

# Mindfulness-based cognitive therapy reduces chronic cancer-related fatigue: a treatment study

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## Abstract

**Introduction:** About one-third of cancer survivors suffer from severe chronic fatigue. Aim of this study was to evaluate the efficacy of mindfulness-based cognitive group therapy in reducing severe chronic fatigue in cancer survivors with mixed diagnoses.

**Patients and Methods:** Participants ( $n = 100$ ) were randomly selected from a cohort and allocated to an intervention and a waiting list condition. Analyses were based on 59 participants in the intervention condition and 24 in the waiting-list condition. Fatigue severity (Checklist Individual Strength), functional impairment (Sickness Impact Profile) and well being (Health and Disease-Inventory) were assessed before and after the 9-week intervention. The intervention group had a follow-up 6 months following the intervention.

**Results:** At post-treatment measurement the proportion of clinically improved participants was 30%, versus 4% in the waiting list condition ( $\chi^2(1) = 6.71; p = 0.007$ ). The mean fatigue score at post-measurement was significantly lower in the intervention group than in the waiting list group corrected for pre-treatment level of fatigue. The mean well-being score at post-measurement was significantly higher in the intervention group than in the waiting list group corrected for pre-treatment level of well-being. The treatment effect was maintained at 6-month follow-up. No difference between the two conditions was found in functional impairment.

**Discussion:** Mindfulness-based cognitive therapy is an effective treatment for chronic cancer-related fatigue.

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## Introduction

### Chronic cancer-related fatigue

Chronic fatigue is one of the most disturbing long-term consequences of cancer and its treatment [1,2]. It can persist for years after treatment and has a considerable impact on a patient's life through its interference with daily activities [3]. Chronic fatigue after cancer differs from everyday fatigue in terms of prevalence [4], severity and persistence [5]. For approximately one-third of the cancer survivors, fatigue becomes a distressing and activity-limiting chronic condition [1,6–9].

The cause of chronic cancer-related fatigue (CCRF) is unclear. During cancer treatment, level of fatigue is related to the type of surgery and adjuvant therapy, but CCRF is not related to kind of treatment [9–11]. The majority of studies have found no association between post cancer fatigue and time since treatment [7,8,12–22] or time since diagnosis [18,23–28]. Only one study reported an association between time since diagnosis, with more recently diagnosed patients experiencing

more fatigue [29], whereas another study found that more severe fatigue was reported the longer time since treatment [30]. Patients who receive less intensive treatment seem to be less at risk for persistent fatigue [31]. The majority of studies found no association between CCRF and type of cancer [13,15,17,21,23,31,32]. Although CCRF is related to pain, medicine use, distress, anxiety and quality of sleep [33,34], it remains unclear what is cause and what is consequence.

### Development of CCRF

On the basis of qualitative research, Magnusson and colleagues [35] describe the development of CCRF in three stages. The first stage includes the experience of fatigue. The second stage concerns the consequences of suffering from fatigue: social limitations, affected self-esteem and affected quality of life. The third stage includes all efforts undertaken by the patient to cope with the experience and consequences of fatigue, such as walking, lying down, but also trying to accept and adjust on a cognitive level [35]. This last stage seems decisive for

the transition from temporary into CCRF. When coping strategies pertaining to fatigue are maladaptive or lacking, fatigue is more likely to persist long after treatment has ended. People may, for example, try to limit fatigue by actions that were helpful before they got cancer, even after these activities are no longer effective [35]. These maladaptive coping strategies may include thoughts and behaviours that are unintentional or unconscious. For example, a person with an active problem-focused coping style may unconsciously think 'I have to work as hard as I did before I got cancer to be normal', thereby neglecting the fact that his or her physical condition is not yet quite as good.

### Mindfulness

Mindfulness-based cognitive therapy (MBCT) can help patients to become aware of their potentially maladaptive automatic responses (feelings, thoughts and behaviours) and help patients to inhibit this automatic pilot mode. Several mindfulness-based interventions on consequences of cancer such as distress and physical symptoms have been reviewed [36]. Only one trial has investigated the effects of mindfulness on cancer-related fatigue. This trial demonstrated that the mindfulness-based therapy significantly improved fatigue levels. However, this trial did not include a control group. Therefore, it cannot be ruled out that other factors may have influenced the positive effect [37].

The aim of the present study is to evaluate the efficacy of MBCT, a group therapy aimed at diminishing severe fatigue in curatively treated cancer patients and exploring the effect on well-being and functional impairment. Severe fatigue is defined as a score  $\geq 35$  on the severity of fatigue subscale of the Checklist Individual Strength.

### Patients and methods

#### Sample

Between March 2006 and September 2007 severely fatigued curatively treated adult cancer patients were recruited through general practitioners, ads in local newspapers, e-newsletters and websites of patient-organizations of the Dutch Cancer Society.

Participants had to fulfil the following inclusion criteria: they completed their last anti-cancer treatment (all cancer types were accepted) at least 1 year previously; were curatively treated; older than 18 years; scored  $\geq 35$  on the severity of fatigue subscale of the self-report Checklist Individual Strength (CIS); had no other somatic disease or medicine use that could explain or influence their fatigue. The researcher screened all applicants for eligibility to participate by telephone and the fatigue severity was assessed with the CIS, which was sent by mail. In addition, all participants had

to visit a medical doctor to obtain a referral note for this study. In this referral note the medical doctor indicated whether the cancer was curatively treated. The researcher did not have access to the medical files.

Thereafter participants were seen by one of the two therapists, who also gave the MBCT intervention, for an individual intake. During the intake, the therapists assessed psychiatric morbidity to exclude persons at risk for psychosis or severe depression, which were exclusion criteria for the intervention. The therapists further requested participants not to take part in any other therapy directed at fatigue simultaneously with our intervention. The study has passed Ethical Committee Review.

#### Setting

The intervention was given at the Helen Dowling Institute, a centre for psycho-oncological therapy and research in the Netherlands. Patients are referred to our institute by medical doctors and all costs are compensated by health insurance. The centre is easily accessible for all patients with cancer and their partners. The setting is situated apart from medical cancer centres. Participants in this study lived in the region of the institute and most of them had to travel for approximately 10–30 min. Few participants travelled for an hour.

#### Randomisation procedure

After having given informed consent and after the first assessment participants were randomly assigned, 1 week before the start of each group, to either the intervention condition or the waiting list condition. First, the researcher used SPSS syntax to randomly select 12 participants out of all eligible candidates in file at that moment. The number of eligible candidates varied from 14 to 22. This approach ensured that each intervention group would start with 12 participants. The rest of the candidates, who were not selected for the MBCT, were assigned to the waiting-list control group. If there were, for example, 20 eligible candidates, 12 were randomly selected for the intervention and the other 8 were assigned to the waiting-list condition. All participants received a letter from the researcher with information about the group they were assigned to. Patients in the waiting list condition were informed that they could take part in a MBCT group after their post-measurement (9 weeks later). The random selection was performed using SPSS Version 15 for Windows package (SPSS Inc, Chicago, IL). This study included six MBCT groups. Participation was free of charge.

## Intervention

One of the concepts of mindfulness is the assumption that people often function in an automatic pilot-mode, which makes them unaware of their potentially maladaptive coping strategies. The aim of mindfulness-based training is to teach skills that enhance the ability to raise awareness to present experiences [38]. Being aware of their present experience allows people to choose for more helpful coping behaviour. MBCT adds elements of cognitive therapy [39] to the mindfulness-based stress reduction program of Kabat-Zinn [40]. Participants are, for example, encouraged to make a list of automatic negative thoughts they have become aware of. In contrast to Cognitive Behavioural Therapy, MBCT does not emphasize on changing the content or specific meaning of negative automatic thoughts. It simply attempts to teach the participant to use a detached perspective as a skill to prevent the escalation of automatic negative thinking patterns [39]. In the current study, MBCT consisted of a 9-weeks protocolized [41] group therapy, including eight weekly sessions of 2.5 h and one 6 h session, plus one 2.5 h follow-up session 2 months after the ninth session. The total duration of the intervention was 28.5 h.

## MBCT for CCRF

The MBCT under study followed exactly the same order, exercises and text as is described by Segal *et al.* [41], except for the points described below. Exercise and the exploration of experiences with the exercises are essential in MBCT. The feedback was given as described in the book, only where Segal *et al.* relate the experience and interpretation of participants to relapse into depression, our therapists have related their feedback to the maintenance of fatigue. In week 3 an extra exercise in coping with boundaries was added to the protocol. Participants were asked to walk towards one another. Thereafter their experience is explored with the focus on how it feels when someone moves too close and what participants did automatically in reaction to this: did they indicate their boundary to the other person or not? The reader that was handed out to participants did not contain specific information about depression and relapse prevention, it did contain information about the relation between cancer and fatigue, how fatigue can become chronic and how MBCT can help to cope with fatigue. The exact text is available on request. The case described is about a patient with cancer-related fatigue and his automatic pilot mode, and not about a patient with depression. This MBCT did not include the video 'healing from within', nor poems from Mary Oliver, it did contain a story from Portia Nelson and a poem: 'Yesterday is history, tomorrow is a mystery, today is a gift. That's why they call it the present'. MBCT was developed from MBSR, and elements of

cognitive therapy were added. What Segal *et al.* [41] have left out of the MBSR is a long day of 6 h doing exercises in silence. We did include this day in our MBCT program, so our program included eight sessions of 2.5 h and one long session of 6 h. Plus one 2.5 h follow-up session 2 months after the ninth session.

Participants received information and instructions about a particular theme each week (Figure 1) and were encouraged to practice at home for 45 min, 6 days a week. Patients were given compact disks with breathing instruction and awareness exercises to facilitate practice at home.

All groups were led by the same couple of therapists. Both therapists had followed mindfulness-based stress reduction training courses with Kabat Zinn [40], who developed the mindfulness training. One therapist had led MBCT groups with cancer patients 40 times the last 16 years; the first 5 years under supervision of an experienced trainer. The other therapist had led MBCT groups with cancer patients 30 times the last 8 years, initially under supervision of the first therapist.

## Assessment

Fatigue severity, functional impairment and well-being were assessed before and after the 9-week intervention. The intervention group had a follow-up assessment 6 months after the ninth session.

Participants received all questionnaires at home by mail, and returned them by mail. They filled out the first assessment in the week prior to the start of the intervention and the second assessment was completed in the week after the ninth session.

## Primary outcome variable

Fatigue was assessed with the fatigue severity subscale of the CIS [42], which has shown to be a reliable and valid instrument sensitive to change [43]. This subscale consists of eight items, each scored on a 7-point Likert scale (total range 8–56). Based on research with CFS patients and cancer survivors, a score of 35 or higher indicates severe fatigue [44,45]. The questionnaire has been used in cancer survivors [4,31,45,46] and showed good reliability, discriminative validity, and sensitivity to change [43,47,48]. Reliability analyses showed good internal consistency for the CIS in this study (Cronbach's  $\alpha$  for baseline = 0.90; post assessment = 0.91; follow-up = 0.95).

## Secondary outcome variables

Functional impairment was measured with the Sickness Impact Profile [49,50]. The following six subscales were included: home management, mobility, social interaction, walking, work and recreation and pastimes. Respondents are asked to

indicate (yes or no) whether they experience dysfunction in any of these categories (several items per category) as a consequence of their disease. Scores are assigned weights, based on judgments of doctors and patients of the severity of the item for dysfunction [51], and the sum of the weighted scores is divided by the maximum possible score, resulting in the percentage of dysfunction (range 0–100). Reliability analyses showed good internal consistency for the SIP (Cronbach's  $\alpha$  for baseline = 0.81; post assessment = 0.86; follow-up = 0.89).

Well-being was assessed with the well-being scale of the Dutch Health and Disease Inventory questionnaire [52]. The scale consists of 13 items scored on a 6-point Likert scale (total range 13–78). Reliability analyses showed good internal consistency (Cronbach's  $\alpha$  for baseline = 0.82; post assessment = 0.86; follow-up = 0.86).

### Control variables

We checked whether the groups were different with respect to medicine use, sleep quality, anxiety and

depression, since these factors are related to CCRF. Sleep quality was assessed with the Sleep Quality Scale—SQS [53]. The SQS is a self-report questionnaire that comprises 15 statements concerning the quality of sleep of the previous night. A validated cut-off point of 4.0 was used, a score below this norm indicates sleep disturbance [53]. Also, participants using sleep medication were considered to suffer from sleep disturbances. Depression and anxiety were assessed with the Hospital Anxiety Depression Scale (HADS). The HADS is a self-report questionnaire that comprises 14 items measuring feelings of generalized fear and depressive symptoms. The HADS is considered a reliable and valid instrument for assessing depression in medical patients and is sensitive to change [54]. To determine cases of depression at baseline, a cut-off score of 19 for the total scale was used [55].

### Statistical analyses

Analyses were conducted on participants who completed all questionnaires, including participants that dropped out the intervention.

Week 1: Theme: do not strive.

Information about the stress-coping model and the 'automatic pilot mode'. Introduction to 'eating with awareness' and 'body scan'. Homework: 'eating with awareness' and 'body scan'.

Week 2: Theme: do not judge.

Information about how to cope with pain and fatigue during the body-scan exercise and how to handle thoughts during the 'awareness of breathing' exercise. Homework: 'breathing exercise' and the 'body scan' and noticing thoughts and feelings at nice or happy moments.

Week 3: Theme: accepting boundaries.

Recognizing unpleasant experiences. Becoming aware of how one deals with physical and emotional boundaries and cultivating acceptance. Three minute exercise focussing on breathing.

Week 4: Theme: patience.

Recognizing automatic negative cognitions, recognizing daily stress inducing experiences and their emotional impact, promoting free choice how to handle daily stress.

Week 5: Theme: letting go.

Learning how to cope with negative emotions through acceptance. 'Sitting with awareness'.

Homework: 'sitting with awareness', alternated with previous learned exercises.

Week 6: Theme: communication and trust.

Learning how one communicates with others automatically and how it feels to communicate with a different attitude.

Homework: walking and sitting with awareness, alternated with previous learned exercises.

Week 7: Theme: compassion.

Six hours with several awareness and compassion exercises in silence.

Week 8: Theme: seeing from a new perspective.

Explanation how thoughts, behaviour and emotions interact and how one can choose to stop automatic pilot reactions. Making a list of the top ten of negative cognitions.

Homework: make your own program of exercises.

Week 9: Theme: living with awareness.

Participants discuss their own program of exercise and how they will continue the exercises.

Follow up session: Theme: how MBCT has been integrated in daily life.

**Figure 1.** MBCT for CCRF Themes per week

Descriptive statistics were calculated and independent *t*-tests and  $\chi^2$  tests were performed to check for differences between the two conditions at baseline. If a significant difference was found, the baseline score was used as a covariate in further analyses.

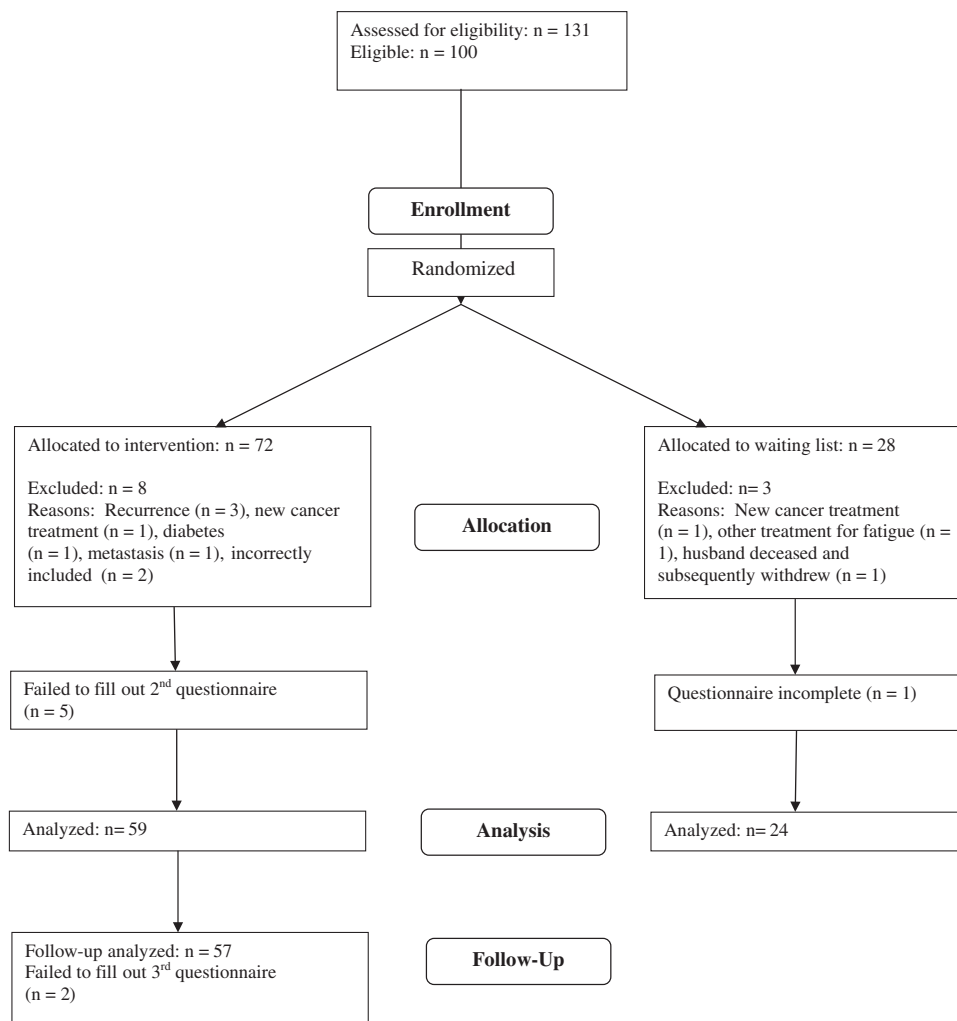
Analysis of co-variance was performed to test whether the outcome variables differed between the intervention group and the waiting list control group, using baseline level as covariate. To assess clinical relevance two criteria were used: (1) the improvement had to be  $>1.96$  according to the reliable change index [56] and (2) the end score had to be within the normal range. This was defined as a score  $<1$  SD above the mean of a normative group [6], i.e. a score  $<30.4$  on CIS fatigue severity was in the normal range. Chi-square tests were used to compare the number of clinically improved patients between the intervention and waiting-list group.

To determine whether improvement reached at post-measurement was maintained at follow-up, baseline and post-measurement were compared with follow-up scores using paired sample *T*-tests. Significance level was set at  $p = 0.05$ . Analyses were

performed using SPSS Version 15 for Windows package (SPSS Inc).

## Results

Figure 2 shows the flow chart of study participants. A hundred patients were randomly allocated to the intervention ( $n = 72$ ) and waiting-list control group ( $n = 28$ ). Eight patients from the intervention group and three from the control group were excluded from the analyses because of recurrence, metastasis, starting a new cancer treatment, or incorrect inclusion. The information that a patient was ineligible because of severe depression, as assessed during the intake, was reported too late by the therapist in two cases. In addition five patients in the intervention group and one patient in the control group did not complete the second assessment, leaving 59 patients in the intervention and 24 in the control group. Five patients discontinued the intervention; four of them did complete the assessment. Since we did not have complete data on all participants we could not do an intention-to-treat analysis in the strict sense, but we did include



**Figure 2.** Flowchart mindfulness-based cognitive therapy

the four participants who dropped out of the intervention, but completed the assessments.

**Table 1.** Baseline characteristics of study participants

	MBCT	Waiting list
	n = 59	n = 24
	Mean (SD)/%	Mean (SD)/%
Age (years) mean (SD)	53.1 (9.1)	49.4 (11.0)
Female	86	78
Marital status		
Married/living together	63	81
Divorced	14	14
Widowed	2	0
Single	22	4
Education level (0 = low to 6 = high)	4.3 (1.6)	3.9 (1.6)
Employment		
Work outside home	22	43
Housekeeper	7	10
Part-time	22	10
In search of employment	2	14
Disability insurance act	35	24
Retirement	12	0
Cancer type <sup>a</sup>		
Breast	63	54
Prostate	5	8
Colon	5	4
Hodgkin	5	12
Cervix	3	4
Ovarian	2	4
Testes	3	0
Other	14	14
Treatment type <sup>a</sup>		
Surgery	95	86
Chemotherapy	50	57
Radiotherapy	66	76
Hormonal therapy	29	48
Medicine use <sup>a</sup>		
Sleep	27	32
Tension	15	21
Pain	40	32
Depression	18	11
Time since treatment (years)	3.0 (2.3)	3.1 (2.4)
Control variable		
Depressive symptoms	16.1 (6.5)	16.0 (7.2)
Sleep quality	8.4 (3.7)	8.9 (4.1)

<sup>a</sup>Percentages do not add up to 100% because more options are possible.

More than half (58%) of the participants were breast cancer patients. Three patients had a history of two types of cancer (breast cancer and Hodgkin Lymphoma in two patients, and vulva cancer and lung cancer in one patient).

At baseline, participants in the two conditions did not significantly differ in demographic, treatment and control variables, or baseline values of the outcome variables ( $p < 0.05$ ) (Table 1). Almost all participants (91%) attended at least seven sessions; the mean number of attended sessions was eight (range 1–9).

About a quarter of all participants (25.8%) scored above the cut-of score of the HADS at baseline. A Chi-square test revealed no differences in percentage of depressive cases between the intervention and the waiting-list control group: ( $p = 0.371$ ). One-third of all participants (30.6%) suffered from sleep disturbances (25% in the waiting-list control group; 32% in the intervention group). A Chi-square test revealed no differences in percentage of cases of sleep disturbance between the intervention and the waiting-list control group ( $p = 0.718$ ).

### Effect of the intervention

The mean fatigue severity score (the subjective feeling of fatigue participants experienced over the last week) at post-measurement was significantly lower in the intervention group (95% CI = 33.2–37.9) than in the waiting list group (95% CI = 40.0–47.4) controlled for pre-treatment level of fatigue (Table 2). The effect size for fatigue is 0.74 ( $d = (\text{mean post intervention} - \text{mean post control}) / \text{pooled SD}$ ).

No difference was found in functional impairment between the two conditions (Table 2). The mean well-being score at post-measurement was significantly higher in the intervention group than in the waiting list group corrected for pre-treatment level of well-being (Table 2). Results of the  $\chi^2$ -test indicated that the proportion of clinically improved participants in the intervention

**Table 2.** Effect of MBCT on fatigue severity, functional impairment and well-being analysed with ANCOVA

	Baseline		Post-measurement		ANCOVA estimated Means Post-measurement <sup>a</sup>		
	Mean	SD	Mean	SD	Mean	95% CI	p
Fatigue severity							
MBCT (N = 59)	47.6	6.6	35.7	11.0	35.6	33.2 to 37.9	0.00
Waiting list (N = 24)	47.2	6.7	43.4	8.7	43.7	40.0 to 47.4	
Functional impairment							
MBCT (N = 58)	16.9	8.9	13.4	8.8	13.2	11.5 to 14.9	0.49
Waiting list (N = 21)	15.5	6.4	13.5	8.1	14.3	11.5 to 17.2	
Well-being							
MBCT (N = 58)	46.4	8.2	51.8	9.5	52.0	50.2 to 53.7	0.00
Waiting list (N = 21)	47.1	11.0	47.3	10.5	46.4	43.6 to 49.3	

<sup>a</sup>Controlled for baseline level.

**Table 3.** Follow up compared with baseline and post-measurement

	Follow up		Difference with baseline		Difference with post-measurement	
	Mean	SD	95% CI	<i>p</i>	95% CI	<i>p</i>
Fatigue severity						
MBCT (N = 57)	34.4	12.7	10.4 to 16.5	0.00	−0.8 to 3.9	0.20
Functional impairment						
MBCT (N = 56)	11.9	12.9	1.4 to 8.4	0.01	−1.5 to 4.8	0.30
Well-being						
MBCT (N = 56)	54.2	9.2	−9.8 to −5.4	0.00	−4.2 to −0.4	0.02

condition (30%) was significantly larger than in the waiting-list condition (4%;  $\chi^2(1) = 6.71$ ;  $p = 0.007$ ).

### Follow up

Six months after the intervention, participants reported significantly less fatigue severity, more well-being and less functional impairment (Table 3) than at baseline. Treatment effects at post-measurement were maintained for fatigue, functional impairment and well-being (Table 3). Well-being at follow up was significantly further improved compared with post-measurement ( $p < 0.02$ ). At follow up 39% of the participants in the intervention group showed clinically relevant improvement in fatigue severity.

### Discussion

The findings of this study showed that MBCT is an acceptable and potentially effective treatment for CCRF. Directly after the 9-week intervention, one-third of patients were no longer suffering from CCRF, compared with 4% in the inactive waiting-list group. Six months after the intervention up to 39% was no longer suffering from CCRF. This follow-up finding could not be compared with a control group, because patients in the waiting-list control group were given the opportunity to follow an intervention after their assessment at 9 weeks. Furthermore, MBCT-enhanced well-being of participants in comparison with the control group. Effect of the intervention on functional impairment was not seen directly after the training, but after 6 months there was improvement in functioning. A decrease in fatigue severity apparently has to occur, some time before one may notice that activities are no longer impaired by chronic fatigue. Although the further improvement of functional impairment at follow-up is reassuring, no comparison could be made with a control group. Future studies need to include a controlled follow-up to learn more about the effect of the intervention on longer-term functioning.

We used an inactive control group and can therefore not control for non-specific factors, such

as therapist attention, social support and positive expectancy, which may also have a positive effect on outcome. The same two therapists led all groups, which limits the generalizability of our findings to other therapists. Another limitation is that we did not assess adherence to the protocol by the therapists. However, there was not much freedom to depart from the protocol, since it was predetermined in a program with themes that participants received each week (Figure 1). Participants made records of their homework exercises in logs that were photocopied each session for research purpose and these logs showed that participants did the exercises in the same order in all groups. We used a special method of randomization, because we wanted to ascertain that each group would start with 12 participants. This procedure led to an unequal number of participants in the two conditions, which is somewhat unfavourable from a statistical viewpoint, but does not undermine any of the conclusions.

Our findings are in line with the conclusion based on two systematic reviews and meta-analyses that psychological interventions have a significant effect on cancer-related fatigue [2,57]. The mean effect size  $d$  in this meta-analysis was 0.10 (95% CI 0.02–0.18). The effect size in this study was large:  $d = 0.74$ . Thus far three types of interventions have proven successful in treating CCRF in an RCT: a home-based activity program [58], cognitive behaviour therapy [59–61], and a combined aerobic and resistance exercise program [62]. Our MBCT outperformed the home-based activity program in terms of effect size (0.74 versus 0.64), was comparable to the group CBT (effect size 0.81) [60] and did less well than the individual CBT (effect size: 1.05) [59].

Differences between CBT and MBCT were that the former was given individually over a period of 6 months, whereas our MBCT was a group therapy given over a period of 9 weeks. The content of CBT and MBCT is similar in the sense that both interventions provide insight into thoughts and behaviour that influence fatigue. The way in which these thoughts and behaviour are handled is different. In CBT participants are asked to actively dispute the content of the thoughts and replace them with more helpful thoughts. In MBCT

participants learn to detach themselves from their thoughts, without actively changing them. The drop-out rate in the intervention group was very low (7%). This low drop out rate suggests that MBCT had been an acceptable intervention for most participants.

This study was carried out in a clinical setting (an institute specialized in psycho-oncology) and the current study sample is considered representative for the future population that will most likely seek help for their CCRF. Our sample was heterogeneous and small, and control of medical confounding variables was very limited. Therefore, results have to be replicated in a larger multi-centre randomized controlled trial with a longer follow-up before firm conclusions can be drawn. It would be interesting to study whether sleep quality and level of mindfulness are mediators of the intervention effect. Future studies have to shed more light on the economic offset of these interventions. CCRF is an increasing problem, since both the incidence as well as the survival of cancer are expected to increase in the next decade. Findings of this study are therefore highly relevant: MBCT is an acceptable and potentially effective treatment for the growing number of people suffering from CCRF.

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