Multidisciplinary fatigue management programme in multiple sclerosis: a randomized clinical trial

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Objective To establish the efficacy of a multidisciplinary fatigue management programme (MFMP) in MS.

Method Fifty-one subjects with MS were randomly allocated to group A, who only received the four weeks MFMP, or group B receiving a placebo intervention programme first and the MFMP after 6 months. In both groups, assessment was performed at baseline, 3 weeks and 6 months after the programmes and included Modified Fatigue Impact Scale (MFIS), Fatigue Severity Scale (FSS), MS Self-Efficacy scale (MSSE), Mental Health Inventory (MHI) and Impact on Participation and Autonomy (IPA).

Results The MFIS showed a significant change over time ($F(4,152) = 3.346$, $P = 0.012$), which was similar in both groups (time*group interaction: $F(4,152) = 1.094$, $P = 0.361$). A clinically relevant reduction of MFIS score of 10 points or more was found in 17% of individuals following the MFMP, compared to 44% after the placebo intervention programme ($P = 0.06$). Compared to no intervention, a significant effect of the MFMP after 6 months ($P = 0.003$) was found in five participants (31%). No significant changes in FSS, MSSE, MHI and IPA, in both groups, were found.

Conclusion Although an additional effect was found, the multidisciplinary fatigue management programme showed no efficacy in reducing the impact of fatigue compared to a placebo intervention programme. *Multiple Sclerosis* 2007; **13**: 996–1003. http://msj.sagepub.com

Key words: education; energy management; fatigue management programme; modified fatigue impact scale; multidisciplinary; self-care

Introduction

Fatigue is one of the most frequent and most disabling symptoms in individuals with multiple sclerosis (MS) [1,2]. The management of MS-related fatigue usually includes (a combination of) pharmacological agents, exercise, body cooling and energy conservation strategies [3,4]. Researchers have studied the efficacy of some of these strategies separately, but did not reach consensus concerning the best (combination of) strategies [5–16].

In daily life, individuals with MS have to cope with fatigue and often initiate self-care management based on information, experimentation and professional support [17,18]. Persons with MS look for information in magazines, books or on the internet, but professional guidance may be necessary to provide practical information and prevent rigorous actions [18,19]. However, individuals with MS are more likely to discuss their self-care strategies with others with MS than with their physicians [18]. Based on these results, both theoretical and practical information delivered by a combination of specialist health professionals and others with MS, would be the best approach to promote self-care management.

Several methods to promote strategies to deal with MS-related fatigue have been reported. O'Hara *et al.* reported better mental health and higher vitality scores following a professionally guided self-care programme for the management of MS, although not specifically developed for fatigue [20].

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Mathiowetz and colleagues found reduced fatigue impact, higher self-efficacy and better quality of life after a 6-week energy conservation course led by an occupational therapist [7,8]. Embrey described the importance of a self-management education programme for individuals who recently received their diagnosis of MS, but did not report its efficacy [21].

Since the management of fatigue involves various approaches [22], we developed a multidisciplinary fatigue management programme (MFMP). Except for the energy saving methods and strategies instructed by an occupational therapist, the MFMP also highlights medical treatment, psychosocial support and physiotherapeutic approaches. The goal of this programme is to support and stimulate self-care strategies to cope with MS-related fatigue.

The randomized controlled study described in this paper aimed at establishing the short and long term efficacy of the MFMP in reducing the impact of fatigue in daily life in individuals with multiple sclerosis.

Sample and methods

Design

We used a single blind randomized placebo-controlled design, with matched pairs (Figure 1). Group A started the 4 weeks multidisciplinary fatigue management programme one week after the assessment (Figure 2). At the same time, group B received a placebo intervention programme during 4 weeks. In both groups, assessment was repeated 3 weeks after the end of the programme and 6 months later. Then group B received the MFMP, followed by two assessment sessions for both groups 3 weeks and 6 months later.

Sample

Approval of the ethics committee of the Vrije Universiteit Brussel was obtained prior to the start of the trial. Participants were recruited by flyers and personal invitation through the Belgian National MS Society and on referral by the treating neurologist. A pilot study indicated that a sample size of 50 subjects was necessary to obtain a power of 85% [23].

Subjects were included when they were diagnosed with MS, had a high impact of fatigue (score 3 or more on the fatigue subscale of the Guy's Neurological Disability Scale) [24], were living in community, were able to walk for 100 m without (a walking) aid, had not been attending a rehabilitation programme for the last 2 years, did not receive any energy management programme in the past and were not under psychiatric treatment for depression. A research assistant performed this first screening by telephone. After signing the informed consent form, subjects performed the tests of the Multiple Sclerosis Functional Composite (MS-FC): 25 feet walking test, Nine Hole Peg Test and Paced Auditory Serial Addition Test (PASAT). All tests were performed twice. The PASAT score was used as a measure of cognitive performance. Individuals with a score adjusted for education lower than the 10th percentile (PASAT score of 35) [25] were excluded for analysis. All self-report instruments (primary and secondary outcome measures) were completed during this session.

Matched pairs were composed based on the Modified Fatigue Impact Scale score, age, gender and MS-FC score. The identity number of every subject was written down on a paper and put in an envelope together with the other pair member. An independent research assistant separated each pair and divided the individuals over two groups (group A or group B) by random draw. Group allocation was kept concealed for data analysis. Due to the nature of the intervention, blinding of participants was not possible.

Interventions

The multidisciplinary fatigue management programme (MFMP) and placebo intervention programme consisted of four sessions of 2 h, spread over 4 weeks. Each session started with information provided by the instructor, followed by an interactive part, in which participants discussed the strategies they used and planned in the near future. During the MFMP, information was provided concerning possible strategies to manage fatigue and reduced energy levels, ie, pharmacological treatment, diet, informing and involving the social environment, regular sleep, exercise, relaxation, cooling, assistive devices, adaptation of home or work environment and energy saving methods [22]. For the placebo intervention programme, we chose topics that were interesting enough to avoid dropouts and did not concern themes directly related to fatigue (ie, car adaptations and driving abilities, communication skills, lift techniques for back protection and general information about MS).

Primary outcome measure

Fatigue impact was evaluated with the Modified Fatigue Impact Scale (MFIS) [22]. In the MFIS, subjects rate how often fatigue influenced 21 physical, cognitive and psychosocial activities during the past 4 weeks. Summation of the score of all items gives a total score ranging from 0 to 84. The total

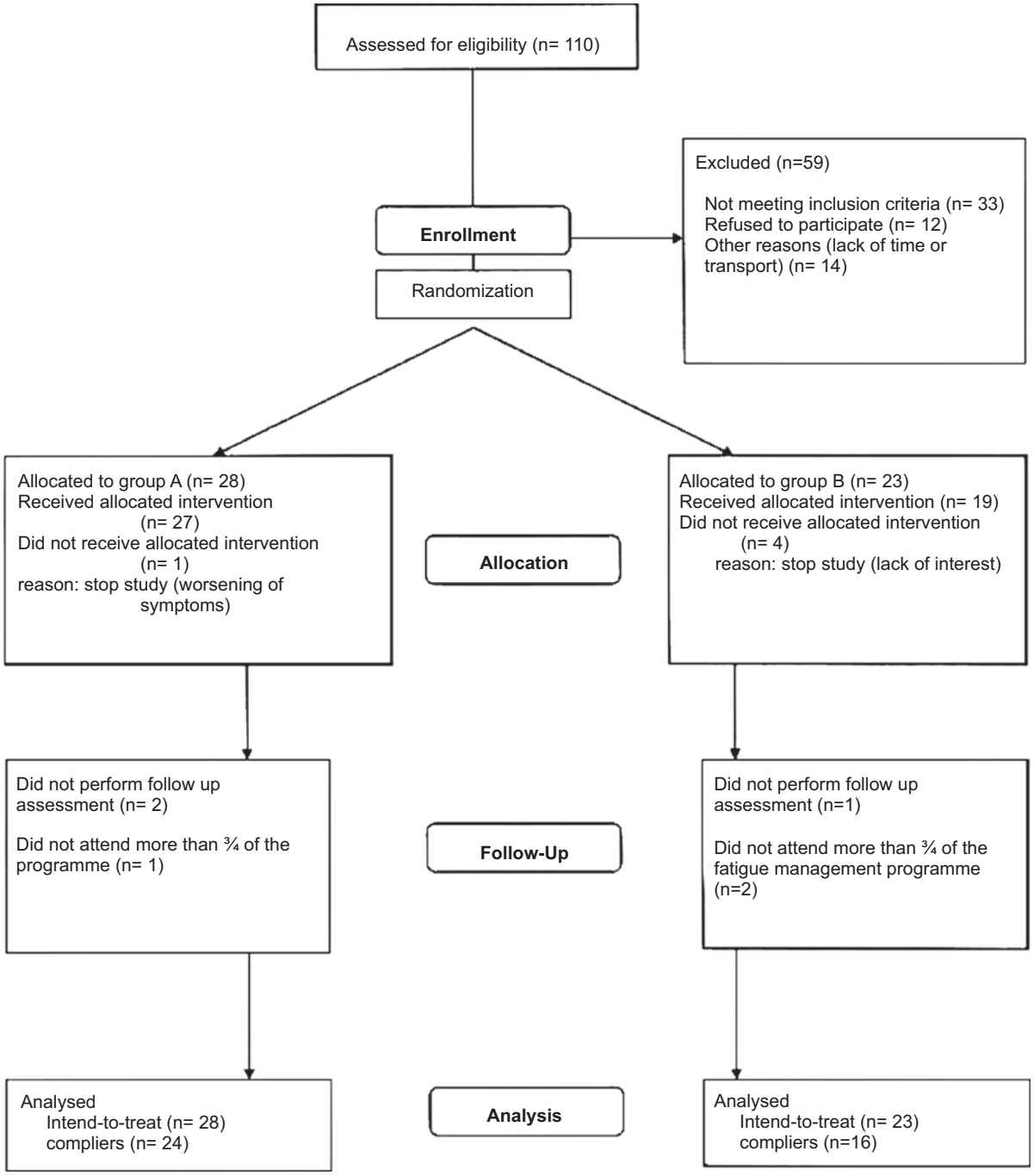

Figure 1 Flow chart.

score can be subdivided in a physical (score range 0–36), a cognitive (range 0–40) and a psychosocial subscale (range 0–8). The MFIS showed high reproducibility and good validity in subjects with MS [26,27]. We considered a change in score of 10 or more as clinically relevant, based on other studies that found differences in MFIS score of 7–20.1 [10,26,28,29].

Secondary outcome measures

The Fatigue Severity Scale (FSS) (score range 9–63) evaluates the severity, frequency and impact of fatigue on daily life in nine statements and has good reliability and acceptable validity [30].

Self-efficacy is the confidence of one's ability to perform a certain behaviour and therefore important

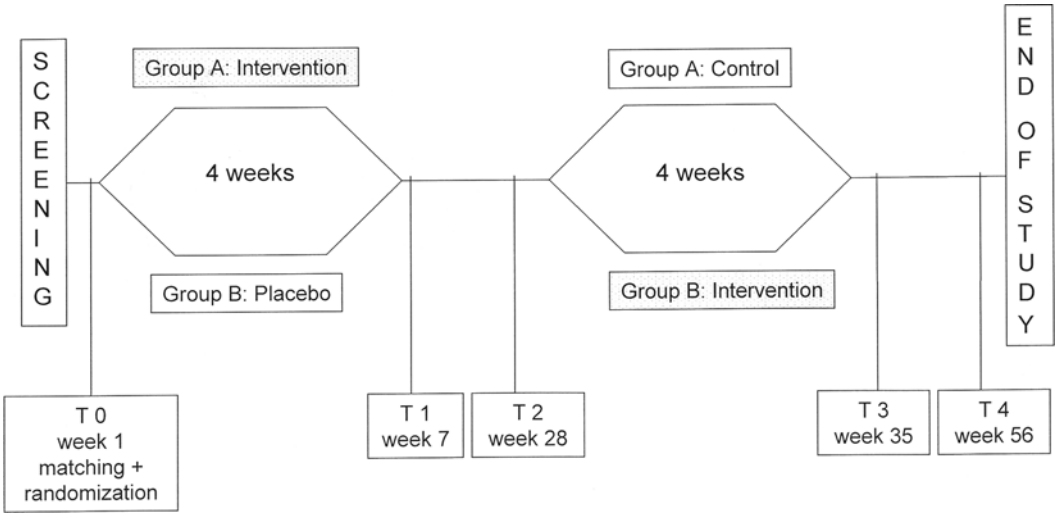

Figure 2 Design of the study.

to evaluate when interventions aim at changing behaviour [33]. To assess self efficacy, we used the Multiple Sclerosis Self-Efficacy (MSSE) Scale [31]. In the MSSE subjects rate the confidence (ranging from 10, very uncertain to 100, very certain) in their ability to perform specific activities (function subscale, nine items) and to cope with symptoms and disease impact (control subscale, nine items). The scale is internally consistent and showed good reproducibility and validity [31].

The Impact on Participation and Autonomy scale is used to assess the perceived impact of the disease (and related symptoms) on five life domains (interior and exterior autonomy, family role, social relations and job and education). Subjects rate their perception on participation and autonomy and on problems. The scale showed good reliability and validity and acceptable responsiveness [32–34].

The Mental Health Inventory (MHI) assesses depression, anxiety, behavioural control and positive affect [35]. Subjects rate on a Likert scale (0–6) how often they experienced certain feelings during the last week. The scale is a reliable, valid and responsive instrument [36].

In all assessment sessions, participants were asked to record the strategies they used to manage fatigue, in an open question.

Statistical analyses

All results were analysed using the software package SPSS for Windows Standard Version 13.0.1, 2004. All outcome measures are sum scores and showed a normal distribution. Therefore they were analysed with parametric statistics. Differences between groups were analysed with a one way analysis of variance (ANOVA) for continuous variables, a Mann–Whitney test for ordinal variables and a chi-square test for nominal data.

Attrition rate was 21.6% ($n = 11$). Non-compliers were analysed as intend-to-treat (ITT) by replacing missing values with the linear trend at that point. We performed an ANOVA for repeated measures with time (T0, T1, T2, T3 and T4) as within subject factor and group (A or B) as between subject factors. If significant, pairwise comparison was performed with Bonferroni correction for multiple comparisons. Effect sizes were considered with the partial eta squared. A value of eta squared of 0.01 is considered a small effect size, 0.06 is medium and 0.14 large [37]. The difference in clinically relevant changes in MFIS scores between group A and B was considered with a chi square. Changes in energy management strategies over time were analysed with a Friedman ANOVA. To search for a profile of responders, a stepwise discriminant analysis was performed with 10 points or more progression on the Modified Fatigue Impact Scale as effect parameter. Factors introduced were: years of fatigue complaint, type of MS, age, gender, education, type of referral (neurologist, MS society and friends/family), work status, baseline fatigue impact and self efficacy.

Results were considered statistically significant when $P < 0.05$.

Results

A sample of 51 subjects was selected and matched pairs were randomly assigned to two groups (Figure 1). The final sample (ie, compliers) included 40 subjects. Reasons for dropout were worsening of symptoms, lack of interest after allocation and not

Table 1 Demographic and baseline clinical variables

		Group A ($n=28$)	Group B ($n=23$)	*P*-value
Age[a]		42.9 (9.1)	44.5 (9.9)	0.575
Gender (F/M)[b]		20/8	15/8	0.863°
Years since diagnosis[a]		6.1 (4.9)	8.2 (9.0)	0.310
Years since fatigue complaint[a]		8.3 (7.0)	8.2 (9.5)	0.965
Type of MS[b]	Relapsing-remitting	20 (72%)	14 (61%)	0.193
	Primary progressive	2 (7%)	3 (13%)	
	Chronic progressive	2 (7%)	4 (17%)	
	Data not available	4 (14%)	2 (9%)	
Years of education[a]		13.4 (2.8)	13.6 (2.9)	0.787
MS-Functional Composite score[a]		0.13 (0.6)	−0.16 (0.7)	0.116
VAS for fatigue impact[c]		6 (5–8)	5.5 (5–7)	0.190
Modified Fatigue Impact Scale[c]	Total sum score	46 (38–54)	46 (42–54)	0.719
	Physical subscale	22 (17–26)	22.5 (19–26)	0.468
	Cognitive subscale	21 (16–26)	20.5 (16–25)	0.792
	Psychosocial subscale	4 (3–6)	5 (4–6)	0.302
MS Self Efficacy scale[c]	Function subscale	760 (655–810)	670 (530–800)	0.123
	Control subscale	540 (390–660)	510 (400–590)	0.399

[a]Mean (SD); [b]frequencies (%); [c]median (IQR).
°Chi-square.

Table 2 Mean changes (with *P*-values) in Modified Fatigue Impact Scale scores from baseline in intend-to-treat and compliers group at all assessment points

	Intend-to-treat ($n=51$)	Compliers ($n=40$)
T1: 3 weeks following MFMP+placebo	2.28 (1.0)	3.96 (0.091)
T2: 6 months following MFMP + placebo	1.93 (1.0)	4.08 (0.147)
T3: 3 weeks following MFMP in control group	4.12 (0.078)	**5.15*** (0.034)
T4: 6 months following MFMP in control group	2.87 (0.34)	**4.52*** (0.015)

*$P<0.05$, Bonferroni adjusted for multiple comparisons.

willing to perform the follow up assessment. Within the dropout group, two subjects had an adjusted PASAT score lower than 35. Three subjects were absent more than once during the programme and therefore excluded in the final sample.

At baseline, demographic and clinical variables did not differ between group A and B (Table 1). In the compliers group, group A and B showed similar changes in MFIS scores over time ($F_{time}(4,152) = 3.346$, $P=0.012$; $F_{time*group}(4,152)=1.094$, $P=0.361$). A trend toward a significant time effect was found in the intended-to-treat group ($P=0.05$). Three weeks and 6 months following the fatigue management programme in group B, MFIS significantly decreased from baseline scores in compliers (T3 and T4, Table 2). No significant effects were found in secondary outcome measures however.

The clinically relevant improvement of fatigue impact after the MFMP did not differ from those of the placebo intervention programme (Table 3). However, the post-MFMP scores differed significantly from no intervention after six months (difference T2–T4) (compliers $P=0.003$; ITT $P=0.045$).

At baseline, some strategies were already incorporated in the daily life of the participants (Table 4). No significant changes occurred at the short or long term

Table 3 Proportion of participants with clinically relevant changes of MFIS scores (improvement of 10 or more)

	Compliers $n=40$			
	Group A $n=24$	Group B $n=16$	*P**	Effect size° (power)
T1: 3 weeks following MFMP + placebo	4 (17%)	7 (44%)	0.06	0.3 (47%)
T2: 6 months following MFMP + placebo	9 (38%)	5 (31%)	0.685	0.06 (<10%)
T3: 3 weeks following MFMP in group B	7 (29%)	3 (19%)	0.456	0.12 (10%)
T4: 6 months following MFMP in group B	7 (29%)	6 (38%)	0.581	0.09 (<10%)
difference T2-T3	2 (8%)	4 (25%)	0.148	0.23 (24%)
difference T2-T4	0 (0%)	5 (31%)	**0.003**	0.46 (85%)

Percentages are proportions within the group.
*Based on chi-square.
°Effect size w = square root (chi square/*n*) [37].

Table 4 Strategies implemented to manage fatigue in daily life at baseline, 3 weeks and 6 months following the fatigue management programme [number of participants (%)] ($n = 40$)

Strategy	Baseline	3 weeks post programme	6 months post programme	Friedman chi-square *r*	*P*
Naps	28 (70)	29 (73)	34 (85)	0.310	0.212
Sleep routine	14 (35)	11 (28)	9 (23)	3.455	0.178
Diet	3 (8)	4 (10)	5 (13)	1.500	0.472
Regular life	2 (5)	2 (5)	1 (3)	1.00	0.607
Rest/activity ratio	17 (43)	15 (38)	13 (33)	1.330	0.513
Pace activities	2 (5)	1 (3)	2 (5)	0.500	0.779
Plan ahead	4 (10)	9 (23)	4 (10)	4.167	0.125
Prioritize	7 (18)	4 (10)	6 (15)	1.167	0.558
Spread activities over time	13 (33)	13 (33)	11 (28)	0.500	0.779
Organization of material	0	3 (8)	0	6.0	0.05
Equipment/assistive devices	1 (3)	3 (8)	5 (13)	4.00	0.135
Relaxation	7 (18)	10 (25)	8 (20)	1.00	0.607
Temperature control	3 (8)	5 (13)	7 (18)	4.800	0.091
Physical activity	5 (13)	9 (23)	4 (10)	4.308	0.116
Introduce help	4 (10)	4 (10)	4 (10)	0.000	01.00
Part-time job	3 (8)	0	2 (5)	3.5	0.174
Stress management	5 (13)	3 (8)	5 (13)	0.727	0.695

following the MFMP. Fifty-two percent of all participants already implemented three or more strategies at baseline, whereas 54% reported the implementation of three or more strategies three weeks after attending the MFMP, and 48% after 6 months.

Discriminant analysis revealed that course of MS was the only determining factor in the clinically relevant change three weeks after the programmes (T1). The responders group consisted of five subjects with a relapsing-remitting course of MS and four of those with a chronic progressive type (two missing data). Non-responders were 20 subjects with relapsing-remitting, four with primary progressive course and one person with a chronic progressive disease course (four missing data).

At baseline, 28 subjects (55%) used disease modifying drugs, 12 (24%) fatigue medication, 11 (20%) antidepressants and 17 (31%) used other non-MS-specific drugs for MS. No significant changes in medication use occurred during the study.

Discussion

This study assessed the efficacy of a multidisciplinary fatigue management programme (MFMP) in persons with multiple sclerosis.

The changes in Modified Fatigue Impact Scale score did not differ between subjects in group A, who immediately followed the MFMP, and those in group B, who participated in the placebo intervention programme first, at any of the assessment points. An obvious explanation of the lack of difference between groups is that the placebo intervention programme also influenced the perceived impact of fatigue. We did find a significant difference after 6 months in response to the MFMP compared to no intervention (Table 3), supporting this hypothesis. In particular for newly diagnosed individuals with MS, the information concerning MS in the placebo intervention programme may provide a better understanding of the disease [18]. This may have contributed to a reduction of their fatigue impact, although we found no differences with participants with longer disease duration. Other studies have inconsistent results: O'Hara *et al*. found higher vitality following a non-fatigue-specific professionally guided self-care management programme [20] whereas Mathiowetz *et al*. [7] did not find any effects of their support group. However, Mathiowetz and colleagues used a repeated measures design without a washout period after the control intervention, with the possibility of an effect accumulation. The other study of this research group did not include a control intervention [8]. A trial with the pharmacological agent modafinil also resulted in a large placebo effect [15]. Fatigue may be so heterogeneous that a specific treatment is not superior to a general approach of the symptom. Future research should include both placebo and control (without intervention) groups to clarify the net effect of the specific fatigue and the placebo intervention programme.

Although most participants already used some of the strategies before entering the programme, it was expected that subjects would introduce additional ways of dealing with fatigue. The additional implementation of fatigue management strategies after the MFMP was however poor (Table 4). This may be due to practical barriers (lack of time, unable in work situation and so on) or to unsuccessful instruction. We evaluated the implementation of fatigue reducing strategies with an open question. Compared to a checklist, this avoided marking strategies that are not

actually performed and a learning effect by just reading possible strategies [38]. However, we did not request participants to mark whether they used the strategies on account of the programme. Mallik et al. developed the Energy Conservation Strategies Survey, specifically for the evaluation of an energy conservation course [39]. This instrument can be used in future research to assess the (barriers to) implication. The MFMP was instructed by four different therapists, who stimulated participants to try out the discussed strategies. Due to the exchange of instructors, no structured homework was planned in the sessions. Probably subjects need more concrete stimulation to change their actual behaviour and implement the strategies. A tailor-made programme on an individual basis, requiring more concrete action plans feasible in daily life and providing a more structured feedback system may be more effective than group sessions. However, to date no evidence is available for the superiority of an individual approach.

Our programme consisted of four group sessions. With an additional amount of sessions, subjects may be more encouraged to change their behaviour and more effect may have been found.

The power of the non-significant difference in clinically relevant changes between groups after the MFMP relative to the placebo intervention programme reached 47%. With an effect size of 0.3 (at T1), we would need a sample of 87 to reach a power of 80% to find significant differences. In a pilot study however we found an effect size of 0.50 which indicated a sample size of at least 50 subjects to reach a power of 85% [23].

Although disability did not correlate with fatigue (impact) in several studies [26,40,41], a (sudden) change in functional possibilities may influence the way individuals are dealing with fatigue. The functional possibilities of participants were assessed by means of MS-Functional Composite scores. Four subjects had a clinically relevant functional deterioration (MS-FC change of 0.5 points) [42] after one year, but their modified fatigue impact scores did not differ statistically significant from the scores of the individuals who remained stable.

Results may be influenced by the existence of an exacerbation of the disease or change in medication use. Six months after the programmes, five subjects of group A reported an exacerbation, one in group B. We reanalysed the data without these subjects, but did not find any differences in results. No significant changes occurred in medication use.

The course of MS appears to be a determining factor in the responders. Three weeks after the programme (T1), individuals with a chronic progressive course seem to respond better to the programme than persons with relapsing-remitting (RR) type of MS. This may be due to the fluctuating nature of the RR course, although participants did not change significantly in physical or cognitive performance at T1. One study reported an improvement in fatigue impact following the 8-week energy conservation course in subjects with chronic progressive MS [43]. Other previous studies used a mixed sample without specification of disease course in responders [7,8]. Future research should include groups with a relapsing-remitting course to confirm our results.

No other discriminating factors have been identified to explain the difference between responders and non-responders. Future studies with larger sample sizes may be needed to provide a profile of responders.

Conclusion

The multidisciplinary fatigue management programme presented in this study provided information and strategies to deal with MS-related fatigue and reduced energy in daily life. The MFMP did not reduce the impact of fatigue in daily life in individuals with MS compared to the placebo intervention programme, both at the short and the long term. However, sample size was small and both programmes may be too similar. Although an accumulation of effect is possible, the MFMP showed a medium effect when compared with no intervention. Future work should include a placebo intervention and a control group to confirm our results.

For newly diagnosed individuals with MS, the MFMP may be an introduction to start self-care in managing fatigue. In a later stage, when persons are more experienced in several self-care techniques, a programme acquiring structural behavioural changes, may be more effective.

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