



MINDFULNESS-BASED COGNITIVE THERAPY FOR SEVERELY FATIGUED MULTIPLE SCLEROSIS PATIENTS: A WAITING LIST CONTROLLED STUDY

Alexandra E. W. HOOGERWERF, MSc¹, Yvonne BOL, PhD^{1,2}, Jill LOBBESTAEL, PhD^{3,4}, Raymond HUPPERTS, PhD^{2,5} and Caroline M. VAN HEUGTEN, PhD⁶

From the ¹Department of Clinical and Medical Psychology, Zuyderland Medical Centre, ²Academic MS Centre Limburg, Zuyderland Medical Centre, Sittard-Geleen, ³Department of Clinical Psychological Science, Faculty of Psychology and Neuroscience, Maastricht University, ⁴RINO Zuid, Postdoctoral Education Institute, Eindhoven, ⁵Faculty of Health Medicine and Life Sciences, Maastricht University, and ⁶School for Mental Health and Neuroscience, Department of Psychiatry and Neuropsychology, Faculty of Health, Medicine and Life Sciences, Department of Neuropsychology & Psychopharmacology, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, The Netherlands

Background: Fatigue is the most common symptom in multiple sclerosis. Evidence-based treatment options are scarce.

Objective: To study the feasibility and potential effectiveness of mindfulness-based cognitive therapy in severely fatigued multiple sclerosis patients.

Methods: Non-randomized pilot study with a waiting list control period including 59 multiple sclerosis patients with severe fatigue. Primary outcome measure: fatigue severity subscale of the Checklist Individual Strength-20. Secondary measures: Hospital Anxiety and Depression Scale, Life Satisfaction Questionnaire, subscale sleep of the Symptom Checklist-90, Cognitive Failure Questionnaire, Fatigue Catastrophizing Scale, Coping Inventory of Stressful Situations, and Five Facet Mindfulness Questionnaire-Short Form. Measurements were taken before treatment (double baseline), after treatment, and at follow-up (3 months).

Results: Adherence rate was 71%. Eight out of 10 participants who completed the intervention were satisfied with the intervention. Significant time effects were found for 7 out of 11 outcome measures ($p = 0.006$ to < 0.001). The effect size was moderate for all outcome measures that were significant post-treatment and/or at follow-up ($\eta^2 = 0.10$ – 0.17). Improvements were maintained at follow-up. Of the completers, 46% showed a clinically relevant change regarding fatigue.

Conclusion: Mindfulness-based cognitive therapy is feasible in severely fatigued multiple sclerosis patients and has positive results in the reduction of severe fatigue and several psychological factors.

Key words: multiple sclerosis; mindfulness-based cognitive therapy; fatigue; mindfulness.

Accepted Apr 6, 2017; Epub ahead of print Jun 8, 2017

J Rehabil Med 2017; 49: 497–504

Correspondence address: Sandra Hoogerwerf, Clinical and Medical Psychology, Zuyderland Medical Centre, PO-5500, NL-6130 MB Sittard, The Netherlands. E-mail: s.hoogerwerf@zuyderland.nl

Multiple sclerosis (MS) is a chronic and unpredictable inflammatory demyelinating disease of the central nervous system (CNS). MS is one of the most

common neurological disorders affecting young adults. The clinical symptoms are diverse, including both physical and neuropsychiatric symptoms (1). Depression, anxiety and cognitive impairment are very common in MS. The prevalence of depressive disorders is high, ranging from 7% to 70% (2). The prevalence of anxiety disorders ranges from 1% to 36% (2). Between 45% and 65% of MS patients show cognitive deficits (3), particularly impairments of processing speed, cognitive flexibility, sustained attention, and memory retrieval.

The most common symptom of MS is fatigue; up to 90% of patients with MS report fatigue (4). The pathogenesis of fatigue is unknown and the aetiology is at least multifactorial (4). Several variables could perpetuate fatigue, such as depression and sleeping problems (5), catastrophizing thoughts (6) and maladaptive coping styles (7–9). Fatigue is a major reason for disability, decreased participation and poor quality of life (QoL) (10). Unfortunately, evidence-based treatment options are limited (4).

There is growing evidence that cognitive behavioural therapy (CBT) is effective in MS-related fatigue (9). The effectiveness of CBT is based on changing the negative representation of fatigue, making it possible to perceive fatigue as more controllable (8). Recently, a new generation of CBT, including mindfulness components, has been developed (11). In a systematic review on mindfulness interventions in MS (12), the authors concluded that these interventions may be beneficial for MS patients in terms of mental health, QoL and some physical aspects, including pain, fatigue and standing balance. For instance, a group intervention of mindfulness-based stress reduction (MBSR) improved QoL and reduced symptoms of depression, anxiety and fatigue, compared with usual care (13).

Another variant of mindfulness, mindfulness-based cognitive therapy (MBCT), represents a MBSR programme, adapted specifically for recurrent depression, in which cognitive elements are integrated (14). It is possible that, by adding the cognitive elements of MBCT, the effectiveness of the intervention could be improved, since catastrophizing thoughts about fatigue could theoretically increase fatigue levels (15). The effectiveness of MBCT for fatigue has been demon-

strated in fatigued cancer survivors, directly after the training and at 6-month follow-up (16). In MS, one pilot study recently evaluated the effectiveness of a modified version of MBCT, in people with progressive phenotypes, being delivered remotely via Skype. The intervention demonstrated likely effectiveness on distress, but showed only small insignificant effect sizes on fatigue (17). The aim of the current study was to evaluate the feasibility and potential effectiveness of the group protocol of MBCT adapted to MS, in MS patients with severe fatigue.

We hypothesized that MBCT is feasible in MS patients with severe fatigue and that it would result in a reduction in symptoms of fatigue, depression and anxiety, and increased QoL. In addition, we explored the impact of MBCT on sleeping problems, cognitive complaints, catastrophizing thoughts about fatigue, coping styles and the level of mindfulness. Finally, we evaluated whether patients with cognitive disorders benefited as much from MBCT as patients without cognitive disorders.

METHODS

Study design

This was a non-randomized pilot study in which participants acted as their own control. The study was conducted between June 2012 and January 2014. In this period, 5 groups with a mean of 12 patients started consecutively with the intervention. There was a 10-week waiting list control period, a 10-week period of treatment and a 3-month follow-up. During the waiting list period all participants received standard medical care with regular visits to the neurologist and continuing their standard medication.

Participants

Patients with clinically definite relapsing remitting multiple sclerosis (RRMS) or secondary progressive multiple sclerosis (SPMS), according to the McDonald classification criteria (18), were recruited from the Department of Neurology in the Academic MS centre Limburg (Zuyderland Medical Centre ((Orbis Medical Centre at the time)), Sittard-Geleen, the Netherlands). Inclusion criteria were: age 18–60 years, severe fatigue symptoms (score ≥ 35 on the subscale subjective fatigue of the Checklist Individual Strength-20 (19)), and fluent in Dutch. Furthermore, patients had to be motivated for the training; they had to be willing to come to the hospital for 2.5 h each week and were expected to practice at home every day for approximately 1 h, for the duration of the training. Exclusion criteria were: primary progressive MS (on the advice of a neurologist (RH)), other medical problems related to fatigue (such as diabetes mellitus, stroke, inflammatory bowel diseases, major depression, and neurological diseases other than MS), an exacerbation of MS or use of corticosteroids within the past 6 weeks, a current clinical depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)-criteria (20), or another severe psychiatric disorder, and former formal mindfulness training (i.e. MBSR or MBCT, but not yoga). The medical ethics committee of Zuyderland-Zuyd approved the study protocol and all patients gave written infor-

med consent. The trial was prospectively registered at ccm.nl (reference number: NL39852.096.12).

Measures

Primary outcome measure. Fatigue was measured with the fatigue severity subscale of the Checklist Individual Strength-20 (CIS-20). This subscale consists of 8 items, each scored on a 7-point Likert scale, with total scores ranging from 8 to 56. A score of 35 or higher on the subscale indicates severe fatigue. Cronbach's α for subjective fatigue is 0.88, and test-retest reliability $r=0.81$ in MS patients (19, 21).

Secondary outcome measures. Symptoms of anxiety and depression were measured with the Hospital Anxiety and Depression Scale (HADS). Both subscales consist of 7 items, with scores ranging from 0 to 21 per subscale. Higher scores indicate more symptoms. A score above 7 for each subscale indicates depression or anxiety levels likely to be of clinical significance. Reliability is demonstrated for the Dutch population (22) and the validity is adequate for MS patients (23).

As a measure of QoL, we used the first question of the Life Satisfaction questionnaire (LiSat-9). This question concerns satisfaction with life as a whole, and is rated on a 6-point Likert scale. A score of 1–4 reflects dissatisfaction with life and a score of 5–6 indicates satisfaction with life. The Dutch translation of the LiSat-9 has been used previously with patients with acquired brain injury and MS, with Cronbach's $\alpha=0.81$ (24).

Sleeping problems were measured with the subscale sleep of the Symptom Checklist-90 (SCL-90) (25), a frequently used questionnaire for several psychological and physical symptoms. The subscale sleep consists of 3 items, with scores ranging from 3 to 15. Higher scores indicate more sleep problems. Cronbach's α is 0.91. The content validity index (CVI) of the subscale varies from 0.4 to 0.7 (25).

Cognitive symptoms were assessed with the Cognitive Failure Questionnaire (CFQ) (26). This questionnaire consists of 25 items assessing general daily cognitive mistakes, with the total score ranging from 25 to 125. Lower scores indicate more symptoms. Cronbach's $\alpha=0.95$ (26).

Catastrophizing about fatigue was measured with the Fatigue Catastrophizing Scale (FCS), which is an adapted version of the Pain Catastrophizing Scale (PCS) (27). The PCS was adapted by replacing the word "pain" with the word "fatigue" in all items and 3 MS-related items were added (*When I am tired, this is a signal there is something wrong in my brain; When I am tired, this is a warning of physical decline; When I am tired, this is a sign that my MS is getting worse*) (15). Scoring alternatives range from "strongly disagree" to "strongly agree". The FCS consists of 16 items, with total scores ranging from 0 to 64 and with higher scores indicating more catastrophizing thoughts. Cronbach's $\alpha=0.91$ in MS patients (15).

Coping styles were measured with the Coping Inventory of Stressful Situations (CISS) (28). This self-report inventory (48 items, using 5-point Likert scales) measures 3 main coping strategies: task-oriented coping (dealing with the problem at hand); emotion-oriented coping (concentrating on the resultant emotions, e.g. becoming angry or upset); and avoidant coping (trying to avoid the problem). Each coping strategy consists of 16 items. Item scores are summed per scale; higher scores indicate a greater use of that particular coping style. Cronbach's α varied from $\alpha=0.76$ to 0.91 and the test-retest reliability varied from $\alpha=0.66$ to 0.74 (28).

The level of mindfulness was measured with the Five Facet Mindfulness Questionnaire-Short Form (FFMQ-SF) (29). The

FFMQ-SF is a 24-item questionnaire. Items are scored on a 5-point Likert-type scale, with higher scores indicating more mindfulness. Cronbach's alpha of the facets of the FFMQ-SF varied from 0.75 to 0.87 in people with depressive symptomatology (29).

To assess cognitive disorders 3 neuropsychological tests were administered:

First the oral version of the Symbol Digit Modalities Test (SDMT) (30) was used to measure information processing speed. Second, the Paced Auditory Serial Addition Test (PASAT) (30) was used to measure information-processing speed, working memory and attention/concentration. Third, the Controlled Oral Word Association Test (COWAT) (30) was used as a measure of executive functioning. These 3 neuropsychological tests have been proven to be highly sensitive and reliable tests in MS (30).

Feasibility of the intervention

Feasibility was measured by dropout rate during the intervention and the satisfaction of the participants with the intervention, measured by a questionnaire that was designed by the authors (SH, YB). The questionnaire for the participants who completed the intervention (completers) consisted of 14 items (5-point Likert scale), containing questions about the quality of the training, improvement of symptoms, a numerical score from 0 to 10 for the intervention and the satisfaction about the intensity of the intervention as to number of meetings, length of meetings and the practice at home (see Appendix SIA¹). The questionnaire for the participants who dropped out of the intervention (non-completers) consisted of 10 items (5-point Likert scale) with questions about reasons for dropout and their evaluation of the training (see Appendix SIB¹).

Procedure

Patients from the Academic MS Centre Limburg, who previously had given written informed consent to allow contact by our research team regarding future research, were contacted by telephone by the researcher (SH).

Inclusion and exclusion criteria were checked by telephone and the fatigue severity was assessed with the CIS-20, which was sent by email. Potential candidates visited the rehabilitation specialist (RH) to be referred to the treatment because the MBCT was embedded in regular outpatient rehabilitation treatment. At baseline (T0), participants were invited by a research assistant (IS) for baseline measurements and the administration of the neuropsychological tests, administered by several research assistants at Zuyderland Medical Centre, who had a minimum of 10 years of experience with administering tests. All participants started with a 10-week waiting period in which they received standard medical care. They did not receive any other specific treatment focused on reducing fatigue, but general advice could be given. After this period, T1 measurements were conducted (i.e. second baseline). Subsequently, the MBCT intervention (see intervention) was carried out, followed by the post-treatment measures (T2). Follow-up measures (T3) were conducted 3 months after the intervention. T1, T2 and T3 were administered by sending the questionnaires to the participant's home address to be returned by post. When the questionnaires were not returned, reminders to return the questionnaires were sent by email by the research assistant (IS).

Intervention

The MBCT protocol used is described by Segal et al. (14) and is a group intervention. The original protocol was adjusted by giving information about MS-related fatigue (31) instead of relapse in depression, when applicable. For instance, the high prevalence of several factors that can influence fatigue, such as sleep disorders, infections, medication and stress, was mentioned. It was addressed that the focus of the training was on reactions to the fatigue experience, such as anxiety, negative thoughts, and not on reducing fatigue *per se*. Also, the video *Healing from Within* was replaced with mindful movement and yoga exercises, appropriate for severely disabled MS patients, adapted by MS experts, as described in the MBSR protocol (32) and MBCT protocol (14). A summary of the content of the MBCT protocol is given in Table IV. The intervention involves 8 weekly meetings of 2.5 h (20 h in total) spread over a period of 10 weeks, with homework and exercises of up to 1 h, for 6 days a week. Each group was led by 2 certified MBCT trainers with a minimum of 2 years of experience with MBCT and in working with MS patients. All trainers followed at least a MBCT training of 42 h, organized by a Dutch accredited institution (<https://www.mindfulness-training.nl>). A total of 6 trainers participated in the study.

Power calculation

The power calculation was based on a study in which a clinically relevant change of 8 points in the primary outcome variable (CIS-fatigue) was achieved with CBT (33). Based on these data, using an α level of 0.05 and power of 0.8, a minimum sample size of 36 was required.

Statistical analyses

In the data, no variables were significantly skewed (skewness <-1 or >1), nor were there any significant outliers, or extreme values. Classification as cognitively impaired occurred with a z-score of ≤ -2 on 1, or ≤ -1.5 on 2 of the 3 cognitive tests. Descriptive statistics were used to describe the sample, and further analyses were conducted on participants who completed the intervention and all questionnaires. If a questionnaire was missing at T2 or T3, it was imputed with the data of the former measure moment. This was the case for one questionnaire that was missing (at T2). Patients who attended a minimum of 75% of all sessions were defined as completers. Baseline characteristics for patients who completed the intervention and all questionnaires (completers) and patients who dropped out of the intervention (non-completers), were compared by performing χ^2 comparisons for categorical variables and independent *t*-tests for continuous variables. A multivariate analysis of variance (MANOVA) was performed, with time as a within-subjects factor on all outcome measures separately and a pairwise *post-hoc* analysis of variance (ANOVA) to detect in which time period significant changes occurred. Furthermore, patient characteristics were used as within-subjects factors or covariates to detect whether there were significant differences on the outcome measure. Because of the number of outcome variables, alpha was set at 0.01 for statistical significance and *p*-values were Greenhouse-Geiser corrected, where appropriate. Effect sizes were calculated using partial eta-squared values. The partial eta-squared value was considered small when ranging from 0.05 to 0.1, moderate when between 0.1 and 0.2, and large when greater than 0.2 (34).

To determine clinically significant change, the participants who were no longer severely fatigued at follow-up assessment

¹<http://www.medicaljournals.se/jrm/content/?doi=10.2340/16501977-2237>

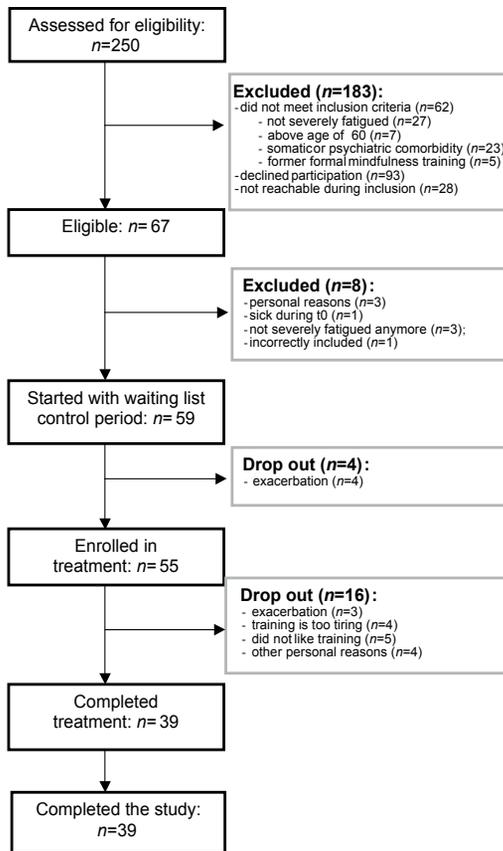


Fig. 1. Flow diagram of study participants.

(T3) (CISS-20-fatigue <35) were identified. Subsequently it was determined which patients showed a clinically significant improvement at follow-up (change of 8 points on CIS-fatigue). The participants who “recovered” or showed a significant improvement were considered clinically significantly improved. Analyses were carried out using SPSS version 19.0 for Windows (SPSS, UK).

RESULTS

Participants

A total of 250 MS patients were screened for eligibility by the researcher (SH) on the basis of their medical records. A total of 67 patients expressed interest and were eligible. Of the 67 patients, 59 were included,

of whom 39 completed the intervention and outcome measurements until T3 (see Fig. 1 for a flow diagram). Data from participants who dropped out of the intervention were excluded from analysis, because analysis was performed only for the completers. There were no statistically significant differences on baseline characteristics between completers and non-completers (see Table I). The mean age of the participants (n=59) was 48.0 (standard deviation; SD=8.5) years and 83% were female. The disease duration varied from 1 to 32 years, with a mean of 11 years (SD=8.2). See Table I for all patient characteristics.

Feasibility

Dropout rate. Sixteen participants (29%) dropped out of the intervention. There were no specific patient characteristics that determined whether the training was completed (see Table I). For 4 participants (7%), extreme fatigue was the reason for drop out. Three participants (5%) dropped out because of an exacerbation of MS. Five participants (8%) did not like the training and 4 dropped out for other personal reasons (7%).

Satisfaction. All participants who completed the study (n=39) completed the evaluation form. The mean mark for the quality of the training was 8.0 out of 10 (SD=0.92); 80% (n=31) would recommend the intervention to another MS patient and 15% were neutral on this subject. Ninety percent of the completers reported improvements in coping with either fatigue, negative emotions or negative thoughts; 75% experienced improvements in coping with 2 of these 3 symptoms. Seventy-six percent thought the intervention was not too tiresome and 80% were satisfied with the length of the intervention sessions. Of the non-completers (n=16) who completed the evaluation form (n=12), 58% would recommend the training to other MS patients and 33% were neutral on the subject. Sixty-seven percent thought the training was of good quality. For 25% of the non-completers, the training was too tiring.

Effectiveness

The means, SDs and 95% confidence interval (95% CI) of the outcome measures at T0 through T3 are shown

Table I. Demographic and clinical characteristics of the sample at inclusion (n=59)

Characteristics	All patients (n=59)	Completers (n=39)	Non-completers (n=20)	p-value
Sex, male/female, %	17/83	18/82	15/85	0.72
Age, years, mean (SD) [range]	48.0 (8.5) [24-60]	48.2 (8.5) [32-60]	47.6 (10.3) [24-60]	0.79
Disease duration, years, mean (SD) [range]	12 [1-32]	11.2 (7.9) [1-32]	12.3 (9.1) [1-32]	0.64
Disease course (RRMS/SPMS), %	73/27	67/33	85/15	0.11
Expanded Disability Status Scale, mean (SD) [range]	3.9 [1-7.5]	3.9 (1.7) [1-7.5]	3.8 (1.7) [1.5-7]	0.87
Education (low/mean/high), %	28/33/39	26/36/38	33/29/38	0.76
Work, Yes/No, %	19/81	21/79	14/86	0.52
Partner, Yes/No, %	77/23	82/18	67/33	0.18
Cognitive disorders, Yes/No, %	20/80	18/82	24/76	0.59

RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; SD: standard deviation.

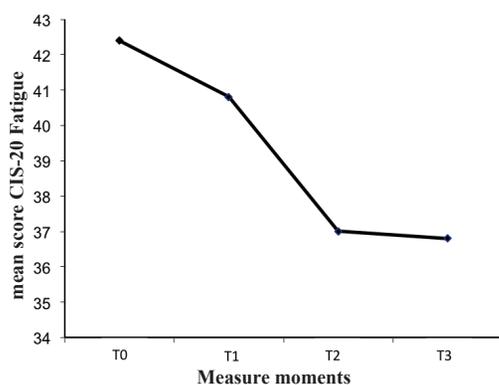
Table II. Effect of mindfulness-based cognitive therapy on primary and secondary outcome measures

Outcome	T0 Mean (SD) [95% CI]	T1 Mean (SD) [95% CI]	T2 Mean (SD) [95% CI]	T3 Mean (SD) [95% CI]	F	df	p-value	η^2
Primary								
CIS-20-Fatigue	42.4 (7.9) [39.8–44.9]	40.8 (8.8) [37.9–43.7]	37.0 (11.7) [33.2–40.8]	36.8 (11.9) [33.0–40.7]	5.9	2.03	0.004*	0.14
Secondary								
HADS-Anxiety	7.3 (3.1) [6.2–8.4]	7.7 (3.1) [6.7–8.7]	6.1 (2.7) [5.2–7.0]	6.4 (3.6) [5.3–7.5]	5.6	3	0.001*	0.13
HADS-Depression	6.3 (3.8) [5.0–7.5]	6.7 (3.5) [5.5–7.8]	5.0 (3.6) [3.8–6.2]	5.1 (3.6) [3.9–6.2]	7.1	3	0.000*	0.16
LISAT-9-life as a whole	4.5 (0.7) [4.2–4.7]	4.2 (0.9) [3.9–4.5]	4.3 (0.9) [4.0–4.6]	4.3 (0.9) [4.1–4.6]	1.5	3	0.220	0.04
SCL-90-sleep	9.1 (3.2) [8.0–10.1]	9.1 (3.0) [8.1–10.1]	8.2 (3.1) [7.2–9.2]	8.0 (3.2) [7.0–9.0]	3.1	3	0.030	0.08
CFQ	74.4 (12.6) [70.6–78.7]	74.4 (13.0) [70.2–78.5]	77.9 (12.6) [73.9–82.0]	77.1 (15.0) [72.3–82.0]	4.3	3	0.006*	0.10
FCS	18.7 (10.1) [15.5–22.2]	20.6 (12.9) [16.4–24.8]	16.6 (12.5) [12.5–20.7]	15.8 (11.4) [12.1–19.5]	4.8	3	0.003*	0.11
CISS-emotion-oriented	40.1 (10.7) [36.6–43.6]	40.4 (10.6) [37.0–43.9]	36.3 (11.4) [32.6–40.0]	35.2 (10.8) [31.7–38.7]	8.2	3	0.000*	0.17
CISS- task-oriented	56.8 (8.7) [53.9–59.6]	54.9 (9.4) [51.9–58.0]	56.1 (10.0) [52.8–59.3]	56.0 (10.3) [52.6–59.3]	0.90	2	0.413	0.02
CISS- avoidant	43.2 (8.7) [40.4–46.0]	43.4 (9.8) [40.2–46.6]	43.8 (10.0) [40.6–47.1]	42.9 (8.8) [40.0–45.8]	0.24	3	0.872	0.01
FFMQ-SF	77.4 (9.3) [74.4–80.4]	78.1 (11.9) [74.2–81.9]	82.4 (12.8) [78.2–86.5]	81.4 (12.2) [77.5–85.4]	5.6	3	0.001*	0.13

* $p < 0.01$

CIS-20-Fatigue: Checklist of Individual Strength-20-subscale fatigue; HADS-Anxiety: Hospital Anxiety and Depression Scale - subscale anxiety; HADS-Depression: Hospital Anxiety and Depression Scale - subscale depression; LISAT-9: Life Satisfaction questionnaire; SCL-90-sleep: Symptom Checklist-90 - subscale sleep; CFQ: Cognitive Failure Questionnaire; FCS: Fatigue Catastrophizing Scale; CISS (emotion): Coping Inventory of Stressful Situations - subscale emotion focused coping; CISS (task oriented): Coping Inventory of Stressful Situations - subscale task focused coping; CISS (avoidance): Coping Inventory of Stressful Situations - subscale avoidant coping; FFMQ-SF: Five Facet Mindfulness Questionnaire - Short Form; T0: baseline; T1: second baseline; T2: post-treatment; T3: follow-up; η^2 0.05–0.1: small; η^2 0.1–0.2: medium; $\eta^2 > 0.2$: large; SD: standard deviation.

in Table II for the 39 participants who completed the training. MANOVA analyses showed significant time effects for CIS-20-fatigue (also shown in Fig. 2) and for all secondary outcomes, except for LiSat-9-life, SCL-90-sleep, and CISS-avoidant and -task-oriented. Effect sizes were moderate for CIS-20-fatigue (partial $\eta^2=0.17$) and for HADS - anxiety and depression, CFQ, FCS, CISS-emotion-oriented and FFMQ-SF (ranging from 0.10 to 0.17). For SCL-90-sleep, the effect size was small (partial $\eta^2=0.08$). One-way repeated-measures ANOVAs showed that there were no significant changes for the outcome measures during the waiting list period. Directly after the training (see T1–T2 in Table III) significant changes were found for HADS-Anxiety, HADS-Depression, CFQ, CISS emotion-oriented and FFMQ-SF ($p \leq 0.01$). Three months after the intervention treatment effects for all these outcome measures were maintained, meaning that no significant decreases in post-treatment effects were found at follow-up (see T2–T3 in Table III).

**Fig. 2.** Effect of mindfulness-based cognitive therapy on fatigue. Data are presented as mean scores of the 4 measurement times.

There were no differences in the effectiveness of CIS-20-fatigue between patients with and without cognitive disorders ($F=1.28$; $p=0.29$). Furthermore, these 2 groups did not differ regarding sex ($F=0.5$; $p=0.61$), age ($F=0.11$; $p=0.90$), type of MS (except for PPMS) ($F=0.47$; $p=0.63$), disease duration ($F=0.45$; $p=0.64$), neurological disability measured by Expanded Disability Status Scale ($F=0.34$; $p=0.71$) and education ($F=0.25$; $p=0.78$).

Clinical relevance. After the intervention, 12 participants (31%) scored under the severely fatigued cut-off score of the CIS-20-fatigue (<35), as opposed to zero participants at inclusion of this study. Furthermore, despite still scoring above the cut-off after the intervention, 6 participants (15%) reached a clinically relevant decline of 8 points on the CIS-20-fatigue. Hence, in total 46% of the group that completed the intervention reached a clinically relevant result.

Table III. Pair-wise comparisons for 3 time intervals

Outcome	T0–T1		T1–T2		T2–T3	
	F value	p-value	F value	p-value	F value	p-value
Primary						
CIS-20-Fatigue	2.1	0.158	7.03	0.012	0.006	0.939
Secondary						
HADS-Anxiety	0.95	0.335	17.2	$<0.001^*$	0.58	0.450
HADS-Depression	0.85	0.362	14.1	0.001*	0.05	0.834
CFQ	0.09	0.766	8.2	0.007*	0.65	0.426
FCS	1.7	0.200	6.5	0.015	0.45	0.505
CISS-emotion oriented	0.05	0.826	9.7	0.004*	0.95	0.336
FFMQ-SF	0.28	0.601	7.3	0.010*	0.655	0.423

* $p < 0.01$.

CIS-20-Fatigue: Checklist of Individual Strength-20 - subscale fatigue; HADS-Anxiety: Hospital Anxiety and Depression Scale - subscale anxiety; HADS-Depression: Hospital Anxiety and Depression Scale - subscale depression; CFQ: Cognitive Failure Questionnaire; FCS: Fatigue Catastrophizing Scale; CISS (emotion): Coping Inventory of Stressful Situations - subscale emotion focused coping; FFMQ-SF: Five Facet Mindfulness Inventory - Short Form. T0: Baseline; T1: second baseline; T2: post-treatment; T3: follow-up.

Table IV. Mindfulness-based cognitive therapy for severely fatigued patients with multiple sclerosis (MS); themes and contents per week

Session	Theme	Contents of each session		
		During session	Homework	Workbook
1	Automatic pilot	Eating with awareness (the raisin exercise), body-scan exercise, breathing exercise.	Eating with awareness, doing a daily activity with awareness and doing the body scan exercise 6 out of 7 days,	Poem "Yesterday was History", information about MS-related fatigue and mindfulness*, case study MS patient*
2	Dealing with barriers	Body-scan exercise, homework review, exercise "thoughts and feelings", pleasant moment-diary.	Doing a daily activity with awareness, breathing exercise 6 out of 7 days, the body scan exercise 6 out of 7 days and noticing thoughts and feelings at pleasant moments using a diary	Tips for the body-scan and other exercises.
3	Mindfulness of the breath	Seeing or hearing exercise, sitting with awareness, homework review, 3-min breathing space, mindful walking and mindfulness yoga (also possible for severe disabled patients), unpleasant moment-diary.	3-min breathing space (3 times a day), alternating sitting with awareness and mindful walking or mindfulness yoga, noticing thoughts and feelings at unpleasant moments using a diary, filling out homework record form.	Instructions and tips for 3-min breathing space and mindful walking/mindfulness yoga.
4	Staying present	Seeing or hearing exercise, sitting with awareness, homework review, 3-min breathing space, making a list of the top 5 of negative cognitions about fatigue, mindful walking and mindfulness yoga (*instead of MBSR-video Healing from Within).	Sitting with awareness 6 out of 7 days, 3-min breathing space (3 times a day regular and coping),	Poem "Wild Geese" (Mary Oliver), education about stress and stress reactions*, instructions and tips for 3-min breathing space coping.
5	Allowing/let it be	"Sitting with awareness" (ending with the story "the king who had three sons", 3-min breathing space (regular and coping), homework review, discussing acceptance.	Sitting with awareness 6 out of 7 days, 3-min breathing space (3 times a day regular and coping),	Poem "The Guest House" (Rumi), education about acceptance.
6	Thoughts are not facts	Sitting with awareness, homework review, introducing mood induction (with exercises to illustrate "thoughts are not facts"; John was on his way to school...), 3-min breathing space.	Sitting with awareness (with and without MP3), 3-min breathing space (3 times a day regular and coping), filling out homework record form.	Tips and education about coping with thoughts, 40,000 thoughts (Gijs Jansen, Denk wat je wilt, doe wat je droomt)*.
7	How can I best take care of myself?	Sitting with awareness, 3-min breathing space, homework review, reflection: energy giving and energy taking activities (what nourishes and depletes me?), action after the 3-min breathing space ("the four doors").	Choose a meditation exercise to do on a daily base, 3-min breathing space (coping), make your own alarm system for relapse signs and an action plan for relapse, preparing evaluation,	Education about "the four doors", poem "A Summer Day" (Mary Oliver).
8	Using what has been learned to cope with fatigue in the future	Body-scan exercise; homework review, including relapse prevention and action plans, evaluation, final meditation.		Tips for integrating mindfulness in daily life, case study MS patient*, poem "Love After Love" (Derek Walcott).*

*not included in the protocol of Segal et al. (14).

DISCUSSION

The main objective of this study was to examine the feasibility and the potential effectiveness of a MBCT group intervention in severely fatigued MS patients. In this study, MBCT was feasible and likely effective on a group level for RRMS and SPMS patients with severe fatigue, and the effect remained stable 3 months post-treatment. For almost half of the group, the beneficial effect on fatigue was clinically significant.

Regarding feasibility, the dropout rate for the intervention was satisfactory (29%) compared with other relevant studies (12) and of those who started the intervention, only 7% of participants dropped out because the intervention was too tiring to attend. Eight percent dropped out because they did not like the training. We have no information about which aspects of the training were not liked; whether it was related to the mindfulness aspects of the training or to being in a psychological training in general, and this is a limitation. Exacerbation of MS was another reason for drop out (5%). Because this was an exclusion criterion, we have not been able to evaluate whether

those participants would have been able to finish the intervention despite the increase in MS-complaints. The other reasons for dropout were personal in nature (7%) and not related to the severe fatigue of the participants. The satisfaction of the participants was very high, even among participants who dropped out and evaluated the training afterwards. The majority of participants (completers and non-completers) did not consider the intervention too tiring. Hence, we can conclude that the group MBCT-training is a feasible intervention for MS patients with severe fatigue.

To the best of our knowledge, this is the first evaluation of MBCT, primary focused on severely fatigued MS patients. Regarding the likely effectiveness, our findings were largely in line with our hypotheses. The overall effect on fatigue was significant, with a moderate effect size. We expected a reduction in fatigue, but nonetheless, it is notable because MBCT aims to help people to adapt their maladaptive automatic feelings, thoughts and behaviours, but is not focused on reducing the fatigue symptoms itself. Even though the MBCT training is rather intensive (2.5 h sessions over 8 con-

secutive weeks and home practice for up to 1 h for 6 days a week), it still allows for reduction in fatigue.

Furthermore, there were reductions in almost all secondary outcomes, including depression and anxiety, cognitive complaints, catastrophizing thoughts about fatigue and emotion-oriented coping. This further emphasizes that this intervention seems to have a broad effect on many symptoms.

There have only been 3 previous studies on the effect of formal protocolled psychological mindfulness-based interventions (MBSR and MBCT) in MS patients (13, 17, 35). The study by Grossman et al. (13) found reductions in fatigue (measured with the modified Fatigue Impact Scale), and the effect was retained after 6 months. In the study by Bogosian et al. (17), a Skype distance-delivered MBCT intervention resulted in lower distress scores in progressive MS patients, but not in improvement in fatigue. However, this intervention was not focused on severely fatigued MS patients, had no mindful movement, and was limited to progressive phenotypes. Therefore, it is possible that the effect was not there because of the different population, or differences in the protocol/delivery of MBCT. In a study by Kolahkaj & Zargar (35), MBSR had a positive effect on depression, anxiety and stress in women with MS, but fatigue was not a measure in this study.

The current study showed a statistically significant decrease in emotional coping after group-based MBCT. There is evidence that emotion-focused coping is related to worse adjustment in MS (36). A possible explanation for the reduction in emotional coping could be that, by being more mindful, the subjective experience of emotional distress may become less threatening (37).

The decrease in emotional coping seems to be in line with the decrease in catastrophizing thoughts about fatigue in this study. There is evidence that catastrophizing allows for attribution of fatigue to the illness, by interpreting the consequences of fatigue in terms of physical damage (15). Also, unhelpful cognitive responses are associated with worse social adjustment (36), but we did not incorporate this. In MBCT the purpose is to detach one's self from the identification with thoughts, rather than suppressing or changing their content (14), potentially leading to a reduction in catastrophic thoughts and emotion-focused coping. Thus, the cognitive elements within MBCT may have been of added value in comparison with other mindfulness-based interventions that place less emphasis on cognitions, such as MBSR (38).

QoL did not improve after the intervention. In a study by Grossman et al. (13), who studied MBSR, QoL did improve. This may be explained by the fact that QoL was measured differently. We only evaluated satisfaction with life as a whole and not other aspects, such as

the physical domains of QoL (39), while Grossman et al. used health-related QoL measures, including an MS-specific measure. Also, our participants scored relatively high at baseline on QoL, making it difficult to improve at all, raising questions about the choice of measure.

We found no differences in the effectiveness on improving fatigue regarding age, sex, type of MS, duration of the disease, neurological disability, and the existence of cognitive disorders. This suggests that MBCT may allow for improvements in a broad range of patients. These results are only exploratory, due to the lack of sufficient power for these outcomes. Future studies could explore this in larger, powered samples.

This study was a controlled and sufficiently powered study and the first to study MBCT exclusively in severely fatigued MS patients. The study also has some limitations. It had a waiting list controlled design. Although we controlled for non-specific factors through the waiting list and the sample size calculation showed we had sufficient power based on our primary outcome measure, replication in a large scale randomized controlled trial is needed. Comparing MBCT with an active control intervention, such as CBT, could help clarify whether our findings are mindfulness specific. Also, we did not perform intention to treat analyses; participants who dropped out did not receive the entire intervention and therefore we did not collect post-treatment and follow-up data. Therefore, we were only able to perform "on treatment analyses". Furthermore, the dropout rate during the whole study was 35%. Comparing the dropout rate with other studies, we found a wide range, from 5% to 43% in mindfulness-based interventions in MS patients (12). A possible explanation for the dropout is that, in our study, patients were approached by the researcher instead of seeking help themselves, which may have created selection bias. This could have negatively affected their motivation or their expectation of the intervention, because it is desirable that mindfulness is actively chosen (40). Furthermore, for psychological interventions in general, and possibly even more for those based on mindfulness, the effect applies for people who are open to the intervention (40). Finally, although our 3-month follow-up results were positive, we do not know what the longer term effects of the intervention are. Future research should therefore assess the impact over a longer follow-up period of up to 1 year.

In conclusion, MBCT is a feasible intervention in people with MS, which leads to improvements, not only in fatigue, but also in a broad range of psychological factors. Feasibility of MBCT is reflected in high compliance rates and satisfaction. The intervention can be applied to various MS patients (RRMS and SPMS) who are willing to participate in a psychological intervention and are motivated to practice mindfulness on

an almost daily basis. Therefore, MBCT seems to be a valuable addition to the existing (non)-pharmacological treatments for fatigue in MS.

ACKNOWLEDGEMENTS

The authors would like to thank all the patients who took part in this study; the therapists, psychological assistants and MS nurses of Zuyderland Medical Centre, location Sittard-Geleen; research assistant Inge Sagis for her assistance and precise method; rehabilitation specialist Roger Haenen for his kind cooperation and time investment and Sebastian Köhler for statistical advice.

The authors declare no conflicts of interest.

REFERENCES

- Compston A, Coles A. Multiple sclerosis. *Lancet* 2008; 372: 1502–1517.
- Marrie RA, Reingold S, Cohen J, Stuve O, Trojano M, Sorenson PS, et al. The incidence and prevalence of psychiatric disorders in multiple sclerosis: a systematic review. *Mult Scler* 2015; 21: 305–317.
- Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol* 2008; 7: 1139–1151.
- Bol Y, Duits AA, Hupperts RMM, Vlaeyen JWS, Verhey FRJ. The psychology of fatigue in patients with multiple sclerosis: a review. *J Psychosom Res* 2009; 66: 3–11.
- Strober LB, Arnett PA. An examination of four models predicting fatigue in multiple sclerosis. *Arch Clin Neuropsychol* 2005; 20: 631–646.
- Lukkahatai N, Saligan LN. Association of catastrophizing and fatigue: a systematic review. *J Psychosom Res* 2013; 74: 100–109.
- Ukueberuwa DM, Arnett PA. Evaluating the role of coping style as a moderator of fatigue and risk for future cognitive impairment in multiple sclerosis. *J Int Neuropsychol Soc* 2014; 20: 751–755.
- Knoop H, van Kessel K, Moss-Morris R. Which cognitions and behaviours mediate the positive effect of cognitive behavioural therapy on fatigue in patients with multiple sclerosis? *Psychol Med* 2012; 42: 205–2013.
- Van Kessel K, Moss-Morris R, Willoughby E, Chalder T, Johnson MH, Robinson EA. Randomized controlled trial of cognitive behavior therapy for multiple sclerosis fatigue. *Psychosom Med* 2008; 70: 205–213.
- Janardhan V, Bakshi R. Quality of life in patients with multiple sclerosis. The impact of fatigue and depression. *J Neurol Sci* 2002; 205: 51–58.
- Ludwig DS, Kabat-Zinn J. Mindfulness in medicine. *JAMA* 2008; 300: 1350–1352.
- Simpson R, Booth J, Lawrence M, Byrne S, Mair F, Mercer S. Mindfulness based interventions in multiple sclerosis – a systematic review. *BMC Neurol* 2014; 14: 15.
- Grossman P, Kappos L, Gensicke H, d'Souza M, Mohr DC, Penner IK, et al. MS quality of life, depression, and fatigue improve after mindfulness training: a randomized trial. *Neurology* 2010; 75: 1141–1149.
- Segal ZV, Williams JMG, Teasdale JD. [Mindfulness-based Cognitive Therapy for Depression: A New Approach to Preventing Relapse.] New York: Guilford Press; 2002 (in Dutch).
- Weijenberg MLM, Stapert SZ, Kohler S, Bol Y. Explaining fatigue in multiple sclerosis: cross-validation of a biopsychosocial model. *J Behav Med* 2016; 39: 371–550.
- Van der Lee ML, Garssen B. Mindfulness-based cognitive therapy reduces chronic cancer-related fatigue: a treatment study. *Psychooncology* 2010; 21: 264–272.
- Bogosian A, Chadwick P, Windgassen S, Norton S, McCrone P, Mosweu I, et al. Distress improves after mindfulness training for progressive MS: a pilot randomised trial. *Mult Scler* 2015; 21: 1184–1194.
- McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001; 50: 121–127.
- Rietberg MB, Van Wegen EE, Kwakkel G. Measuring fatigue in patients with multiple sclerosis: reproducibility, responsiveness and concurrent validity of three Dutch self-report questionnaires. *Disabil Rehabil* 2010; 32: 1870–1876.
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4th edn, text rev.). Washington, DC: American Psychiatric Association; 2000.
- Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. *J Psychosom Res* 2004; 56: 157–170.
- Spinoven PH, Ormel J, Sloekers PPA, Kempen GIJM, Speckens AEM, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychol Med* 1997; 27: 363–370.
- Honarmand K, Feinstein A. Validation of the Hospital Anxiety and Depression Scale for use with multiple sclerosis patients. *Mult Scler* 2009; 15: 1518–1524.
- Visser-Meily A, Post M, Schepers V, Lindeman E. Spouses' quality of life 1 year after stroke: Prediction at the start of clinical rehabilitation. *Cerebrovasc Dis* 2005; 20: 443–448.
- Arrindell WA, Ettema JHM. Manual for the Dutch version of the SCL-90 Lisse: Swets Test Publishers; 1986.
- Ponds R, Van Boxtel M, Jolles J. [De cognitive failures questionnaire.] *Tijdschr Neuropsychol* 2006; 1: 37–42. (in Dutch).
- Crombez G, Vlaeyen JWS. De Pain Catastrophizing Scale. Ongepubliceerde geautoriseerde Nederlandstalige bewerking; 1996.
- Endler NS, Parker JDA. Coping Inventory for Stressful Situations (CISS): Manual. Toronto: Multi-Health Systems, Inc.; 1990.
- Bohlmeijer E, ten Klooster PM, Fledderus M, Veehof MM, Baer R. [Psychometric properties of the five facet mindfulness questionnaire in depressed adults and development of a short form.] *Assessment* 2011; 18: 308–320 (in Dutch).
- Benedict RHB, Fischer JS, Archibald CJ, Arnett PA, Beatty WW, Bobholz J, et al. Minimal neuropsychological assessment of MS patients: a consensus approach. *Clin Neuropsychol* 2002; 16: 381–397.
- Zedlitz A. *Zorgwijzer vermoeidheid. Praktische gids voor mensen met vermoedelijk door niet-aangeboren hersenletsel (NAH).* Den Haag: Hersenstichting Nederland; 2010. (in Dutch).
- Stahl B, Goldstein E, Kabat-Zinn J, Santorelli S. [A mindfulness-based stress reduction workbook.] Oakland: New Harbinger Publications; 2010 (in Dutch).
- Gielissen MF, Verhagen S, Witjes F, Bleijenberg G. Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: a randomized controlled trial. *J Clin Oncol* 2006; 24: 4882–4887.
- Cohen J. *Statistical power analysis for the behavioral sciences.* NY: Academic Press; 1966.
- Kolahkaj B, Zargar F. Effect of mindfulness-based stress reduction on anxiety, depression and stress in women with multiple sclerosis. *Nurs Midwifery Stud* 2015; 4: e29655
- Dennison L, Moss-Morris R, Chalder T. A review of psychological correlates of adjustment in patients with multiple sclerosis. *Clin Psychol Rev* 2009; 29: 141–153.
- Bishop SR, Lau M, Shapiro S, Carlson L, Anderson ND, Carmody J, et al. Mindfulness: a proposed operational definition. *Clin Psychol - Sci Pract* 2004; 11: 230–241.
- Kabat-Zinn J. *Full Catastrophe living (revised edition): using the wisdom of your body and mind to face stress, pain, and illness.* New York: Random House Publishing Group; 2013.
- Lobentanzen IS, Asenbaum S, Vass K, Sauter C, Klösch G, Kolleger H, et al. Factors influencing quality of life in multiple sclerosis patients: disability, depressive mood, fatigue and sleep quality. *Acta Neurol Scand* 2004; 110: 6–13.
- Ledesma D, Kumano H. Mindfulness-based stress reduction and cancer: a meta-analysis. *Psychooncology* 2009; 18: 571–579.