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Physical activity goal progress and self-regulation skills mediate medium-term effects of a self-regulation based physical activity program for chronic fatigue

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Abstract

**Background:** Physical activity is considered to be beneficial for patients suffering from unexplained chronic fatigue.

**Purpose:** Examine the medium-term effects of a brief physical activity (PA) self-regulation (SR) based intervention (4-STEPS program), and explore the mediating effects of PA and SR skills.

**Methods:** A two-arm randomized controlled study (Usual Care vs 4-STEPS) was carried out. The 4-STEPS program consisted of Motivational Interviewing and SR-skills training. Fatigue severity (primary outcome) and impact, PA, health-related quality of life (HrQoL), somatic and psychological distress were assessed at baseline, post-treatment (12 weeks) and 12 months follow-up.

**Results:** Ninety-one patients (45 intervention and 46 controls) were included. At follow-up, there were significant treatment effects on fatigue severity (g=0.72) and fatigue impact, leisure-time PA, and physical and psychological HrQoL. Fatigue severity at follow-up was partially mediated by post-treatment progress on a personal PA goal and SR skills (effect ratio= 26% and 32%).

**Conclusions:** Results suggest that a brief intervention, focusing on the formulation and pursuit of personal PA goals and the use of SR skills, produces sustained benefits for fatigue severity.

**Trial Registration:** ISRCTN70763996

**Keywords:** chronic fatigue, randomized controlled trial, physical activity, self-regulation, skills, goals.
**Introduction**

Fatigue is a common symptom, usually transitory and explained by life circumstances, but for some, fatigue is medically unexplained and severe, resulting in disability and lower health-related quality of life [1, 2]. Unexplained fatigue is considered to be chronic if it lasts for at least 6 months (i.e. idiopathic chronic fatigue-ICF). If additional somatic symptoms as defined by the Centres for Disease Control and Prevention (CDC) are present, it is classified as Chronic Fatigue Syndrome (CFS) [3].

Prolonged physical inactivity (rest) and decreased physical capacity are considered to be perpetuating factors in CF(S) [4-6]. At the same time, high levels of physical activity can cause overexertion and perpetuate fatigue symptoms [7, 8]. Not surprisingly, it is common to find a “boom-and-bust pattern” in these patients, which is the systematic alternation between periods of over-activity (when feeling good) and, as a consequence of that, feeling extremely fatigued and having to rest for longer periods of time [9, 10]. It is therefore recommended that CF(S) patients engage in physical activity based on Graded Exercise Therapy (GET) [1, 11].

GET consists of exercise prescription (aerobic activities) adapted to the patient’s physical capacity. GET aims to gradually increase exercise at a level that does not exacerbate symptoms. Patients are advised not to exceed the recommended levels of physical activity (in order to avoid overexertion) and are encouraged to maintain these levels even if symptoms get worse. GET has been shown to have beneficial effects on chronic fatigue management [12-14].

Because of the benefits of physical activity in patients suffering from CF(S), many Cognitive Behavioural Therapy (CBT) trials have also incorporated a graded exercise component. CBT also has beneficial effects on chronic fatigue [12, 13, 15]. Despite the beneficial effect of both GET and CBT on CF(S) patients, effects of trials are of small magnitude and heterogeneous [12,13]. Some trials found limited effects of these interventions [e.g. 16, 17], while others proved to be very effective [e.g. 18, 19]. One explanation for the differences in effectiveness may be that some interventions result in creating cognitive or behavioural changes that may mediate the
effect of the intervention on fatigue, while others do not result in such changes. In the present article we will therefore not only report on the medium-term effects of a self-regulation physical activity based program for CF(S) patients, but we will also explore possible mediators of these effects, more specifically physical activity and self-regulation skills.

Recent studies have shown that self-regulation (SR) based interventions are effective in promoting long-lasting health behaviour change in various patients suffering from chronic diseases [20-22]. SR is one of the most prominent perspectives on health behaviour change, and considers that behaviour is a goal driven process [23, 24]. This dynamic-goal process consists of a goal selection and goal setting phase, an active goal pursuit or action phase and a goal attainment or maintenance phase, in which motivational and volitional aspects interact. Several SR cognitions and skills are guiding this process, such as self-efficacy, personal goal-setting, planning, self-monitoring, feedback, emotional and attention regulation and relapse prevention [23]. Personal goal setting, a central aspect in SR theory, is a first step and implies that formulating self-chosen and personally important goals guide behavior change and increase the likelihood of goal achievement and maintenance [23-25].

Motivational interviewing (MI), a “collaborative conversation style for strengthening a person’s own motivation and commitment to change” ([26] p. 12) is frequently used to evoke and strengthen patients’ own motivation and confidence to change, and to support patients in setting personal health-related goals by increasing the personal relevance of health goals. MI is considered especially helpful in helping patients move from ambivalence towards behavior change [26]. While MI mainly focuses on SR cognitions, SR skills play an important part not only in the formulation of health-related goals (e.g. physical activity) but also during active goal pursuit and during the maintenance phase of the behavioral change process [23]. Recent meta-analyses showed that interventions employing a combination of SR-skills (including self-monitoring) were more effective than interventions not using these techniques in increasing PA in the general population [27] and in improving chronic disease related outcomes [28].
Based on the self-regulation cognitions and skills described above we developed a brief SR-intervention targeting physical activity for patients with CF(S) (the “4-STEPS to control your fatigue” program). The 4-STEPS program consists of a combination of MI sessions, telephone self-regulation counseling, and SR skills based patient manuals. In this program participants set their own physical activity goals and are advised to gradually increase their physical activity levels according to a specific personal scheme [29], allowing flexibility in the intensity and duration of exercise according to symptom fluctuation, without exceeding one’s own capacity. This also implies that physical activity can be reduced or even stopped when symptoms get worse [29-31]. Furthermore, balance between activity and rest is also taken into account.

The 4-STEPS program was tested in a randomized controlled trial [32], in which patients were either assigned to the control group (usual care) or to a 12-week self-regulation intervention (4-STEPS program). Post-treatment beneficial effects of the 4-STEPS program were found for fatigue severity, health-related quality of life, leisure-time physical activity and perceived physical activity goal progress. No effects were found for fatigue impact on daily life, daily steps, somatic distress, and psychological distress (depression and anxiety) [33].

The first objective of the present study is to report the 12-months follow-up results of the 4-STEPS intervention on fatigue severity (subjective experience and fatigue severity) and impact on daily life, physical activity (leisure-time physical activity and daily steps), health-related quality of life (physical and psychological component), somatic distress and psychological distress (anxiety and depression). The second objective is to examine the mediators of intervention effects on the subjective experience of fatigue. It is hypothesized that the intervention increases the intermediate targets of our intervention – physical activity and the use of self-regulation skills -, and that this increase mediates the medium-term effects of the intervention on fatigue improvement.
Method

Trial design
This study concerns the follow-up results of a randomized controlled trial that has been previously described in full detail [32]. It was a two-arm 12-week multicentre randomized controlled trial. Randomisation was stratified by sample (Health care centre and Patient Association), and within the first sample also by centre, with equal randomisation (1:1) to either the intervention condition (4-STEPS program) or the control condition. Allocation sequence was based on computer-generated allocation numbers carried out by a member of the research team, who did not take part in the subsequent phases of the trial. Group allocation was known to participants, therapist and outcome assessors. Patients were assessed at baseline (T1), and 3 (post-treatment-T2) and 12 months (follow-up- T3) thereafter. Approval was obtained from the Portuguese Medical-Ethics Committee of the North Regional Health Administration and from the board of each participating health care center. 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 six months duration) were eligible to participate in the study [3]. Additional inclusion criteria were to fully understand and speak Portuguese and to have the capacity to provide 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 [3]) were excluded.

The trial was conducted in (a) several Portuguese Health Care Centres (public primary care centres and one private practice) and (b) via the Portuguese Fibromyalgia and Chronic Fatigue Syndrome Patient Association. In the first case, physicians referred patients based on the inclusion/ exclusion criteria. Patients from the patient association who met the criteria (i.e. clinical diagnosis of unexplained chronic fatigue) and indicated their willingness
to participate in the study received a letter from the association containing a description of the trial. All participants were informed of the content and structure of the trial and invited for the baseline assessment in the health care centre or at the office of the patient association. Patients willing to participate signed a written informed consent before enrolment. Baseline assessment consisted of a structured interview with each patient in which self-reported questionnaires were completed. The research team checked inclusion and exclusion criteria, using self-report measures based on the CDC criteria. A similar procedure was used for the assessments at T2 and T3.

**Intervention**

Participants continued to receive their usual 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 [34]. In addition, they set a personal physical activity goal for the upcoming months. Participants assigned to the intervention condition additionally received the “4-STEPS to control your fatigue” program.

One health psychologist (with expertise in motivational interviewing) delivered the “4-STEPS” program to individual patients. The intervention was based on the self-regulation phases of goal pursuit (goal selection and setting, active goal pursuit and goal attainment, maintenance and disengagement) [23]. First, participants received two 1-hour 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) reducing ambivalence towards change (c) increasing participants’ motivation and confidence to be physically active and (c) setting a specific personal physical activity goal. This personal physical activity goal, which took into consideration the graded activity principles of flexibility and balance, developed by Nijs and colleagues [29] 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).
Second, participants received a booklet containing information regarding: (a) the diagnosis of CF(S), (b) the 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).

Third, a self-regulation based workbook was given to the patients. The self-regulation workbook was divided in four steps, each one focusing on specific self-regulation 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, 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).

Fourth, patients received two brief self-regulation based telephone-counseling sessions (weeks 5 and 9). This telephone support aimed at reviewing the participants’ physical activity goal and providing relapse prevention strategies.

Fifth, patients received a pedometer to register their physical activity levels on a daily basis (steps taken) during the intervention period. In addition, at the end of the first MI session, patients received a weekly daily activities record to fill in, between sessions, with the amount of time each day spent in physical activities, mental activities and rest. This provides information on activity fluctuation throughout the week (possible erratic rest and activity pattern) and how to best include PA in the daily schedule. The first record was used to facilitate goal setting at the second MI session. After that, patients received several records that they could use to self-monitor daily activity patterns, if they would like to do so.

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 (Table 1). 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 [35]. The checklist presents 19 major and minor symptoms of CFS as defined by the CDC criteria [3]. Respondents were asked to indicate if they experienced each of the symptoms during the last 6 months. For the purpose of this study a dichotomous scale (Yes/No) was used. A total symptom score was 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 4 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 was assessed using the Checklist of Individual Strength (CIS20-P) [36], a well-validated and reliable measure for assessing fatigue severity in chronic fatigue patients [37] {Vercoulen, 1999, De Checklist Individual Strenght (CIS);Marques M.,, Psychometric properties of the Portuguese version of the Checklist of Individual Strength (CIS20-P)}. The CIS20-P is a 20 item self-report measure that assesses four dimensions of fatigue: subjective experience of fatigue, concentration, motivation and daily activities. Items are rated on a 7-point scale. Total score of fatigue severity is calculated by adding up the scores from each dimension. For the purpose of this study only the subjective experience of fatigue dimension (primary outcome) and the total fatigue severity score were used. A cut-off point of 35 on the subjective experience of fatigue dimension of CIS20-P (range: 8-56) is usually used to define a clinical level of fatigue [38].

Fatigue impact was measured by means of a modified version of the pain interference dimension of the well validated Brief Pain
Inventory (BPI) consisting of 7 items [39]. Participants were asked to rate on a 10-point scale how their fatigue interfered with several aspects of their life. Total score was used as the outcome, ranging from 0 to 10. Higher scores indicate a higher impact of fatigue.

Physical activity was assessed by means of:

(a) A self-report measure of leisure-time physical activity based on the Short Questionnaire to Assess Health-enhancing Physical Activity (SQUASH) [40]. 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 [41, 42], total minutes of physical activity per week are calculated by multiplying frequency (days/week) and duration (minutes/day). Total minutes of leisure-time physical activity (moderate to vigorous physical activity - MVPA) per week are calculated by taking the sum of each activity score.

(b) Physical activity was also measured by means of a pedometer. Daily steps were assessed using Yamax Digiwalker SW-200 pedometers, which proved to be accurate and reliable [43, 44]. 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 seven days was used as an outcome measure.

(c) Physical activity goal progress and achievement was assessed at T1 and T2. Using a standardized goal-elicitation procedure, respondents specified at baseline a personal physical activity goal that they wished 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) [45].

Health-Related Quality of Life (HRQoL) was measured using the Short Form Health Survey-12 (SF-12V.2) [46]. 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** was assessed with the Patient Health Questionnaire-15 (PHQ-15), which measures the presence and severity of 15 somatic symptoms (e.g. back pain), scored on a 0-3 scale. Higher scores indicate higher somatic symptom severity (range: 0-30) [47].

**Psychological distress** was assessed using the Depression and Anxiety subscales from the well-validated and widely used Brief Symptom Inventory (BSI) [48]. Individuals rank each symptom on a 5-point scale, with higher scores representing more psychological distress. Scores were calculated by taking the mean of the items of each subscale (range: 0-4).

**Self-regulation skills** were measured at T2 using the Self-Regulation Skills Battery (SRSB) [45], which assesses the extent to which participants use self-regulation skills in pursuing a previously stated personal physical activity goal. We assessed six self-regulation skills (18 items): planning, self-monitoring, seeking feedback, focus attention on goal pursuit, emotional regulation, coping with problems and goal persistence. A composite score was calculated by taking the average of the mean scores of each subscale (range 1-5). The internal consistency of the total scale was very high (Cronbach’s alpha=0.95).

Outcomes were assessed at baseline (T1), post-treatment (T2) and follow-up (T3). The T2 measures of perceived physical activity goal progress and self-regulation skills were used as mediators.

**Sample size**

An a priori analysis [49] using an independent sample t-test (5% significance level) showed that a sample of 34 participants in each group would have 80% power to detect a mean difference of 7 points [50, 51] on the subjective experience of fatigue dimension of the CIS20-P between the intervention and the control group. Anticipating 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 T1 were analyzed using t-tests.
(for continuous variables) and univariate chi-square tests (for dichotomous variables). At T3, an independent samples t-test was conducted to assess the difference in subjective experience of fatigue between the intervention group and the control group (primary outcome). The effects of the intervention on the proposed outcomes were examined using a 3 (timeline: T1, T2 and T3) x 2 (condition: control and intervention) mixed-model repeated measures analysis of covariance (ANCOVA), controlling for setting (Health care centres vs. Patient association) and disease duration. Whenever there was a significant time x group interaction, contrasts were tested for significance. We calculated effect sizes for contrasts, which were the standardized mean differences with Hedge’s $g$ correction for small samples [52], interpreted according to Cohen’s guidelines (values of 0.20, 0.50 and 0.80 correspond to small, medium and large effect sizes). Prior to the analyses, data was inspected for normality and homogeneity of variance. Leisure-time physical activity was not normally distributed at any of the time points and a logarithmic transformation was carried out for further analyses. Assumption of sphericity was checked using Mauchly’s test. Whenever this assumption was violated, the Greenhouse-Geisser correction was applied. Data was analysed 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 by repeating all analyses with completers only, and no significant differences were found between the two approaches. For this reason, main results report the ITT analysis. Missing values at baseline (incomplete assessment on daily steps and goal progress) were imputed using Multiple Imputation. Additional chi-square analyses were conducted for the complete dataset to compare the number of patients in each group who a) did not meet non-clinical levels of fatigue severity (<35) assessed by the subjective experience of fatigue dimension of the CIS20-P, and b) who were physically active. Effect sizes were Risk Ratio’s (RR).

To test mediation, we conducted a bootstrapping procedure developed by Preacher and Hayes [53], using the PROCESS macro for SPSS. We used simple mediation models, in which separate
analyses were conducted to test the indirect effect of treatment condition (independent variable) on changes in subjective experience of fatigue at follow-up (dependent variable) through the putative mediators: 1) daily steps taken (a more objective physical activity measure), 2) perceived physical activity goal progress, and 3) use of self-regulation skills. The mediator is assumed to be significant at p<0.05 if the corresponding 95% confidence interval (CI) for the indirect effect does not include zero. In addition, when there were significant indirect effects, the ratio of the indirect effect to the total effect was calculated to express the strength of the mediation effects (i.e. the amount of the total effect that is explained by the indirect effect via the mediator). We used a resample procedure of 5000 bootstrap samples (bias corrected), controlling for setting (Health care centres vs. Patient association) and disease duration. Data analyses were conducted using the statistical software SPSS v22.

Results

Participant flow and patient characteristics
The flow of patients through the trial and reasons for exclusions and withdrawals are shown in Figure 1. A total of 165 individuals were identified as eligible to participate and were informed about the study. Of these, 91 patients randomly allocated to either the 4-STEPS program or the control condition completed baseline assessment and received allocated treatment (n=45 and n=46, respectively). Sixteen (35%) participants in the intervention group and fifteen (32%) participants in the control group were lost to follow-up.

Demographics and clinical characteristics are presented in Table 1. No significant differences were found for demographics and clinical variables between the intervention and the control group at T1.

Intervention effects
At T3, there was a significant difference of 6.57 points in subjective experience of fatigue between the intervention and the control
group (t=-3.58, p=0.01 95% CI -10.3 to -2.80, g=0.72). There was a near-significant difference in the number of patients presenting non-clinical levels of fatigue between the intervention (7/29-24.1%) and control group (2/31-6.5%; $X^2$=3.68, p=.076, RR= 3.74, 95% CI 0.85 to 16.52). Mixed-design repeated measures analyses of covariance (ANCOVA) revealed a significant time by group effect for subjective experience of fatigue ($p=.003$) and total fatigue severity ($p=.003$), after controlling for the effect of the covariates (Table 2). In both analyses, contrasts revealed that significant changes occurred between T1 and T3 ($p=.004$, g= 0.66 and $p=.005$, g= 0.54, respectively). In the intervention group there was a significant decrease from T1 to T3 in the subjective experience of fatigue (- 4.04; mean change control group = +1.52) as well as in total fatigue severity (mean change intervention group= -5.98; mean change control group = +4.85). In addition, there was a significant effect of the intervention on fatigue impact ($p=.018$). Contrasts revealed a significant time by group interaction when comparing impact of fatigue between T2 and T3 ($p=.003$, g= 0.39).

Regarding physical activity there was a significant time by group interaction for level of leisure-time physical activity ($p=.011$). Statistical contrasts revealed that changes were significant from T1 to T3 ($p=.012$, g= 0.21). No significant group x time interaction was found for number of daily steps taken ($p=.151$). Furthermore, there was a significantly higher number of physically active participants in the intervention group (19/29 – 65.9%) in comparison to the control group (11/31 – 35.5 %; $X^2$= 5.41, $p=.020$; RR=1.84, 95% CI 1.07 to 2.21) at T3.

There was a significant time by group effect for both physical and psychological HrQoL ($p=.002$). Contrasts revealed that changes were significant from T1 to T3 ($p=.002$, g=0.39 and $p=.004$, g=0.057, respectively). In the intervention group there was a significant increase from T1 to T3 in physical HrQoL (+4.55; vs. mean change control group = -3.03) and psychological HrQoL (+8.82; vs. mean change control group = -1.32).

No significant time x group effects were found for somatic symptoms ($p=.624$), depression ($p=.605$) and anxiety ($p=.365$).
Mediation analysis
Table 3 shows the results of the mediation analysis for each proposed mediator. Mediation tests showed that daily steps at T2 (objective measure of physical activity) did not mediate the effects of treatment on fatigue severity at T3 (95% CI -1.92 to 1.49). By contrast, physical activity goal progress for which a significant time by group effect was found at T2 (F=16.37, p=.000, g=0.83), partially mediated the effect of the 4-STEPS program on subjective experience of fatigue (point estimate= -1.65, 95% CI -4.15 to -0.36). The mediation effect averaged about 26% of the total treatment effect.

Regarding self-regulation skills, there was a significant difference (t=2.89 p=.006, 95% CI 0.15 to 0.83, g=0.72) between the intervention (M=3.68, DP=0.51) and the control group (M=3.19, DP=0.82) at T2. Mediation analyses showed a significant indirect effect of treatment through the use of self-regulation skills (T2) on fatigue at T3 (point estimate= -2.22, 95% CI of -5.41 to -0.56), accounting for 32% of the total effect.

Discussion
This trial tested the medium-term (12-months follow-up) effects of a brief self-regulation (SR) based intervention for patients with unexplained chronic fatigue (4-STEPS), which combined face-to-face motivational interviewing with SR skills training. Post-treatment (3-months) results showed beneficial effects of the 4-STEPS on subjective experience of fatigue (primary outcome) and total fatigue severity [33]. At 12-months follow-up, these beneficial effects were maintained and a larger difference was found for subjective experience of fatigue between groups (6.57). Furthermore, we found an increase from baseline for the number of patients in the intervention group presenting non-clinical levels of fatigue (~21%) in comparison to the control group (0%). In addition, the effects of the intervention on fatigue impact in daily life became significant.

Sustained beneficial treatment effects were also found for health-related quality of life (HrQoL). In fact, larger effects on
psychological HrQoL were found at follow-up in comparison to the
3 months post-treatment results ($g=0.33$ vs. $g=0.57$). Treatment
effects on additional somatic complaints as well as on psychological
distress (depression and anxiety) remained non-significant.
These results are in line with the average effects found in previous
systematic reviews and meta-analyses of graded exercise and
psychological interventions in CF(S) [12, 13]. However, few trials
present medium to long-term follow-up effects and there is
also heterogeneity in the effects. Two earlier trials with similar
treatment duration (3-months) that also provided 2 initial face-to-
face sessions and additional self-management manuals focusing
on educational and behavioural strategies, differ from each other
with respect to follow-up results. While in the trial conducted by
Powell et al [19] the authors found large effects of the intervention
on fatigue, physical functioning and depression, in the trial by
Friedberg and colleagues [54] beneficial effects were only found for
fatigue severity.

The results for physical activity (PA) reveal that the intervention
has a non-significant effect on number of daily steps. In fact, the
average difference in daily steps between the two conditions
at 12 months was only -383 steps/days. The average number of
daily steps of participants in each condition met however the
recommended guidelines for patients with chronic diseases of
minimum 6500-8000 steps/day [55]. Furthermore, the magnitude
of the interaction effect between treatment condition and time
(baseline to follow-up) on leisure-time PA was small. There was
a decrease in PA levels from post-treatment to follow-up in the
intervention condition; there was, however, still an increase from
baseline to follow-up of approximately 30 minutes/week of leisure-
time PA. At the same time, the percentage of physically active
participants was maintained from post-treatment to follow-up. It
may be that patients, who were physically active at post-treatment,
set new personal PA goals that did not focus on increasing PA levels
but rather on maintaining PA levels or balance between activities
(e.g. accumulation of leisure-time PA with daily steps taken). Many
behavioral and psychological trials presenting a graded exercise
component have found trivial to small beneficial effects on physical
activity and capacity in CF(S) patients [50, 56]. However, very few
studies present follow-up results. These studies also measured physical activity mainly in laboratory settings making use of functional capacity measures [e.g. 57], an accelerometer [e.g. 50] or walking tests [e.g. 58].

Since physical activity is a key target in many interventions designed for CF patients, it is important to analyse if changes in PA actually lead to improved fatigue. In the present study, we conducted a mediation analysis to test if the effect of treatment on subjective fatigue severity at follow-up could be explained by (a) an increase in the number of daily steps (a more objective measure of PA) and (b) progress towards a personal PA goal. Results showed that an increased number of daily steps did not mediate treatment effects on fatigue. A recent study by Wiborg and colleagues [59] analysing the mediation effect of PA on fatigue severity and including data from two CBT trials targeting PA in CFS adult patients [18, 50], did not find a significant mediation effect. However, none of the trials included in the analysis had a significant impact on PA levels. In the present trial the effect of the intervention on daily number of steps at post-treatment was only marginally significant. At the same time, we did find that personal goal progress partially explained the effects of treatment on sustained fatigue improvement. This result suggests that it may not be the mere increase in PA that explain fatigue improvement, but rather the formulation of self-chosen and personally meaningful goals that not only increase the likelihood of goal progress and achievement but can also impact positively on disease related outcomes. Likewise, it may be that flexible PA related goals that take into consideration patients’ own symptoms and capability as well as the need to regulate daily activity can also explain the beneficial effects of treatment upon sustained fatigue improvement [7]. Thus, PA goals can facilitate the increase of PA levels and maintain these levels or lead to a more balanced form of PA, taking into consideration other daily activities. Future studies could further explore this by using daily activities diaries or other remote activity monitoring systems.

One of the main targets of the 4-STEMS intervention was to increase patients’ use of SR skills [23]. Although recent trials have shown that interventions using a combination of theoretically
derived SR-skills [23, 24] were more effective than other interventions [27, 28], only few studies analyzed the mediation effect of SR-skills on health behavior changes and disease related outcomes [20, 21]. Mediation analysis showed that the effect of treatment on fatigue at follow-up could be partly explained by a treatment effect on SR-skills at post-treatment. Encouraging patients to set personal active goals and providing them with skills to attain these goals seems to explain part of the intervention effect on fatigue severity.

**Study limitations**

The present study has a number of limitations. First, the small sample size limits the generalizability of our findings.Employing complex moderated mediation models with larger samples can provide more insight in differential effects of SR skills (e.g. self-monitoring) and other proximal targets and explore for which subgroups and in which phases of health behaviour change these interventions works best. Furthermore, the intervention combined motivational interviewing, the use of self-regulation techniques and motivational tools (e.g. pedometer), but the effect of each components could not be separated out in present study. Future studies should address this issue by using a full-factorial design.

Second, this trial was carried out in health care centres and in a patient association. To deal with potential bias the randomisation procedure was stratified by sample, and statistical analyses were conducted controlling for setting. Differences in recruitment strategy within these settings may, however, have led to a selection bias. Third, confirmation of CF(S) inclusion and exclusion criteria was based on self-reported CDC criteria and it can therefore not be excluded that some patients did not fulfill the criteria. Ideally, the diagnosis should also rule out other somatic and psychiatric causes of the symptoms, by means of a full clinical assessment and standardised psychiatric interview. Fourth, men were largely underrepresented in the sample; more studies are therefore needed to determine the effects of this program in men suffering from CF(S). Fifth, 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.
Furthermore, future trials should investigate the benefits of self-regulation based interventions in a design that includes an active control condition, e.g. a treatment such as GET. Finally, we expected a brief intervention with less direct contact to have a lower dropout rate than more lengthy interventions, but this was not the case. Attrition from baseline to 12-months follow-up was however lower in this study than what was recently found in other randomized controlled trials of brief interventions [54, 60].

**Conclusion**

Despite its limitations, this study found that a brief intervention has sustained small to medium effects on fatigue severity and impact, health-related quality of life, and leisure-time PA. Minimal direct contact interventions that can be easily implemented in standard health care can be useful for patients presenting difficulties in attending regular health care facilities [60] and/or for patients who do not need more intensive forms of treatments [61]. Furthermore, our results suggest that using motivational and self-regulation principles and techniques can lead to improved fatigue in CF(S) patients. Self-chosen, personally meaningful goals appear to motivate these patients, while SR-skills training facilitate the attainment of their goals. By providing continued remote contact with patients, making use of e.g. e-health and m-health in order to provide maintained tailored feedback, intervention effects could be sustained over a longer period of time.
Other information

The trial is registered at http://www.controlled-trials.com, number ISRCTN70763996 and we have previously published the protocol of our trial [32]. This report followed the revised CONSORT guidelines for reporting randomized trials [62].

Acknowledgement

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Author(s) Statement of Conflict of Interest and Adherence to Ethical Standards: Marta Marques, Véronique de Gucht, Isabel Leal and Stan Maes, declare that they have no conflict of interest. Marta Marques has received a research grant from the Portuguese Foundation for Science and Technology (SFRH/BD/47579/2008). All procedures, including the informed consent process, were done in accordance with the ethical standards of the responsible committee on human experimentation (Portuguese Medical-Ethics Committe 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.
References


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2009.
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Figure 1 Flow diagram of participants through the intervention.

Enrollment

Assessed for eligibility (N=165)

→ Excluded (n= 66)
  · Not meeting inclusion criteria (n= 19)
  · Not interested (n=47)

Randomized (N=99)

Allocation

Allocated to intervention condition (n=49)
  · Did not complete baseline assessment (n=4)
    Not feeling well enough (n=2)
    Lack of time (n=2)
  · Received allocated intervention (n=45)

Allocated to control condition (n=50)
  · Did not complete baseline assessment (n=4)
    Not feeling well enough (n=3)
    Lack of time (n=1)
  · Received allocated intervention (n=46)

Post-treatment (3-months)-T2

Discontinued intervention (n=5)
  Lack of time (n=5)
  Lost to follow-up (n=5)
  Couldn’t contact (n=2)
  Failing to provide a reason (n=2)
  Not feeling well enough (n=1)

Discontinued intervention (n=0)
  Lost to follow-up (n=13)
    Couldn’t contact (n=4)
    Failing to provide a reason (n=3)
    Lack of interest (n=3)
    Lack of time (n=3)

Follow-up (12 months)-T3

Lost to follow-up at T3 (n=6)
  Couldn’t contact (n=3)
  Failing to provide a reason (n=2)
  Lack of time (n=1)
  Lost to follow-up at T2, re-included at T3(n=0)

Lost to follow-up at T3 (n=6)
  Couldn’t contact (n=4)
  Failing to provide a reason (n=1)
  Lack of interest (n=1)
  Lost to follow-up at T2, re-included at T3(n=4)

Analysis

Analyzed in intention to-treat analysis (n=45)
  Per-protocol analysis (n=29)
  Excluded from analysis (n=0)

Analyzed in intention to-treat analysis(n=46)
  Per-protocol analysis (n=31)
  Excluded from analysis (n=0)
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention (n=45)</th>
<th>Control (n=46)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46.96±10.39</td>
<td>49.20±11.49</td>
<td>0.33</td>
</tr>
<tr>
<td>Gender (women)</td>
<td>44 (97.8)</td>
<td>45 (97.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>12 (26.7)</td>
<td>16 (34.8)</td>
<td>0.65</td>
</tr>
<tr>
<td>Secondary</td>
<td>17 (37.8)</td>
<td>17 (37.0)</td>
<td></td>
</tr>
<tr>
<td>Higher</td>
<td>16 (35.6)</td>
<td>13 (28.3)</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>24 (54.3)</td>
<td>25 (54.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Not working due to fatigue</td>
<td>10 (45.5)</td>
<td>11 (47.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>Absentism (n. days)</td>
<td>6.20 ± 10.44</td>
<td>14.36 ± 22.61</td>
<td>0.14</td>
</tr>
<tr>
<td>Physically active</td>
<td>15 (33.3)</td>
<td>17 (37)</td>
<td>0.82</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>9.81 ± 8.02</td>
<td>10.96 ± 9.06</td>
<td>0.53</td>
</tr>
<tr>
<td>Number of medical consultations</td>
<td>4.03± 2.88</td>
<td>5.10 ± 4.43</td>
<td>0.20</td>
</tr>
<tr>
<td>Number of major CDC CFS symptoms</td>
<td>6.42 ± 1.29</td>
<td>6.70 ± 1.38</td>
<td>0.33</td>
</tr>
<tr>
<td>Diagnostic criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICF</td>
<td>5 (11.1)</td>
<td>3 (6.5)</td>
<td>0.49</td>
</tr>
<tr>
<td>CFS</td>
<td>40 (88.9)</td>
<td>43 (93.5)</td>
<td></td>
</tr>
<tr>
<td>Clinical Levels of Fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>42 (93.3)</td>
<td>43 (93.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>No</td>
<td>3 (6.7)</td>
<td>3 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Setting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Care Centres</td>
<td>24 (53.3)</td>
<td>25 (54.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Patient Association</td>
<td>21 (46.7)</td>
<td>21 (45.7)</td>
<td></td>
</tr>
</tbody>
</table>

*Note. Values are presented as Mean ± Standard Deviation or Frequencies (%). 1 n=21 in each condition. 2 n=20 (Intervention condition); n=22 (Control condition). 3Results for completers [Physically active: Intervention group = 11/29 (37.9%); Control condition= 13/31 (41%); p= 0.75]. 4Cut-off score of 35 on the Subjective Fatigue sub-scale of the CIS20. 5Results for completers [clinical levels: Intervention group= 28/29(96.6%) and 29/31 (93.5%); p=01.00]. CDC = Centres for Disease Control and Prevention; ICF = Idiopathic Chronic Fatigue; CFS = Chronic Fatigue Syndrome.*
Table 2 Changes in outcomes between baseline (T1), post-treatment (T2) and follow-up (T3)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time</th>
<th>Intervention (n=45)</th>
<th>Control (n=46)</th>
<th>Group x Time interactiona</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>Subjective experience of fatigue</td>
<td>T1 46.00±6.30</td>
<td>47.00±7.66</td>
<td>6.70 .003</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 42.62±9.93</td>
<td>47.35±8.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3 41.96±10.08</td>
<td>48.53±7.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue severityi</td>
<td>T1 98.40±16.43</td>
<td>103.54±19.07</td>
<td>6.14 .003</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 93.73±22.37</td>
<td>106.76±20.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3 92.42±22.30</td>
<td>108.39±20.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue impact</td>
<td>T1 6.25±1.89</td>
<td>6.88±1.90</td>
<td>4.12 .018</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 5.89±2.38</td>
<td>6.33±2.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3 5.13±2.52</td>
<td>6.49±2.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leisure-time PA2</td>
<td>T1 41.56±70.59</td>
<td>58.37±106.28</td>
<td>4.83 .011</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 120.67±146.19</td>
<td>57.39±152.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3 71.67±110.36</td>
<td>66.08±121.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA (steps/day)</td>
<td>T1 6629±2716</td>
<td>6773±2820</td>
<td>1.96 .151</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 7077±2746</td>
<td>6385±2830</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3 6941±2728</td>
<td>6557±2949</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical HRQoL</td>
<td>T1 38.22±17.78</td>
<td>31.30±18.90</td>
<td>7.06 .002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 43.33±21.87</td>
<td>28.15±20.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3 42.78±21.20</td>
<td>28.27±19.68</td>
<td></td>
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<tr>
<td>Mental HRQoL</td>
<td>T1 41.57±16.13</td>
<td>37.59±17.62</td>
<td>6.39 .002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 46.85±19.71</td>
<td>36.79±19.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3 50.39±18.80</td>
<td>36.27±18.35</td>
<td></td>
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</tr>
<tr>
<td>Somatic distress</td>
<td>T1 14.02±4.04</td>
<td>16.20±4.47</td>
<td>0.43 .624</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 13.05±4.72</td>
<td>15.76±4.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3 13.40±5.50</td>
<td>15.59±4.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>T1 1.49±0.88</td>
<td>1.89±0.91</td>
<td>0.48 .605</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 1.55±0.95</td>
<td>1.91±0.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3 1.39±0.97</td>
<td>1.88±0.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>T1 1.63±0.77</td>
<td>1.66±0.79</td>
<td>1.01 .365</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 1.44±0.79</td>
<td>1.64±0.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3 1.37±0.81</td>
<td>1.61±0.86</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Note. Values are presented as mean ± standard deviation. aMixed design repeated measures using intention to treat analysis, adjusted for disease duration and setting (Health care centres vs. Patient association). iCIS20 total score. 2Descriptives are presented in raw form. PA= physical activity. HRQoL= Health-related quality of life.)
Table 3  Summary of mediation analyses predicting levels of fatigue severity at follow-up

<table>
<thead>
<tr>
<th>Mediators</th>
<th>Daily steps</th>
<th>Goal progress</th>
<th>Self-regulation skills</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paths a (IV→M)</td>
<td>666.47</td>
<td>1.65*</td>
<td>0.49**</td>
</tr>
<tr>
<td>Paths b (M→DV)</td>
<td>-0.00</td>
<td>-4.65*</td>
<td>-4.55*</td>
</tr>
<tr>
<td>Path c (total effect IV→DV)</td>
<td>-6.31**</td>
<td>-6.31**</td>
<td>-7.02**</td>
</tr>
<tr>
<td>Paths c’ (direct effect IV→DV after controlling for M-)</td>
<td>-5.83**</td>
<td>-4.63**</td>
<td>-4.80*</td>
</tr>
<tr>
<td>Estimate of indirect effect (axb paths)</td>
<td>-0.47</td>
<td>-1.65</td>
<td>-2.22</td>
</tr>
<tr>
<td>95% CI of indirect effect</td>
<td>-1.92 to 1.49</td>
<td>-4.15 to -0.36</td>
<td>-5.41 to -0.56</td>
</tr>
<tr>
<td>Effect ratio of indirect effect</td>
<td>0.07</td>
<td>0.26</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Note. * p < 0.05, ** p<0.01 CI=Confidence Interval; IV Independent Variable (treatment condition); DV Dependent Variable (subjective fatigue severity); M Mediator. * Sample size corresponds to completers dataset, as SR skills was only assessed at T2 (n=35 in intervention group and n=33 in control group).