic fatigue patients [27]. The CIS20 is a 20-item self-report measure that assesses four dimensions of fatigue: *subjective experience of fatigue, concentration, motivation and activities*. Items are rated on a seven-point scale. A total score (total fatigue severity) can be calculated by adding up the scores for each dimension. For the purpose of this study, only the subjective experience of fatigue dimension (primary outcome; range 8–56) and the total fatigue severity score (range 20–140) were used. Higher scores indicate more fatigue. A cutoff point of 35 on the subjective experience of fatigue dimension of the CIS20 is usually used to define a clinical level of fatigue [28].

Fatigue Impact It (T1 and T2) was measured by means of a modified version of the pain interference dimension of the well-validated Brief Pain Inventory (BPI) consisting of seven items [29]. Participants were asked to rate on a 10-point scale how their fatigue interfered with several aspects of their life. The total score was used as an outcome. Higher scores indicate a higher fatigue impact (ranging from 0 to 10).

Physical Activity It (T1 and T2) was assessed by means of the following:

1. A self-report measure of *leisure time physical activity* based on the Short Questionnaire to Assess Health-Enhancing Physical Activity (SQUASH) [30]. Participants indicate the number of days per week and minutes per day in which they engage in physical activities (bicycling, walking and other activities such as swimming). For each activity of at least moderate intensity (≥ 3 METs based on the categories of the Ainsworth's compendium of physical activities [31, 32]), total minutes of physical activity per week is calculated by multiplying frequency (days/week) and duration (minutes/day). Total number of minutes of leisure time physical activity (moderate to vigorous physical activity, MVPA) per week is calculated by taking the sum of each activity score.
2. Physical activity was also measured by means of a *pedometer* (T1 and T2). Daily steps were assessed using Yamax Digiwalker SW-200 pedometers, which have been demonstrated to be accurate and reliable [33, 34]. Participants were asked to wear the pedometer for seven consecutive days and register the daily number of steps at the end of each day. The mean of the daily steps over these 7 days was used as an outcome measure.
3. *Personal physical activity goal progress*. Using a standardized goal elicitation procedure, respondents specify a personal physical activity goal which they wish to pursue over the next months. At post-treatment, respondents were reminded of their personal goal and asked to indicate their progress on a 10-cm visual analogue scale (VAS), ranging from "I haven't started yet" (0) to "I have achieved my goal" (10) [35]. Participants of the control group set a personal physical activity goal during the baseline assessment session and participants of the intervention group set their physical activity goal during the second motivational interviewing session.

HRQoL It (T1 and T2) was measured using the Short Form Health Survey-12 (SF-12V.2) [36]. The SF-12v2 is a well-validated measure that allows to calculate a physical functioning score (physical HRQoL) and a psychological functioning score (psychological HRQoL), ranging from 0 to 100, with lower scores representing worse HRQoL.

Somatic Distress It (T1 and T2) was measured by means of the Patient Health Questionnaire-15 (PHQ-15). The PHQ-15 assesses the presence and severity of 15 somatic symptoms (e.g. back pain). Patients are asked to indicate to what extent they have been bothered in the past 4 weeks by each symptom, with higher scores indicating higher somatic symptom severity (range 0–30) [37].

Psychological Distress It was assessed at T1 and T2 using the Depression and Anxiety subscales from the well-validated and

widely used Brief Symptom Inventory (BSI) [38]. Individuals rank each symptom on a five-point Likert scale (from "never" to "very frequently") with higher scores representing more psychological distress. Scores were calculated by taking the mean of the items of each subscale (range 0–4).

Sample Size

An a priori analysis [39] showed that a sample of 34 participants in each group would be sufficient to detect a mean difference of 7 points [12, 40] between the intervention and the control group on the subjective experience of fatigue dimension of the CIS20-P, with 80 % power at a 5 % significance level. Considering a possible dropout of 20 %, we aimed at recruiting 41 subjects per group.

Statistical Analyses

Descriptive analyses were performed for gender, age, education, employment, clinical information and use of health-care resources. Differences between groups at baseline were analyzed using *t* tests (for continuous variables) and univariate chi-square tests (for dichotomous variables). The difference in subjective experience of fatigue (primary outcome) between the intervention and control group at post-treatment was analyzed with an independent samples *t* test.

Effects of the intervention on primary and secondary outcomes were examined using 2 (baseline, T1 vs. post-treatment, T2) \times 2 (intervention vs. control) mixed model repeated measures analysis of covariance (ANCOVA), controlling for setting (health-care centres vs. patient association) and disease duration. Effect sizes (ES) were the standardized mean differences [(mean a – mean b / pooled SD)] with Hedge's *g* correction for small samples [41]. Prior to analysis, data was inspected for normality and homogeneity of variance. Leisure time physical activity was not normally distributed at both time points, and so it was logarithmic-transformed ($\text{Lg}+1$) for further analyses. Descriptive statistics for this variable is presented in a non-transformed format. Mixed design ANCOVAs were conducted with intention-to-treat analyses (ITT) using the last observation carried forward method (LOCF), which included all participants for whom complete baseline data was available. We undertook sensitivity analyses to test the robustness of the results of the mixed design ANCOVAs using (a) complete case analysis and (b) multiple imputation analysis. Five imputation data sets were generated based on the results from the complete case data set using outcome variables as predictors. Linear regression models were adopted for the multiple imputation, with the exception of leisure time physical activity in which we used a predictive mean matching (PMM) approach due to the non-normal distribution of this variable. Assumption that data was missing at random (MAR) was first verified. Each data set was analyzed individually using mixed design ANCOVAs. Sensitivity analyses revealed similar results for the three approaches, with the exception of psychological HrQoL. Therefore,

the main results report the ITT analyses. Missing values at baseline due to incomplete assessment (number of steps per day and goal progress) were also imputed using multiple imputation.

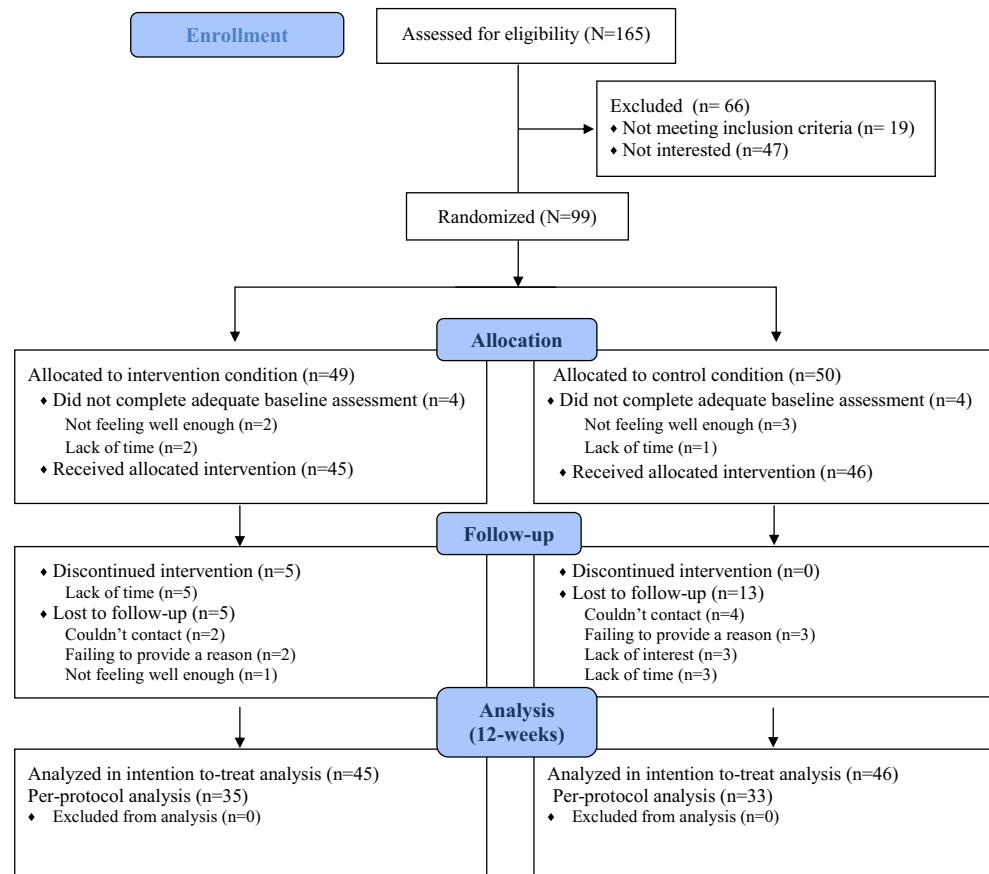
Finally, at T2, additional chi-square analyses were conducted for the complete data set to compare the proportion of patients in each group (a) who did not meet clinical levels for fatigue severity (<35) assessed by the subjective experience of fatigue sub-scale of the CIS20-P and (b) who were physically active. Effect sizes (ES) were risk ratio (RR). We considered p values lower than or equal to 0.05 as significant. Data analyses were conducted using the statistical software SPSS v22.

Results

Participant Flow and Patient Characteristics

Among the 165 individuals who were identified as eligible to participate and who were informed about the study, 99 patients were randomized to either the 4-STEPS program or the control condition and 91 recruited into the trial with adequate baseline measures completed (intervention condition: $n=45$; control condition: $n=46$). The flow of patients through the trial and reasons for exclusions and withdrawals are displayed in Fig. 1.

Fig. 1 Flow diagram of participants through the intervention



Demographics and clinical characteristics are presented in Tables 1 and 2. No significant differences were found for any of the demographics and clinical variables.

Intervention Effects

A significant difference of 4.73 points in the subjective experience of fatigue was found between the intervention and the control group ($t=-2.46$, $p=.016$, 95 % CI -8.54 to -0.91 , $g=0.51$). Patients in the intervention group presented with lower levels of fatigue severity than those in the control group. At T2, there was no significant difference in the proportion of patients presenting non-clinical levels of fatigue in the intervention (10/35, 28.6 %) and control groups (5/33–15.2 %; $X^2=1.779$, $p=0.18$; RR=1.89 95 % CI 0.72 to 4.94). This corresponds to an increase from baseline in the percentage of patients presenting non-clinical levels of fatigue of 25.7 and 6.1 % respectively.

The results of the mixed design ANCOVAs for the ITT (LOCF) approach are presented in Table 2 (for a comparison of results between the three approaches, see Table 3). There was a significant effect of the intervention on levels of subjective experience of fatigue and total fatigue severity after controlling for the effect of the covariates ($p=.028$ and $p=.019$; respectively). In the intervention group, there was a significant decrease from T1 to T2 in the subjective

Table 1 Baseline demographics and patient characteristics

Characteristic	Intervention (<i>n</i> =45)	Control (<i>n</i> =46)	<i>p</i> value
Age	46.96±10.39	49.20±11.49	0.33
Gender (women)	44 (97.8)	45 (97.8)	1.00
Education			
Primary	12 (26.7)	16 (34.8)	0.65
Secondary	17 (37.8)	17 (37.0)	
Higher	16 (35.6)	13 (28.3)	
Employed	24 (54.3)	25 (54.3)	1.00
Not working due to fatigue ^a	10 (45.5)	11 (47.8)	1.00
Absenteeism (<i>n</i> days) ^b	6.20±10.44	14.36±22.61	0.14
Physically active ^c	15 (33.3)	17 (37)	0.82
Disease duration (years)	9.81±8.02	10.96±9.06	0.53
Number of medical consultations	4.03±2.88	5.10±4.43	0.20
Number of major CDC CFS symptoms	6.42±1.29	6.70±1.38	0.33
Diagnostic criteria			
ICF	5 (11.1)	3 (6.5)	0.49
CFS	40 (88.9)	43 (93.5)	
Clinical levels of fatigue ^{d,e}			
Yes	42 (93.3)	43 (93.5)	1.00
No	3 (6.7)	3 (6.5)	
Setting			1.00
Health-care centres	24 (53.3)	25 (54.3)	
Patient association	21 (46.7)	21 (45.7)	

Values are presented as mean±standard deviation or frequencies (%).

CDC Centres for Disease Control and Prevention, ICF idiopathic chronic fatigue, CFS chronic fatigue syndrome

^a *n*=21 in each condition

^b *n*=20 (intervention condition); *n*=22 (control condition)

^c Results for completers [Physically active: intervention group=14/35 (40 %); control condition=15/33 (45.5 %); *p*=0.65]

^d Cutoff score of 35 on the subjective fatigue sub-scale of the CIS20

^e Results for completers [clinical levels=34/35 (97.1 %) and 30/33 (90.9 %); *p*=0.35]

Table 2 Changes in outcomes between baseline (T1) and post-treatment (T2)

Outcome	Intervention (<i>n</i> =45)		Control (<i>n</i> =46)		Group×time interaction ^a		
	T1	T2	T1	T2	F	<i>p</i>	<i>g</i> ^b
Subjective fatigue	46.00±6.30	42.62±9.93	47.00±7.66	47.35±8.31	F=4.965	.028	0.44
Fatigue severity ^c	98.40±16.43	93.73±22.37	103.54±19.07	106.76±20.32	F=5.721	.019	0.39
Fatigue impact	6.25±1.89	5.89±2.38	6.88±1.90	6.33±2.21	F=0.360	.550	0.09
Leisure time PA ^d	41.56±70.59	120.67±146.19	58.37±106.28	57.39±152.00	F=20.38	.000	0.77
PA (steps/day)	6629±2716	7077±2746	6773±2820	6385±2830	F=3.748	.056	0.30
Goal progress	1.50±2.39	4.16±3.30	2.32±3.04	2.51±2.84	F=16.37	.000	0.83
Physical HRQoL	38.22±17.78	43.33±21.87	31.30±18.90	28.15±21.43	F=9.880	.002	0.41
Mental HRQoL	41.57±16.12	46.85±19.71	37.59±17.62	36.79±19.15	F=4.075	.047	0.33
Somatic distress	14.02±4.04	13.05±4.72	16.20±4.47	15.76±4.48	F=0.562	.456	0.12
Depression	1.49±0.88	1.55±0.95	1.55±0.95	1.91±0.93	F=0.182	.671	0.05
Anxiety	1.63±0.77	1.44±0.79	1.66±0.79	1.64±0.81	F=1.203	.276	0.29

Values are presented as mean±standard deviation

PA physical activity, HRQoL health-related quality of life

^a Mixed design repeated measures using intention to treat analysis adjusted for disease duration and setting (health-care centres vs. patient association)

^b *g*=Hedge's *g* (interpreted according to Cohen's *d* (0.20—small; 0.50—medium; 0.80—large)

^c CIS20 total score

^d Descriptives are presented in raw form

Table 3 Comparison between methods of data analysis (complete data set, last observation carried forward, multiple imputation)

Outcome	<i>F</i> ^a	<i>p</i>	<i>g</i> ^b	Model
Subjective fatigue	4.97	.028	0.44	LOCF
	4.49	.038	0.55	Complete case
	7.75	.007	0.58	Smallest MI effect (3/5 sig)
Fatigue severity ^c	5.72	.019	0.39	LOCF
	5.43	.023	0.51	Complete case
	13.51	.000	0.69	Smallest MI effect (4/5 sig)
Fatigue impact	0.36	.550	0.09	LOCF
	0.56	.457	0.15	Complete case
	1.20	.331	0.12	Smallest MI effect (0/5 sig)
Leisure time PA	20.38	.000	0.77	LOCF
	11.19	.001	0.71	Complete case
	13.44	.000	0.70	Smallest MI effect (5/5 sig)
PA (steps/day)	3.75	.056	0.30	LOCF
	3.82	.055	0.40	Complete case
	5.04	.027	0.43	Smallest MI effect (1/5 sig)
PA goal progress	16.37	.000	0.83	LOCF
	16.83	.000	1.04	Complete case
	22.84	.000	1.18	Smallest MI effect (5/5 sig)
Physical HRQoL	9.88	.002	0.41	LOCF
	9.89	.003	0.52	Complete case
	14.46	.000	0.57	Smallest MI effect (3/5 sig)
Mental HRQoL	4.08	.047	0.33	LOCF
	3.91	.052	0.43	Complete case
	9.07	.003	0.57	Smallest MI effect (2/5 sig)
Somatic distress	0.56	.456	0.12	LOCF
	0.42	.521	0.15	Complete case
	1.79	.152	0.26	Smallest MI effect (0/5 sig)
Depression	0.18	.671	0.05	LOCF
	0.21	.646	−0.07	Complete case
	0.83	.210	0.02	Smallest MI effect (0/5 sig)
Anxiety	1.20	.276	0.29	LOCF
	1.02	.317	0.28	Complete case
	5.06	.027	0.51	Smallest MI effect (1/5 sig)

PA physical activity, HRQoL health-related quality of life, LOCF last observation carried forward, MI multiple imputation

^aMixed design repeated measures adjusted for disease duration and setting (health-care centres vs. patient association)

^b*g*=Hedge's *g*

^cCIS20 total score

experience of fatigue (mean change=−3.38, 95 % CI −5.81 to −0.94; control group mean change=+0.35, 95 % CI −1.89 to 2.58) and total fatigue severity (mean change=−4.67, 95 % CI −9.61 to 0.28; control group mean change=+3.22, 95 % CI −0.87 to 7.31). Likewise, there was a significant time by group interaction in three out of five imputed data sets for subjective experience of fatigue ($p=.007$ to $p=.026$) and in four out of

five imputed data sets for total fatigue severity ($p=.000$ to $p=.017$). No significant effects were found for fatigue impact ($p=.550$; imputed data sets non-significant).

As for physical activity-related variables, patients in the intervention group presented significantly higher levels of leisure time physical activity ($p=.000$) and progress toward a personal physical activity goal ($p=.000$), also significant in all five imputed data sets ($p=.000$ to $p=0.21$ and $p<.001$, respectively). There was a significant increase in the intervention group from T1 to T2 for level of leisure time physical activity (mean change=+79.11, 95 % CI 39.71 to 118.52; control group mean change=−0.98, 95 % CI −29.03 to 27.07) and personal physical activity goal progress (mean change=+2.66, 95 % CI 1.79 to 3.53; control group mean change=+0.20, 95 % CI −0.66 to 1.05). The interaction effect for the number of steps/day was of small magnitude and not significant ($p=0.56$; mean change=+448, 95 % CI 33 to 861; control group mean change=−387, 95 % CI −1,096 to 322), but significant in only one (out of five) imputed data set ($p=.027$). There was a significantly higher proportion of physically active participants in the intervention group (26/35–74.3 %) in comparison to the control group (11/33–33.3 %; $X^2=13.22$, $p=0.00$; RR=2.23 95 % CI 1.32 to 3.75). Patients in either group reported no negative effects of exercise or participation in the study.

Repeated measure ANCOVAs also showed a significant time-by-group interaction for physical and psychological HrQoL after controlling for the effect of the covariates ($p=.002$ and $p=.047$, respectively). Mean change in the intervention group from T1 to T2 was +5.11 (95 % CI 1.05 to 9.17 and +5.28 (95 % CI −0.39 to 10.17), respectively (control group mean change=−3.15, 95 % CI −7.30 to 0.88 and −0.81, 95 % CI −381 to 2.20). There was a significant interaction effect in three out of five data sets imputed for physical HrQoL ($p=.000$ to $p=.006$) and only in two out of five data sets for psychological HrQoL ($p=.003$ to $p=.048$). No significant effects were found for somatic symptoms ($p=.456$) and psychological distress (depression and anxiety: $p=.671$ and $p=.276$, respectively) with any of the approaches employed.

Discussion

This study examined the effect of a 12-week brief self-regulation (SR)-based program for unexplained chronic fatigue (4-STEPPS) targeting physical activity. Attrition to the trial was higher than initially anticipated (≥ 20 %), but this study included a larger sample than what was established in the study protocol [23].

At post-treatment, there was a significant beneficial effect of the 4-STEPPS program on the subjective experience of fatigue (primary outcome). Although the difference between

the intervention and control conditions did not reach the seven-point target, the significant decrease in the subjective experience of fatigue in the intervention group (3.38) can be considered to be clinically significant as the difference exceeds 0.5 SD, a criterion used in other GET and CBT trials [42, 43]. Mixed design analysis comparing the intervention and control conditions at T1 and T2 revealed a moderate beneficial effect of the 4-STEPPS program on subjective experience of fatigue and total fatigue severity ($g=0.44$, $g=0.39$). These results are in line with the average effect size for fatigue severity found in a previous meta-analysis of graded exercise and psychological interventions for chronic fatigue management ($g=0.41$ and $g=0.36$) [10]. These effects are however lower than those found in other psychological-based minimal interventions [12, 15]. No significant differences were found between the proportion of patients in each condition who reached non-clinical levels of fatigue (<35) at T2; however, the number of patients presenting non-clinical levels of fatigue in the intervention condition is comparable to what is reported in other trials [12, 13]. Furthermore, we found an increase in the number of patients in the intervention group presenting non-clinical levels of fatigue compared to baseline. Beneficial effects were also found for leisure time physical activity ($g=0.77$), resulting in a significantly higher number of active patients in the intervention group at T2. We observed a small increase in the daily number of steps in the intervention group (~ 450 steps) as compared to a reduction in the daily steps in the control group, but time-by-group interaction was not statistically significant. Current guidelines of physical activity for individuals with chronic disease recommend a minimum of 6500–8500 steps a day, which was achieved by the intervention group at post-treatment. Still, the average increase in the number of steps in pedometer-based interventions is about 2215 steps/day (or effect size of 0.67), which is considerably higher than those obtained in our trial [44]. Earlier trials have found small to medium effects of exercise interventions on the levels of physical activity/capacity in chronic fatigue patients [42, 45]. Other studies did not find these beneficial effects [12, 46]. However, these studies measured physical activity in a different way, mainly in a laboratory setting making use of functional capacity measures, e.g. [46], walking tests [42] or actigraphy [12]. In addition, a large effect ($g=0.83$) of the 4-STEPPS program was found on patients' progress in the attainment of their personal physical activity goal. This result points at the important role of self-regulation cognitions and skills in self-set health behaviour goal pursuit. In addition, patients who received the 4-STEPPS program showed a significant improvement in physical health-related quality of life (HrQoL; $g=0.41$). This effect is in line with the average effect size for functional impairment found in a previous meta-analysis ($g=0.38$) [10]. Furthermore, we found a significant effect of small magnitude for psychological HrQoL ($p=0.47$, $g=0.33$). These results point at the psychological deterioration

and increasing disability resulting from the burden of a prolonged chronic condition. Likewise, no significant beneficial effects were found for psychological distress (depression and anxiety). This last result is in line with previous studies including CBT trials [10].

Because of contradictory findings of physical exercise program in CF(S), it has been suggested recently that physical activity programs should incorporate flexible goals that take into consideration symptom fluctuation and rest [47]. In the present study, goals related to physical activities were personal and planned according to these principles. In addition, the findings of the present study support minimal contact interventions using manuals. As such, this theory-based brief intervention, using motivational interviewing principles and self-regulation skills training, encouraged patients to set self-chosen active and positive goals and provided them with the skills to put them into practice [16, 48].

In spite of its strengths, the present study also has some limitations. First, the small sample size limits the generalizability of the findings. Likewise, the lack of significance found for some of the secondary outcomes may be due to low statistical power, as our study was not powered to detect changes in secondary outcomes. Second, this trial was carried out in health-care centres and in patient associations. To deal with potential bias, the randomization procedure was stratified by sample, and repeated measure analyses were conducted controlling for the setting (health-care centres vs. patient association). Differences in the recruitment strategy within these settings may have led to a selection bias. Furthermore, the findings may also be biased by self-selection due to the high rate of patients not interested in participating in the trial. It may be that patients willing to participate were more motivated to change than non-participants. Third, confirmation of CF(S) inclusion and exclusion criteria was based on self-reports according to the CDC criteria, and it can therefore not be excluded that some patients did not fulfil all the criteria. Ideally, this diagnosis should also rule out other somatic and psychiatric causes of the symptoms by means of a full clinical assessment and standardized psychiatric interview. Fourth, allocation of participants to the conditions was conducted prior to baseline assessments as the goal elicitation procedure took place at different moments for each condition (baseline assessment for the control group and at the second face to face session for the intervention group). This constitutes an additional potential source of bias. Fifth, the intervention was delivered by only one psychologist, which did not allow controlling for therapist effects in our analysis. Furthermore, due to resource constraints, we could not assess treatment integrity, which is an important procedure to enhance validity of interventions. Sixth, men were largely underrepresented in the sample, and as a consequence, more studies are needed to determine the effectiveness of this program in men suffering from CF(S). Seventh, due to the fact that there are no

normative data for the Portuguese CIS20, comparisons made regarding (non-)clinical levels of fatigue severity should be interpreted with care. Finally, this intervention combined motivational interviewing, several self-regulation techniques and motivational tools (e.g. pedometer), and the effect of these components cannot be separated. Future studies could address this issue by using a full-factorial design.

In summary, this study shows that a brief SR intervention targeting (balanced) physical activity has significant post-treatment beneficial effects upon fatigue severity, physical activity, personal goal progress related to physical activity and health-related quality of life in chronic fatigue patients. This low-resource intervention looks promising for the management of chronic fatigue. A follow-up assessment (12 months) will provide the necessary information to evaluate the medium term effects of the 4-STEPS program.

Other Information

The trial is registered at <http://www.controlled-trials.com> number ISRCTN70763996, and we have previously published the protocol of our trial [23]. This report followed the revised CONSORT guidelines for reporting randomized trials [49].

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Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Portuguese Medical-Ethics Committee of the Regional Health Administration guidelines) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients before being included in the study.

Conflict of Interest Marta Marques, Véronique de Gucht, Isabel Leal and Stan Maes declare that they have no conflict of interest.

References

- Fukuda K, Strauss S, Hickie I, Sharpe M, Dobbins J, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med*. 1994;121:953–9.
- Afari N, Buchwald D. Chronic fatigue syndrome: a review. *Am J Psychiatry*. 2003;160:221–36. doi:10.1176/appi.ajp.160.2.221.
- Prins JB, Vand der Meer JWM, Bleijenberg G. Chronic fatigue syndrome. *Lancet*. 2006;367:346–55.
- Clark L, White P. The role of deconditioning and therapeutic exercise in chronic fatigue syndrome (CFS). *J Ment Health*. 2005;14(3):237–52. doi:10.1080/09638230500136308.
- Fulcher K, White P. Strength and physiological response to exercise in patients with chronic fatigue syndrome. *J Neurol Neurosurg Psychiatry*. 2000;69:302–7. doi:10.1136/jnnp.69.3.302.
- Nijs J, Wallman K, Paul L. Chronic fatigue syndrome. In: Saxton JM, editor. *Exercise and chronic disease: an evidence-based approach*. New York: Routledge; 2011. p. 322–38.
- National Institute for Health and Clinical Excellence (NICE). Clinical guideline 53. Chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy: diagnosis and management of CFS/ME in adults and children. London; 2007.
- Edmonds L, McGuire L, Price J. Exercise therapy for chronic fatigue syndrome. *Cochrane Database Syst Rev*. 2004;3, CD003200.
- Price J, Mitchell E, Tidy E, Hunot V. Cognitive behaviour therapy for chronic fatigue syndrome in adults. *Cochrane Database Syst Rev*. 2008;3, CD001027.
- Castell BD, Kazantzis N, Moss-Morris R. Cognitive behavioral therapy and graded exercise for chronic fatigue syndrome: a meta-analysis. *Clin Psychol Sci Pract*. 2011;18(4):311–24. doi:10.1111/j.1468-2850.2011.01262.x.
- Malouff JM, Thorsteinsson EB, Rooke SE, Bhullar N, Schutte NS. Efficacy of cognitive behavioral therapy for chronic fatigue syndrome: a meta-analysis. *Clin Psychol Rev*. 2008;28(5):736–45. doi:10.1016/j.cpr.2007.10.004.
- Knoop H, Van der Meer J, Bleijenberg G. Guided self-instructions for people with chronic fatigue syndrome: a randomised controlled trial. *Br J Psychiatry*. 2008;190:340–1. doi:10.1192/bjp.bp.108.051292.
- Tummers M, Knoop H, van Dam A, Bleijenberg G. Implementing a minimal intervention for chronic fatigue syndrome in a mental health centre: a randomized controlled trial. *Psychol Med*. 2012;42(10):2205–15. doi:10.1017/S0033291712000232.
- Powell P, Bentall R, Nye F, Edwards R. Randomised controlled trial of patient education to encourage graded exercise in chronic fatigue syndrome. *BMJ*. 2001;322:387. doi:10.1136/bmj.322.7283.387.
- Carver CS, Scheier MF. On the self-regulation of behavior. New York: University Press; 1998.
- Maes S, Karoly P. Self-regulation assessment and intervention in physical health and illness: a review. *Appl Psychol: Int Rev*. 2005;54(29):267–99. doi:10.1111/j.1464-0597.2005.00210.x.
- Michie S, Abraham C, Whittington C, McAteer J, Gupta S. Effective techniques in healthy eating and physical activity interventions: a meta-regression. *Health Psychol*. 2009;28(6):690–701. doi:10.1037/a0016136.
- Sniehotta FF, Scholz U, Schwarzer R. Bridging the intention-behaviour gap: planning, self-efficacy, and action control in the adoption and maintenance of physical exercise. *Psychol Health*. 2005;20(2):143–60. doi:10.1080/08870440512331317670.
- Janssen V, Gucht V, Exel H, Maes S. A self-regulation lifestyle program for post-cardiac rehabilitation patients has long-term effects on exercise adherence. *J Behav Med*. 2013;1–14. doi:10.1007/s10865-012-9489-y.
- Knittle K, Gucht V, Hurkmans E, et al. Targeting motivation and self-regulation to increase physical activity among patients with rheumatoid arthritis: a randomised controlled trial. *Clinic Rheumat*. 2013;1–8. doi:10.1007/s10067-013-2425-x.
- Miller W, Rolnick S. Motivational interviewing: helping people change. 3rd ed. NY: The Guilford Press; 2012.
- Lundhal BW, Kunz C, Brownell C, Tollefson D, Burke BL. A meta-analysis of motivational interviewing: twenty-five years of empirical studies. *Res Social Work Pract*. 2010;20(2):137–60. doi:10.1177/1049731509347850.
- Marques M, De Gucht V, Maes S, Leal I. Protocol for the “Four steps to control your fatigue (4-STEPS)” randomised controlled trial: a self-regulation based physical activity intervention for patients with

- unexplained chronic fatigue. *BMC Public Health*. 2012;12(202). doi:[10.1186/1471-2458-12-202](https://doi.org/10.1186/1471-2458-12-202)
24. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. 8th ed. Baltimore: Lippincott Williams & Williams; 2009.
 25. Wagner D, Nisenbaum R, Heim C, Jones JF, Unger ER, Reeves WC. Psychometric properties of the CDC symptom inventory for assessment of chronic fatigue syndrome. *Popul Health Metrics*. 2005;3:8. doi:[10.1186/1478-7954-3-8](https://doi.org/10.1186/1478-7954-3-8).
 26. De Marques M, Gucht V, Gouveia MJ, Cordeiro A, Maes S. Psychometric properties of the Portuguese version of the Checklist of Individual Strength (CIS20-P). *Psychol Commun Health*. 2013;22(1):11–8. doi:[10.5964/pch.v2i1.57](https://doi.org/10.5964/pch.v2i1.57).
 27. Vercoulen J, Alberets M, Bleijenberg G. De Checklist Individual Strength (CIS). *Gedragstherapie*. 1999;32:31–6.
 28. De Vree B, van der Werf S, Prins J, Bazlmans E, Vercoulen J, Servaes P. Meetinstrumenten bij chronische vermoeidheid. *Gedragstherapie*. 2002;35:157–64.
 29. Cleeland C, Ryan K. Pain assessment: global use of the brief pain inventory. *Ann Acad Med Singap*. 1994;23:129–38.
 30. Wendel-Vos G, Schuit A, Saris W, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. *J Clin Epidemiol*. 2003;56:1163–9. doi:[10.1016/S0895-4356\(03\)00220-8](https://doi.org/10.1016/S0895-4356(03)00220-8).
 31. Ainsworth B, Haskell W, Whitt M, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc*. 2000;32 Suppl 9:498–504.
 32. Ainsworth B, Haskell W, Herrmann S, et al. Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc*. 2011;43(8):1575–81. doi:[10.1249/MSS.0b013e31821ece12](https://doi.org/10.1249/MSS.0b013e31821ece12).
 33. Welk GJ, Differding JA, Thompson RW, Blair SN, Dziura J, Hart P. The utility of the Digi-walker step counter to assess daily physical activity patterns. *Med Sci Sports Exerc*. 2000;32(9 Suppl):S481–8.
 34. Le Masurier GC, Tudor-Locke C. Comparison of pedometer and accelerometer accuracy under controlled conditions. *Med Sci Sports Exerc*. 2003;35(5):867–71. doi:[10.1249/01.MSS.0000064996.63632.10](https://doi.org/10.1249/01.MSS.0000064996.63632.10).
 35. Maes S, Karoly P, De Gucht V, Ruehlman LS, Heiser W: The self-regulation skills battery (SRSB). Leiden(NL)/Phoenix (AZ): Leiden University & Arizona State University; 2006.
 36. Ware JE, Kosinski M, Turner-Bowker DM, Gandek B. How to score version 2 of the SF-12® Health Survey. Lincoln: Quality Metric Incorporated; 2002.
 37. Kroenke K, Spitzer R, Williams J. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. *Psychosom Med*. 2002;64:258–66.
 38. Degoratis L. Brief Symptom Inventory: administration, scoring and procedures manual. 4th ed. Minneapolis: National Computer System; 1993.
 39. Faul F, Erdfelder E, Lang A, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioural and biomedical sciences. *Behav Res Methods*. 2007;39:175–91. doi:[10.3758/BF03193146](https://doi.org/10.3758/BF03193146).
 40. Stulemeijer M, de Jong L, Fiselier T, Hoogveld S, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. *BMJ*. 2005;330(7495):820. doi:[10.1136/bmj.38301.587106.63](https://doi.org/10.1136/bmj.38301.587106.63).
 41. Hedges LV. Distribution Theory for glass's estimator of effect size and related estimators. *J Educ Behav Stat*. 1981;6(2):107–28.
 42. White PD, Goldsmith KA, Johnson AL, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet*. 2011;377(9768):823–36. doi:[10.1016/S0140-6736\(11\)60096-2](https://doi.org/10.1016/S0140-6736(11)60096-2).
 43. Vos-Vromans DC, Smeets RJ, Rijnders LJ, et al. Cognitive behavioural therapy versus multidisciplinary rehabilitation treatment for patients with chronic fatigue syndrome: study protocol for a randomised controlled trial (FatiGo). *Trials*. 2012;13(1):71. doi:[10.1186/1745-6215-13-71](https://doi.org/10.1186/1745-6215-13-71).
 44. Tudor-Locke C, Craig CL, Aoyagi Y, et al. How many steps/day are enough? For older adults and special populations. *Int J Behav Nutr Phys Act*. 2011;8(1):80. doi:[10.1186/1479-5868-8-80](https://doi.org/10.1186/1479-5868-8-80).
 45. Wallman K, Morton A, Goodman C, Grove R, Guilfoyle A. Randomised controlled trial of graded exercise in chronic fatigue syndrome. *Med J Aust*. 2004;180(9):444–8.
 46. Moss-Morris R, Sharon C, Tobin R, Baldi J. A randomized controlled graded exercise trail for chronic fatigue syndrome: outcomes and mechanisms of change. *J Health Psychol*. 2005;10(2):245–59. doi:[10.1177/1359105305049774](https://doi.org/10.1177/1359105305049774).
 47. Nijs J, Paul L, Wallman K. Chronic fatigue syndrome: an approach combining self-management with graded exercise to avoid exacerbations. *J Rehabil Med*. 2008;40:241–7. doi:[10.2340/16501977-0185](https://doi.org/10.2340/16501977-0185).
 48. De Gucht V, Maes S. Explaining medically unexplained symptoms: toward a multidimensional theory-based approach to somatisation. *J Psychosom Res*. 2006;60:349–52. doi:[10.1016/j.jpsychores.2006.01.021](https://doi.org/10.1016/j.jpsychores.2006.01.021).
 49. Schulz K, Altman D, Moher D, and the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMC Med*. 2010;8(1):18. doi:[10.1136/bmj.c332](https://doi.org/10.1136/bmj.c332).