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Efficacy of a randomized controlled self-regulation based physical activity intervention for chronic fatigue: Mediation effects of physical activity progress and self-regulation skills

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ABSTRACT

Objective: Examine the medium-term effects of a brief physical activity (PA) self-regulation (SR) based intervention (4-STEPS program) for chronic fatigue, and explore the mediating effects of PA related variables and SR skills.
Methods: A two-arm randomized controlled trial (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), and 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. No significant effects were found for number of daily steps and somatic and psychological distress. Fatigue severity at follow-up was partially mediated by post-treatment progress on a personal PA goal (effect ratio = 18%).
Conclusion: 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. Despite these promising results, dropout was high and the intervention was not beneficial for all secondary outcomes.

1. 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]. Guidelines for CFS management [1,4,5] recommend non-pharmacological treatments such as Graded Exercise Therapy (GET) or Cognitive Behavior Therapy (CBT), mainly because of the combination of psychological and behavioral factors that contribute to the perpetuation of chronic fatigue [1,6,7]. One of the main behavioral factors is prolonged physical inactivity (rest) and decreased physical capacity. It has been suggested that prolonged physical inactivity can result in physical deconditioning as well as in other physiological and psychosocial consequences that may perpetuate fatigue severity and disability [8–10]. At the same time, high levels of exercise can cause overexertion and perpetuate fatigue symptoms [11,12].

GET is based on the assumption that aerobic exercise (e.g. brisk walking) or physical activity (e.g. housework, gardening) must be initiated at a level (intensity and frequency) that doesn't exacerbate symptoms and must be gradually increased until patients reach an optimal level of activity. GET follows the exercise prescription guidelines of the American College of Sports Medicine [13], tailored to each patient's initial level of physical capacity, and most interventions follow a similar protocol [14,15]. GET has been shown to have beneficial effects on chronic fatigue management [16–18]. Because of the benefits of physical activity in patients suffering from ICF/CFS, many Cognitive Behavioral Therapy (CBT) trials have also incorporated a graded exercise component. Despite some beneficial effects of both GET and CBT on ICF/CFS patients, effects of these trials are heterogeneous [16,17], and present limited effects upon physical capacity and daily activity [17]. One explanation for the differences in the effectiveness may be that some interventions result in creating cognitive or behavioral changes that may mediate the effect of the intervention on fatigue, while others do not result in such changes. Available research on the mechanisms of treatment effects in the context of CFS, has found evidence for the

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prospective mediating role of cognitive factors, mainly fear avoidance beliefs (e.g. [19,20,21]), avoidance behavior, and catastrophizing [19,21]. Regarding behavioral mediators, such as physical activity, while a secondary mediation analysis of the PACE trial found a mediation effect of timed walking distance in a GET treatment [21], the study by Wiborg and colleagues [22] analysing the mediation effect of PA on fatigue severity and including data from two CBT trials targeting PA in CFS adult patients [23,24], 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 article we will therefore not only report on the medium-term effects of a self-regulation physical activity based program for ICF/CFS patients, but we will also explore possible mediators of these effects in the context of a self-regulation based intervention, more specifically physical activity related variables, and self-regulation skills.

Adopting a health behavior change framework can contribute to the understanding and promotion of physical activity in chronic fatigue patients. Recent studies have shown that self-regulation (SR) based interventions are effective in promoting long-lasting health behavior change in patients suffering from various chronic diseases (e.g. [25,26]). SR can be defined as a "sequence of actions and/or steering processes intended to attain a personal goal" [27]. Central in self-regulation theories (e.g. Control Theory, [28]) is the assumption that human actions are goal-oriented and that self-regulation processes (e.g. skills) guide the achievement of personally relevant goals [27,28]. Thus, health behavior change is a dynamic goal-guidance process consisting of a goal selection and setting phase, active goal pursuit and goal attainment phase, in which motivational and volitional aspects interact [27]. 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 [27,29]. As a consequence, SR models may also encourage patients to change their personal goals from symptom avoidance to more active and positive goals [30].

Motivational interviewing (MI), a "collaborative conversation style for strengthening a person's own motivation and commitment to change" ([31] 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. 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 [27]. In a meta-analysis, Michie et al. [32] found that interventions combining self-monitoring with other skills derived from self-regulation theory, such as goal setting, provision of feedback, planning and goal reformulation, were more effective in promoting changes in PA and healthy eating in the general population than other interventions not using these techniques. Moderation effects of SR-skills on effects in relevant outcomes were also found in other meta-analyses of trials conducted with chronic patients [33–35].

Based on the SR approach described above, we developed a brief intervention targeting physical activity for patients with ICF/CFS (the "4-STEPS to control your fatigue" program) [36]. The 4-STEPS is a brief intervention, requiring minimal contact with participants. Recent minimal direct contact trials have shown promising results [23,37]. 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 [11], allowing for flexibility in the intensity and duration of exercise according to symptom fluctuation, without exceeding one's own capacity.

The 4-STEPS program was tested in a randomized controlled trial [38], 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 (physical and psychological components), 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).

The first objective of the present study is to examine the sustained effects of the 4-STEPS over time, reporting on the 12-months follow-up results of the 4-STEPS intervention on fatigue severity and impact on daily life, physical activity, health-related quality of life, somatic distress and psychological distress. 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 (Appendix A).

2. Method

2.1. Trial design

This study concerns the follow-up results of a randomized controlled trial that has been previously described in full detail, including the intervention and measures description [36,38]. It was a two-arm 12-week parallel multicentre randomized controlled trial. Randomisation was stratified by sample (from Health care centres and Patient Association), with equal randomisation (1:1) to either the intervention condition 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, and 3 (post-treatment) and 12 months (follow-up) 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 centre. The trial (recruitment, intervention and assessments) took place between January 2011 and December 2013.

2.2. 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 and (b) via the Portuguese Fibromyalgia and Chronic Fatigue Syndrome 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 post-treatment and follow-up. An a priori analysis [39] 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 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.

2.3. Treatment conditions

Patients in both conditions continued to receive standard usual care (routine consultations with assistant physician). Participants assigned

to the control condition received a flyer with information about the general physical activity [13], and could 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 health behavior change and motivational interviewing) delivered the "4-STEPS" program to individual patients. The intervention was based on the self-regulation phases of goal pursuit [27]. Participants received two face-to-face individual motivational interviewing sessions aimed at reducing ambivalence towards change, and increasing participants' motivation and confidence to be physically, during which they set a personal physical activity goal that took into consideration the graded activity principles of flexibility and balance, developed by Nijs and colleagues [11]. In addition, participants received two brief self-regulation based telephone-counselling sessions aimed at reviewing goal progress, and prompt relapse prevention strategies. Participants also received a booklet containing information about chronic fatigue and physical activity, and a self-regulation based workbook divided in four steps, each one focusing on specific self-regulation cognitions and skills: Step 1-"Am I ready to start?" (e.g. focus on self-efficacy and control over competing goals); Step 2- "My physical activity goal" (e.g. goal-setting, action planning); Step 3 "Overcoming obstacles" (e.g. coping efficacy and planning, feedback); and Step 4 "I am physically active...and I want to keep it this way" (relapse prevention strategies). Participants were given a pedometer to register their daily steps during the intervention period.

2.4. Outcomes

Patient characteristics Socio-demographic characteristics included age, gender, education and employment status (Table 1). The following clinical indicators were gathered: (1) presence of persistent fatigue, duration of symptoms, impact on daily activities, and whether it was alleviated by rest, and (2) a CDC based 19 major and minor symptoms checklist for CFS [40], asking for experience of each symptom in the last 6 months. 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.

Fatigue (primary outcome) was assessed using the Checklist of Individual Strength (CIS20-P) [41,42]. For the purpose of this study only the subjective experience of fatigue dimension (primary outcome) and the total fatigue severity score were used.

The following measures were used for secondary outcomes. *Fatigue impact* was measured using a modified version of the pain interference dimension of the Brief Pain Inventory (BPI) [43]. 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. Physical activity was assessed by means of: 1) a self-report measure of *leisure-time physical activity* based on the Short Questionnaire to Assess Health-enhancing Physical Activity (SQUASH) [44]. 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 [45,46]. 2) Daily steps was assessed using Yamax Digiwalker SW-200 pedometers [47]. The mean of the daily steps over seven consecutive days was used as an outcome measure. 3) Physical activity goal progress and achievement was assessed at baseline and post-treatment, using a standardized goal-elicitation procedure [48]. The Short Form Health Survey-12 (SF-12V.2) [49] assessed physical functioning (Physical HRQoL) and psychological functioning (Psychological HRQoL). Somatic distress was assessed with the Patient Health Questionnaire-15 (PHQ-15) [50]. Psychological distress was assessed using the Depression and Anxiety subscales from the Brief Symptom Inventory (BSI) [51]. Self-regulation skills were measured at post-treatment using the Self-Regulation Skills Battery (SRSB) [48], 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 SRSB presents good reliability.

Outcomes were assessed at baseline, post-treatment and follow-up. The exceptions were perceived physical activity goal progress and self-regulation skills, for which the post-treatment measures were used for the mediation analysis. All measures selected are well-validated measures, described in full detail in previous papers [36,38].

2.5. Statistical analyses

At follow-up, an independent samples *t*-test was conducted to assess the difference in subjective experience of fatigue (primary outcome) between the intervention group and the control group. The effects of the intervention on the proposed outcomes were examined using a 3 (timeline: baseline, post-treatment and follow-up) × 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 × group interaction, contrasts were tested for significance. Estimates and 95% confidence intervals were considered. Effect sizes for contrasts were the standardized mean difference with Hedge's *g* correction for small samples [52]. Data was analysed with intention-to-treat analyses (ITT) from last observation point. We undertook sensitivity analyses to test the robustness of the results of the mixed design ANCOVAs by repeating all analyses with values carried-forward from baseline and with completers only, and no significant differences were found between the three approaches (for a comparison of results between the three approaches). Additional chi-square analyses were conducted for the complete dataset to compare the number of patients in each group who a) did not meet clinical levels of fatigue severity

Table 1
Baseline demographics and patient characteristics.

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

Note. 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] Cut-off score of 35 on the Subjective Fatigue sub-scale of the CIS20.

[d] Comparison results for completers [clinical levels: Intervention group = 28/29(96.6%) and 29/31 (93.5%); $p = 1.00$].

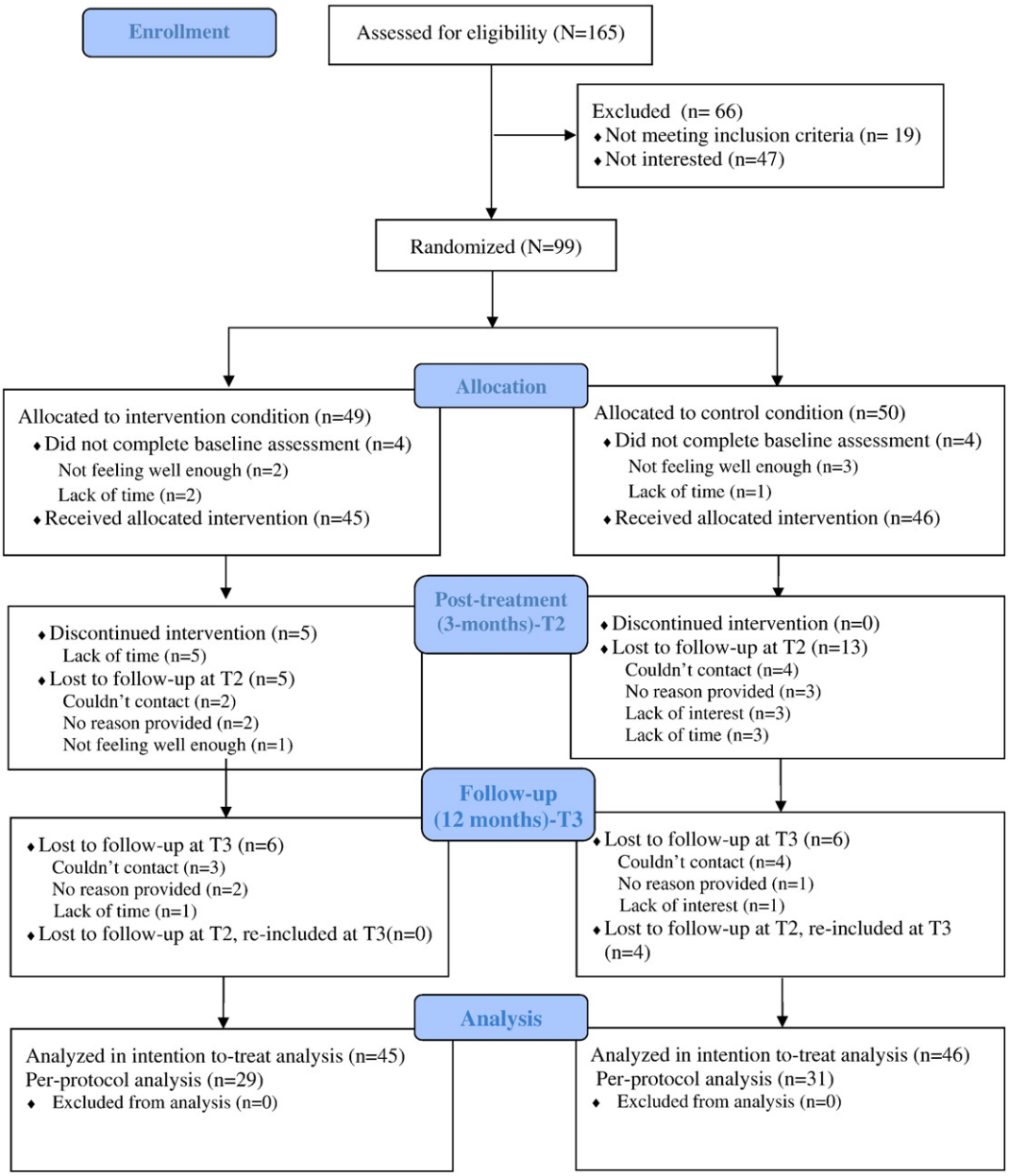

Fig. 1. Flow diagram of participants through the intervention.

(<35) assessed by the subjective experience of fatigue dimension of the CIS20-P.

To test mediation, we first examined multicollinearity between variables through bivariate (Pearson) correlations between the independent variable (treatment condition), the putative mediators and the dependent variable (follow-up subjective fatigue severity) (Appendix B). Each mediation model (Appendix A) was tested using a bootstrapping procedure developed by Preacher and Hayes [53], using the PROCESS macro for SPSS. Mediation model 1 tested the indirect effect of treatment condition on the level of subjective experience of fatigue severity at follow-up through the putative mediators: 1) daily steps taken, and 2) perceived physical activity goal progress, assessed at post-treatment. Model 2 predicted the follow-up level of subjective experience of fatigue, through the use of self-regulation skills at post-treatment. Model 3 tested a sequential mediation of the effect of treatment condition on subjective fatigue, through the use of self-regulation skills influencing perceived physical activity goal progress. 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, the ratio of the indirect effect to the total effect was calculated to express the strength of the mediation effects. We used a resample procedure of 5000 bootstrap samples (bias corrected), controlling for setting, disease duration, baseline levels of the dependent variable and respective putative mediators, with the exception of Self-regulation skills that was not assessed at baseline. Data analyses were conducted using the statistical software SPSS v22.

3. Results

3.1. Participant flow and patient characteristics

The flow of patients through the trial and reasons for exclusions and withdrawals are shown in Fig. 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 any of the demographics and clinical variables.

3.2. Intervention effects

At follow-up, there was a significant difference of 6.57 points in subjective experience of fatigue (primary outcome) between the intervention and the control group ($t = -3.58, p = 0.01$ 95% CI [−10.3–−2.80], $g = 0.72$).

There was not a 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%; $X^2 = 3.68$, $p = 0.076$, 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 ($p = 0.003$) and total fatigue severity ($p = 0.003$), after controlling for the effect of the covariates (Table 2). In both analyses, contrasts revealed that significant changes occurred between baseline and follow-up ($p = 0.004$, $g = 0.66$ and $p = 0.005$, $g = 0.54$, respectively). In the intervention group there was a significant decrease from baseline to follow-up 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 ($p = 0.018$). Contrasts revealed a significant time by group interaction when comparing impact of fatigue between post-treatment and follow-up ($p = 0.003$, $g = 0.39$).

Regarding physical activity there was a significant time by group interaction for level of leisure-time physical activity ($p = 0.011$). Statistical contrasts revealed that changes were significant from baseline to follow-up ($p = 0.012, g = 0.21$). No significant group × time interaction was found for number of daily steps taken ($p = 0.151$).

There was a significant time by group effect for both physical and psychological HrQoL ($p = 0.002$). Contrasts revealed that changes were significant from baseline to follow-up ($p = 0.002$, $g = 0.39$ and $p = 0.004$, $g = 057$, respectively). In the intervention group there was a significant increase from baseline to follow-up 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 × group effects were found for somatic symptoms ($p = 0.624$), depression ($p = 0.605$) and anxiety ($p = 0.365$). None of the participants reported negative effects of exercise or any other harm from participating in the trial.

3.3. Mediation analysis

Table 3 shows the results of the mediation analysis for each proposed mediator. In the mediation model 1 only physical activity goal progress, for which a significant time by group effect was found at post-treatment ($F = 16.37, p = 0.000, g = 0.83$) [39], partially mediated the effects of the 4-STEPS program on subjective experience of fatigue at follow-up (point estimate = −0.96, 95% CI [−2.75 to −0.11]). The mediation effect averaged about 18% of the total treatment effect. With regard to self-regulation skills (Model 2) there was a significant difference ($t = 2.89$ $p = 0.006$, 95% CI [0.15–0.83], $g = 0.72$) between the intervention (M = 3.68, DP = 0.51) and the control group (M = 3.19, DP = 0.82) at post-treatment. Mediation analyses showed a non-significant indirect effect of treatment through the use of self-regulation skills on fatigue at follow-up (point estimate = −1.18, 95% CI [−3.64 to −0.15]), accounting for 17% of the total effect. The unadjusted model presents a significant estimated indirect effect (point estimate = −2.22, 95% CI [−5.42 to −0.53]; effect ratio = 0.32). Further, the sequential model of self-regulation skills and perceived goal progress was not significant.

4. Discussion

This trial tested the 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 [38]. 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. 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 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 CFS [16–18]. Two earlier trials with a similar treatment duration (3-months) that also provided 2 initial face-to-face sessions and additional self-management manuals focusing on educational and behavioral strategies differ from each other with respect to follow-up results. While in the trial conducted by Powell et al. [54] the authors found large effects of the intervention on fatigue, physical functioning and depression, in the trial by Friedberg and colleagues [55] 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. The average number of daily steps of participants in each condition met however the recommended guidelines for people diagnosed with chronic diseases of minimum 6500–8000 steps/day [56]. Furthermore, the magnitude of the interaction effect between treatment condition and time (baseline to follow-up) on leisure-time PA was small. Many behavioral and psychological trials presenting a graded exercise component have found trivial to small beneficial effects on physical activity and capacity in people diagnosed with CFS [17]. However, few studies present follow-up results.

Since physical activity is a key target in many interventions designed for people with CFS, 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 physical activity related variables. Results showed that an increased number of daily steps did not mediate treatment effects on fatigue. This result is in line with the study by Wiborg and colleagues [22] analysing the mediation effect of PA on fatigue severity and including data from two CBT trials targeting PA in CFS adult patients [23,24]. At the same time, we did find that personal goal progress partially explained the effects of treatment on sustained fatigue improvement. In addition, a recent study on CFS found that perceived activity level, and not objective activity explained the variance in fatigue during a CBT based treatment [57]. Interesting in a brief self-regulatory (planning) intervention conducted with patients after cardiac rehabilitation, it was found that the subjective achievement of a personal physical activity goal at posttreatment (4 months) mediated treatment effects on depressive symptoms at 12 months, and not self-reported physical activity levels [58]. These results suggest that it may not be the mere increase in PA that explains fatigue improvement, but rather the formulation of self-chosen and personally meaningful or relevant goals that not only increase the likelihood of goal progress and achievement but can also impact positively on disease related outcomes.

Table 2
Changes in outcomes between baseline (T1), post-treatment (T2) and follow-up (T3):

Outcome	Time	Intervention ($n = 45$)	Control ($n = 46$)	Group × time interaction[a]			
				F	*p*	Contrasts	
						Time	*p*
Primary outcome							
	T1	46.00 ± 6.30	47.00 ± 7.66	6.70	0.003		
Subjective experience of fatigue[b]	T2	42.62 ± 9.93	47.35 ± 8.31			T1-T3	0.004
	T3	41.96 ± 10.08	48.53 ± 7.92			T2-T3	0.140
Secondary outcomes							
	T1	98.40 ± 16.43	103.54 ± 19.07	6.14	0.003		
Fatigue severity[c]	T2	93.73 ± 22.37	106.76 ± 20.32			T1-T3	0.003
	T3	92.42 ± 22.30	108.39 ± 20.07			T2-T3	0.282
	T1	6.25 ± 1.89	6.88 ± 1.90	4.12	0.018		
Fatigue impact[d]	T2	5.89 ± 2.38	6.33 ± 2.21			T1-T3	0.436
	T3	5.13 ± 2.52	6.49 ± 2.23			T2-T3	0.003
	T1	41.56 ± 70.59	58.37 ± 106.28	4.83	0.011		
Leisure-time PA[e]	T2	120.67 ± 146.19	57.39 ± 152.00			T1-T3	0.012
	T3	71.67 ± 110.36	66.08 ± 121.17			T2-T3	0.054
	T1	6629 ± 2716	6773 ± 2820	1.96	0.151		
PA (steps/day)	T2	7077 ± 2746	6385 ± 2830				
	T3	6941 ± 2728	6557 ± 2949				
	T1	38.22 ± 17.78	31.30 ± 18.90	7.06	0.002		
Physical HRQoL[f]	T2	43.33 ± 21.87	28.15 ± 20.23			T1-T3	0.002
	T3	42.78 ± 21.20	28.27 ± 19.68			T2-T3	0.790
	T1	41.57 ± 16.13	37.59 ± 17.62	6.39	0.002		
Mental HRQoL[f]	T2	46.85 ± 19.71	36.79 ± 19.15			T1-T3	0.004
	T3	50.39 ± 18.80	36.27 ± 18.35			T2-T3	0.063
	T1	14.02 ± 4.04	16.20 ± 4.47	0.43	0.624		
Somatic distress[g]	T2	13.05 ± 4.72	15.76 ± 4.48				
	T3	13.40 ± 5.50	15.59 ± 4.61				
	T1	1.49 ± 0.88	1.89 ± 0.91	0.48	0.605		
Depression[h]	T2	1.55 ± 0.95	1.91 ± 0.93				
	T3	1.39 ± 0.97	1.88 ± 0.98				
	T1	1.63 ± 0.77	1.66 ± 0.79	1.01	0.365		
Anxiety[h]	T2	1.44 ± 0.79	1.64 ± 0.81				
	T3	1.37 ± 0.81	1.61 ± 0.86				

Note. 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] Range: 8–56.
[c] CIS20 total score, range: 20–140.
[d] Range: 0–10.
[e] Total number of minutes of leisure time physical activity (moderate to vigorous physical activity, MVPA) per week; descriptives are presented in raw form.
[f] Range: 0–100.
[g] Range: 0–30.
[h] Range: 0–4.

Table 3
Summary of mediation analyses predicting levels of fatigue severity at follow-up.

	Model 1		Model 2	Model 3
	Daily steps	PA goal progress	SR skills	SR skills → PA goal progress
Paths a (IV → M)	599.99	1.53*	0.49**	–
Paths b (M → DV)	−0.00	−0.67**	−4.54*	–
Path c (total effect IV → DV)	−5.43**	−5.43**	−7.07**	–
Paths c' (direct effect IV → DV after controlling for M)	−5.16**	−4.40**	−5.89*	–
Estimate of indirect effect (*axb paths*)	−0.21	−0.96	−1.18	−0.78
95% CI of indirect effect	−1.20 to 0.12	−2.75 to −0.11	−3.64 to 0.15	−0.27 to 0.16
Effect ratio of indirect effect	0.04	0.18	0.17	0.12

Note. CI = Confidence Interval; IV = Independent Variable (treatment condition); DV = Dependent Variable (subjective fatigue severity at follow-up); M = Mediator (assessed at post-treatment); PA = Physical activity. Model 1: $R^{2:} = 0.67$ $p = 0.00$; Model 2: $R^{2=}0.59 = p = 0.00$; Model 2 not controlling for the baseline level of the dependent variable: $R^2 = 0.41$, $p = 0.01$, estimate of the indirect effect: −2.22, 95% CI [−5.42 to −0.53], effect ratio = 0.32. Model 3 = $R^2 = 0.61$, $p = 0.00$.
* $p < 0.05$.
** $p < 0.01$.

A possible explanation for this mediation effect, are that participants who are pursuing an own PA goal, may experience a change in other cognitive factors such as focusing less on symptoms and negative consequences, get a higher sense of control over fatigue, feel more confident to continue making necessary efforts and changes to recover, experience greater satisfaction with their progress, and/or increase their sense of goal ownership, leading to better disease management and improvement [20,59]. 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 [10]. 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.

One of the main targets of the 4-STEPS intervention was to increase individuals' use of SR skills [27]. Although recent research has shown that interventions using a combination of theoretically derived SR-skills [23,32,34] were more effective than other interventions, only few studies analysed the mediation effect of SR-skills on health behavior changes and improved disease related outcomes (e.g. [25,26,60]). Mediation analysis showed that the effect of treatment on fatigue at follow-up was only partly explained by a treatment effect on SR-skills at post-treatment, in the unadjusted model (i.e. not controlling for baseline fatigue severity). The sequential mediational model showed similar results, indicating that also other factors than self-regulation skills or

specific self-regulation skills may have an impact on physical activity goal progress.

4.1. Study limitations

The present study has a number of limitations. First, the small sample size limits the generalizability of our findings. The lack of significance found for some of the secondary outcomes such as daily steps assessed by means of a pedometer may be due to low statistical power, as our study was not powered to detect changes in secondary outcomes or detect clinical differences in fatigue severity. Employing complex moderated mediation models with larger samples can also provide more insight in differential effects of SR skills (e.g. self-monitoring) and explore for which subgroups and in which phases of health behavior change the intervention works best. Furthermore, the number of subjects with ICF was very low and for this reason we could not run a sensitivity analysis to examine differential effects of the 4-STEPS between CFS and ICF patients. Second, intervention combined motivational interviewing, the use of self-regulation techniques and motivational tools (e.g. pedometer), but the effect of each component could not be separated out in the present study. Future studies should address this issue by using a full-factorial design. Third, 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. Fourth, confirmation of ICF/CFS inclusion and exclusion criteria was based on self-reported CDC criteria and it can therefore not be excluded that some participants 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 standardized psychiatric interview. In addition, men were largely underrepresented in the sample; more studies are therefore needed to determine the effects of this program in men suffering from ICF/CFS. Fifth, we made extensive use of self-report measures, which are susceptible to response bias. Nevertheless, the questionnaires used in this study are well validated and reliable Furthermore, the fact that blinding of participants and investigators was not possible could have increased bias. Sixth, 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 [55,61]. Seventh, the intervention was delivered by only one psychologist, which did not allow for controlling therapist effects in our analysis.

Finally, in this controlled trial the 4-STEPS program was compared against a passive control group whose participants only received general information about physical activity and formulated a goal without additional guidelines. Future trials should also investigate the benefits of self-regulation based interventions in a design that includes an active control condition, e.g. a treatment such as GET.

5. Conclusion

Despite its limitations, this study found that a brief intervention has sustained effects in fatigue management. Minimal direct contact interventions that can be easily implemented in standard health care can be useful for people diagnosed with ICF/CFS presenting difficulties in attending regular health care facilities [61] and/or for those who do not need more intensive forms of treatments [37]. Furthermore, our results suggest that using motivational and self-regulation principles and techniques can lead to improved fatigue in people diagnosed with ICF/CFS. Self-chosen, personally meaningful goals appear to motivate these individuals, while SR-skills training may facilitate the attainment of their goal.

5.1. Other information

The trial is registered at http://www.controlled-trials.com, number ISRCTN70763996 and we have previously published the protocol of our trial [36]. This report followed the revised CONSORT guidelines for reporting randomized trials [62].

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.

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Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jpsychores.2016.12.012.

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