

# A multisite randomized controlled trial of two group education programs for fatigue in multiple sclerosis: Very long term (5–6 year) follow-up at one site

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## Abstract

**Background:** A multicomponent group MS fatigue self-management program reduced fatigue impact compared to a rigorous control 12 months after enrollment.

**Objectives:** Assess and compare changes between groups in fatigue impact and behavior changes implemented 5–6 years after enrollment.

**Methods:** The Modified Fatigue Impact Scale (MFIS) and a behavior change questionnaire were administered 5–6 years after enrollment.

**Results:** There were no significant changes in mean MFIS scores within or between groups from baseline to 5–6 years later. Behavior changes were of similar frequency in both groups.

**Conclusion:** Fatigue impact was stable and behavior changes were similar between groups 5–6 years after a fatigue self-management program.

**Keywords:** multiple sclerosis, fatigue, rehabilitation, clinical trial, symptomatic treatment

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**Table 1.** Contents of FTC and MSTC programs.

| Fatigue: Take Control (FTC)   | MS: Take Control (MSTC)   |
|---|---|
| 6-weeks, small groups (8–10)  | 6-weeks, small groups (8–10)  |
| <ul style="list-style-type: none"> <li>• Medical Management of Fatigue</li> <li>• Making Proactive Energy Choices</li> <li>• Adding Exercise to Your Life</li> <li>• Modifying Your Environment</li> <li>• Making Changes and Choices to Take Control of Fatigue</li> <li>• Summary and Overview</li> </ul> | <ul style="list-style-type: none"> <li>• Food for Thought: MS and Nutrition</li> <li>• Vitamins, Minerals and Herbs in MS</li> <li>• Taming Stress in MS</li> <li>• MS and Your Emotions</li> <li>• Solving Cognitive Problems</li> <li>• Urinary Dysfunction and MS</li> </ul> |

## Introduction

Over 80% of people with multiple sclerosis (MS) report disease-associated fatigue that substantially affects their quality of life.<sup>1</sup> Our multicenter randomized controlled trial (RCT) (n = 204) compared the effects of a multi-component, small group, fatigue self-management program, *Fatigue: Take Control* (FTC) with a general MS education control program, *MS: Take Control* (MSTC) on fatigue impact. See Table 1. Contents of FTC and MSTC programs. There were no significant within or between group differences in fatigue measured by Modified Fatigue Impact Scale (MFIS) mean scores at baseline, at program completion, or at three or six month follow-ups compared to baseline.<sup>2</sup> A 12 month follow-up at one site (n = 74) found FTC participants had a clinically meaningful improvement compared to baseline and a statistically significant improvement compared to MSTC participants.<sup>3</sup> To evaluate fatigue impact beyond 12 months, we re-administered the MFIS 5–6 years after enrollment.

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We also evaluated behavior changes implemented to manage fatigue 5–6 years later.

### Materials and methods

Original study inclusion criteria were definite MS of any subtype; age 18 years or older; moderate-to-severe fatigue (scores  $\geq 25$  on the MFIS); Expanded Disability Status Scale (EDSS)  $\leq 6.5$ ; Beck Depression Inventory II (BDI)  $\leq 28$ ; stable on disease modifying medications for at least 3 months; free of relapses for the prior 30 days; not pregnant; able to comply with study procedures; and able to complete measures independently.<sup>2</sup> While some MS disease modifying medications may contribute to fatigue, we expected the effects to be equally distributed between groups with randomization. Both programs consisted of six weekly 2-hour small group sessions with trained facilitators. We assessed outcomes 5–6 years after enrollment in subjects who had completed the 12-month follow-up. This assessment was not part of the original study design. All participants had signed an IRB approved consent at enrollment and, 5 to 6 years later, respondents provided verbal consent to receive and complete the MFIS and a new 17-item questionnaire. The latter was based on fatigue management content taught in FTC, and asked about behavior changes implemented since program completion. See supplement A. In this report, we compared 1) baseline characteristics of 5–6 year follow-up respondents with non-respondents; 2) mean MFIS scores compared to baseline within and between FTC and MSTC respondents and non-respondents at all applicable follow-ups; 3) behavior changes implemented by FTC and MSTC respondents.

### Results

All statistical analyses were done using SPSS. We used paired t-tests to assess within group differences and independent sample t-tests to assess between group differences at baseline and between baseline and each time point. Chi square tests were used to determine if the proportions who reported each behavior change differed between treatment groups.

Thirty-eight of the 74 people eligible (51.4%) responded to the 5–6 year follow-up, 15/34 (44%) in FTC and 23/40 (58%) in MSTC. Baseline characteristics did not differ between respondents and non-respondents. However, FTC non-respondents had greater improvement in mean MFIS scores at 6 and 12 months than FTC respondents. (Table 2). At 5–6 years, fatigue scores in both groups were not significantly different from scores at baseline or at 12 months. More than half of all respondents learned something from their programs to help manage

fatigue, with some behavior changes implemented more frequently than others (Table 3). However, the proportions who reported implementing each behavior change did not differ between FTC and MSTC groups; nor did the mean number of changes implemented differ between groups.

### Discussion

This is a 5–6-year follow-up of individuals who completed a 12-month follow-up after the first, large multicenter RCT assessing the efficacy of a multicomponent MS fatigue management program, FTC, compared to a rigorous active general MS education control program, MSTC. Mean MFIS scores in 5–6 year respondents did not improve but were not worse than at baseline or 12 months in either group. Although baseline characteristics did not differ between respondents and non-respondents, FTC non-respondents had greater improvement in MFIS scores at 6 and 12 months than respondents. Our failure to find treatment effects 5–6 years later may have been due, in part, to not capturing those who had shown the most improvement earlier. While MSTC did not teach specific behavior change strategies to manage fatigue, these strategies are well-known and available, and all were being used with similar frequency in both groups 5–6 years later.

There is little literature on very long term follow-ups after rehabilitation trials. In an uncontrolled evaluation of a 5-day program promoting lifestyle modification for people with MS, 60% of the original 274 participants completed the 5 year follow-up with 19.5% median improvement in quality of life compared to baseline.<sup>4</sup> In a follow-up of a RCT of a pain and stress self-management group intervention (PASS) compared to a rigorous control, 73% of the original group (n = 129) responded at 9 years. PASS participants had less pain-related disability and a trend for better self-efficacy than the control.<sup>5</sup> Unlike our study, these studies pre-planned their long-term assessments, had better retention, and found improvements were retained long term.

Although we did not find treatment effects 5–6 years after interventions, fatigue did not worsen in either group. This calls into question the continued progression of fatigue in people with MS, a progressive disease. A prior study based on survey results from 2386 people with MS found that MFIS scores increased sharply for the first 14 years of the disease and then leveled off. Additionally, MFIS scores increased as respondents' functional levels on the Patient Determined Disease Steps changed from no limitations to abnormal gait. However, from abnormal

**Table 2.** Baseline characteristics and mean MFIS scores over time in 5–6-year respondents and non-respondents.

| Characteristics at baseline             | Respondents at 5–6 years<br>(n = 38) |                        | Nonrespondents at 5–6 years<br>(n = 36) |                        |
|---|--------------------------------------|------------------------|---|------------------------|
|   | FTC group<br>(n = 15)                | MSTC group<br>(n = 23) | FTC group<br>(n = 19)                   | MSTC group<br>(n = 17) |
| Female, n (%)                           | 13 (86.7%)                           | 20 (87.0%)             | 16 (84.2%)                              | 10 (58.8%)             |
| Male, n (%)                             | 2 (13.3%)                            | 3 (13.0%)              | 3 (15.8%)                               | 7 (41.2%)              |
| Relapse-Remitting MS, n (%)             | 10 (66.7%)                           | 13 (56.5%)             | 15 (78.9%)                              | 11 (64.7%)             |
| Progressive MS, n (%)                   | 5 (33.3%)                            | 10 (43.5%)             | 4 (21.1%)                               | 6 (35.3%)              |
| EDSS, median, low/high                  | 5.0, 4.0/6.5                         | 5.5, 4.0/6.5           | 5.0, 3.5/6.5                            | 6.0, 4.0/6.5           |
| Age in years, mean (SD)                 | 56.7 (8.5)                           | 53.8 (11.4)            | 55.5 (11.2)                             | 47.0 (12.8)            |
| Median (low, high)                      | 58 (40, 73)                          | 54 (31, 73)            | 58 (28, 72)                             | 50 (29, 64)            |
| Years since diagnosis, mean (SD)        | 14.53 (9.5)                          | 14.0 (9.4)             | 11.74 (7.1)                             | 10.41 (6.97)           |
| median, (low, high)                     | 17 (1, 33)                           | 14 (2, 41)             | 10 (4, 29)                              | 11 (0, 23)             |
| BDI-II, mean (SD)                       | 12.4 (5.7)                           | 11.8 (4.9)             | 9.9 (7.1)                               | 13.9 (6.3)             |
| median (low, high)                      | 11 (4, 24)                           | 13 (2, 19)             | 6 (1, 25)                               | 15 (4, 26)             |
| MFIS, mean (SD)                         | 49.2 (15.8)                          | 44.4 (12.8)            | 45.3 (10.9)                             | 48.7 (9.6)             |
| median (low, high)                      | 44 (28, 82)                          | 42 (27, 81)            | 45 (28, 66)                             | 47 (31, 65)            |
| MFIS scores over time                   |                                      |                        |   |                        |
| Mean (SD) at baseline                   | 49.2 (15.8)                          | 44.4 (12.8)            | 45.3 (10.9)                             | 48.7 (9.6)             |
| Mean (SD) at program completion         | 46.1 (16.4)                          | 44.6 (12.9)            | 41.6 (17.9)                             | 46.3 (11.3)            |
| Mean (SD) change from baseline          | −3.07 (11.6)                         | 0.17 (9.6)             | −3.68 (11.2)                            | −2.36 (8.0)            |
| Within group difference vs. baseline    | p = 0.33                             | p = 0.93               | p = 0.17                                | p = 0.24               |
| Between groups difference after classes | —                                    | p = 0.36               | —                                       | p = 0.69               |
| Mean (SD) at 3 months                   | 45.1 (17.1)                          | 41.7 (14.3)            | 39.6 (18.5)                             | 45.6 (11.1)            |
| Mean (SD) change from baseline          | −4.07 (11.57)                        | −2.78 (12.41)          | −5.68 (14.77)                           | −3.06 (11.13)          |
| Within group difference vs. baseline    | p = 0.20                             | p = 0.29               | p = 0.11                                | p = 0.27               |
| Between groups difference at 3 months   | —                                    | p = 0.75               | —                                       | p = 0.56               |
| Mean (SD) at 6 months                   | 42.3 (19.7)                          | 41.1 (14.3)            | 36.7 (17.2)                             | 45.7 (11.3)            |
| Mean (SD) change from baseline          | −6.9 (12.4)                          | −3.34 (13.2)           | −8.5 (14.7)                             | −2.9 (11.7)            |
| Within group difference vs. baseline    | p = 0.049                            | p = 0.24               | p = 0.021                               | p = 0.32               |
| Between groups difference at 6 months   | —                                    | p = 0.42               | —                                       | p = 0.21               |
| Mean (SD) at 12 months                  | 43.2 (20.8)                          | 42.4 (14.4)            | 35.5 (15.6)                             | 45.3 (10.4)            |
| Mean (SD) change from baseline          | −6.0 (11.2)                          | −2.0 (11.7)            | −9.7 (12.3)                             | −3.4 (10.3)            |
| Within group difference vs. baseline    | p = 0.058                            | p = 0.42               | p = 0.003                               | p = 0.20               |

(continued)

**Table 2.** Continued.

| Characteristics at baseline            | Respondents at 5–6 years<br>(n = 38) |                        | Nonrespondents at 5–6 years<br>(n = 36) |                        |
|--|--------------------------------------|------------------------|---|------------------------|
|  | FTC group<br>(n = 15)                | MSTC group<br>(n = 23) | FTC group<br>(n = 19)                   | MSTC group<br>(n = 17) |
| Between groups difference at 12 months | —                                    | p = 0.30               | —                                       | p = 0.10               |
| Mean (SD) at 5–6 years                 | 46.3 (14.4)                          | 44.5 (14.1)            | NA                                      | NA                     |
| Mean (SD) change from baseline         | –2.9 (10.8)                          | 0.04 (13.8)            |   |                        |
| Within group difference vs. baseline   | p = 0.32                             | p = 0.99               |   |                        |
| Between groups difference at 5–6 years | —                                    | p = 0.50               |   |                        |
| Mean (SD) at 5–6 years                 | 46.3 (14.4)                          | 44.5 (14.1)            | NA                                      | NA                     |
| Mean (SD) change from 12 months        | 3.1 (13.1)                           | 2.0 (11.3)             |   |                        |
| Within group difference vs. 12 months  | p = 0.37                             | p = 0.39               |   |                        |

FTC: *Fatigue: Take Control*; MSTC: *MS: Take Control*; MS: multiple sclerosis; SD: standard deviation; EDSS-S: self-assessed Expanded Disability Status Scale; BDI-II: BDI: Beck Depression Inventory II; MFIS: Modified Fatigue Impact Scale; NA: not available (not collected).

**Table 3.** Behavior changes implemented to manage fatigue: 5–6 years after program completion.

|   | Total       | FTC         | MSTC        |
|---|-------------|-------------|-------------|
| Learned something from the program            | 18/34 (53%) | 8/14 (57%)  | 10/20 (50%) |
| Behavior changes                              |             |             |             |
| Actively prioritize daily/weekly activities   | 28/37 (76%) | 11/15 (73%) | 17/22 (77%) |
| Manage sleep quality                          | 25/36 (69%) | 10/14 (71%) | 15/22 (68%) |
| Manage weakness                               | 23/35 (66%) | 7/14 (50%)  | 16/21 (76%) |
| Change exercise routine                       | 24/37 (64%) | 11/15 (73%) | 13/22 (59%) |
| Increased exercise                            | 12/37 (32%) | 6/15 (40%)  | 6/22 (27%)  |
| Decreased exercise                            | 12/37 (32%) | 5/15 (33%)  | 7/22 (32%)  |
| Manage how/what to eat                        | 24/37 (65%) | 10/15 (67%) | 14/22 (64%) |
| Manage heat sensitivity                       | 22/35 (63%) | 9/15 (60%)  | 13/20 (65%) |
| Regularly rest and/or nap                     | 22/35 (63%) | 9/14 (64%)  | 13/21 (62%) |
| Maintain good posture                         | 16/35 (46%) | 5/14 (36%)  | 11/21 (52%) |
| Change/reorganize environment                 | 15/33 (45%) | 6/14 (43%)  | 9/19 (47%)  |
| Manage depression                             | 14/34 (41%) | 5/13 (39%)  | 9/21 (43%)  |
| Use new equipment                             | 12/35 (34%) | 5/14 (36%)  | 7/21 (33%)  |
| Change in pain medications                    | 11/37 (30%) | 5/15 (33%)  | 5/22 (23%)  |
| Manage other medical conditions               | 9/36 (25%)  | 5/15 (33%)  | 4/21 (19%)  |
| Change in antidepressant medications          | 9/37 (24%)  | 3/15 (20%)  | 6/22 (27%)  |
| Change in sleep medications                   | 8/37 (22%)  | 3/15 (20%)  | 5/22 (23%)  |
| Use an activity diary                         | 3/37 (8%)   | 0/15 (0%)   | 3/22 (14%)  |
| Mean (SD) number of behavior changes reported | 8.68 (3.78) | 8.53 (3.50) | 8.77 (4.03) |
| Range   | (1–17)      | (3–14)      | (1–17)      |

There were no differences between groups in the proportions of behavior changes made or in the mean number of changes made. FTC: *Fatigue: Take Control*; MSTC: *MS: Take Control*.

gait to wheelchair mobility, fatigue impact remained relatively stable.<sup>6</sup> Our 5–6 year respondents averaged 14.2 years since diagnosis and disability ranged from minor gait impairment to needing bilateral support at baseline. Thus, our findings of stable fatigue from baseline to 5–6 years later are consistent with this report of stable fatigue later in the disease course and with more impaired mobility.

The major strength of this study is that it is the first to evaluate impacts of a multicomponent MS fatigue self-management intervention beyond 12 months. The major limitations are that the follow-up only included half of the 74 eligible people, those from FTC who demonstrated the most positive effect on fatigue at 6–12 months did not participate, and this study included few men.

Follow-ups beyond a year for people with a chronic disease, such as MS, are important to understand the long-term effects of both the disease and self-management interventions on associated symptoms. To optimize participant retention, all follow-ups should be planned at initial trial design. Further longitudinal studies are needed to better understand the time course of fatigue in MS and the durability of fatigue management interventions.

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### Supplemental material

Supplemental material for this article is available online.

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