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# Moderators and long-term effectiveness of cognitive behaviour therapy for fatigue during cancer treatment

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## Abstract

***Objective*: A randomised controlled trial (RCT) demonstrated that cognitive behaviour therapy (CBT) for fatigue during curative cancer treatment was effective shortly after cancer treatment. This study aimed to identify which patient characteristics predict fatigue improvement after CBT. In addition, the long-term effectiveness was investigated.**

***Methods*: Patients with various malignancies participated in the RCT ($n = 210$). Participants were assessed before cancer treatment (T1), postintervention (T2), which was at least 2 months after cancer treatment, and after 1-year follow-up (T3). Monthly fatigue assessments were completed between T2 and T3. A regression analysis with interactions was performed to determine if domains of quality of life (EORTC-QLQ-C30) functioning (*Health Survey Short Form-36*) or psychological distress (*Symptom Checklist-90*) moderated the effect of CBT on fatigue. Analyses of covariance were used to study the long-term effectiveness of CBT.**

***Results*: Fatigue at T2 was predicted by a significant interaction between self-reported cognitive functioning and CBT. No interactions were found between other domains of quality of life, functioning, psychological distress and CBT. At T3, no significant difference on fatigue was found between CBT and usual care. Exploratory analyses showed that the difference nearly reached significance until 7 months postintervention.**

***Conclusions*: Patients who experienced more concentration and memory problems at T1 benefited more from CBT for fatigue and are indicators. After a year of follow-up, the effect of CBT for fatigue was no longer observed, and the effect on fatigue seemed to be diminished 7 months postintervention. The implication is that CBT for fatigue should be offered to patients with cancer with the highest chance to benefit.**


**Keywords: cancer; cognitive behaviour therapy; fatigue; oncology; moderator**

## Introduction

Fatigue is one of the most frequently reported symptoms during cancer treatment [1,2]. Unfortunately, not all patients with cancer recover from fatigue after cancer treatment is finished. Many cancer survivors remain severely fatigued for years after finishing cancer treatment with profound effects on daily functioning and quality of life [1-3].

There are strong indications that psychosocial interventions specifically aimed at fatigue during cancer treatment have a high probability of being effective in reducing fatigue [4]. Five (83%) [5–9] of the six interventions [5–10] reported in the literature specifically designed to reduce fatigue were effective. Three (14%) [11–13] of 22 psychosocial interventions with a general approach, aimed at improving psychological distress, mood and physical symptoms, have shown efficacy for fatigue. Most interventions specifically aimed at reducing fatigue were brief, consisting of three individual sessions, provided by (oncology) nurses [5,6,8,9]. One intervention was more intensive. Patients received 12 sessions of cognitive behaviour therapy (CBT) and hypnosis for 6 weeks supported by a therapist [7]. Long-term effectiveness of these interventions was seldom investigated, and none of these studies tested which factors moderated the effectiveness of the interventions.

Recently, we performed a randomised controlled trial (RCT) in which two interventions specifically aimed at fatigue during curative cancer treatment were compared with usual care (UC) [14]. The strength of this RCT was the timing of the assessments, because these took place at clinically relevant moments. First, the baseline assessments (T1) were completed before the start of cancer treatment. This is a clinically relevant moment, because at this stage, fatigue cannot be attributed to oncological treatment. Second, the postintervention assessment (T2) took

place at least 2 months after cancer treatment was finished. A previous study found that the immediate effects of surgery, chemotherapy or radiotherapy on the presence of fatigue disappeared within 6 weeks [15]. T2 was thus chosen at a clinically relevant moment, after a recovery period from the direct effects of cancer treatment.

The interventions evaluated in our recent RCT were a brief nursing intervention (BNI) and CBT for fatigue [14]. The BNI consisted of two 1-h sessions with a nurse and a booklet aimed at increasing and maintaining physical activity. Results showed that compared with UC, the BNI had no effect on fatigue.

The CBT intervention consisted of, on average, six 1-h individual sessions with a cognitive behavioural therapist in about 7 months during cancer treatment. In addition to increasing and maintaining physical activity, the CBT intervention was directed toward changing several dysfunctional cognitions about fatigue, cancer, cancer treatment, the future, and about relations with other people (self-efficacy, catastrophic cognitions, unhelpful attributions and expectations). Methods used included cognitive restructuring, education and behavioural instructions, with homework assignments, and exposure. The intervention focused on six elements. (i) Physical activity: patients received the same information and booklet as provided in the BNI. In addition, dysfunctional activity-related cognitions were challenged. (ii) Fatigue-related cognitions: dysfunctional cognitions were changed to more helpful ones, and excessive focusing on fatigue was minimised. (iii) Sleep–wake rhythm: patients were encouraged to maintain regular bed and wake-up times, and napping during the day was discouraged, taking the phase of cancer treatment into account. (iv) Effects of cancer and treatment: the consequences and side effects of having cancer were discussed (e.g. stoma, amputation), with the aim to help patients to cope and accept them. (v) Cancer and fatigue in contact with others: dysfunctional cognitions were changed, and more helpful coping strategies to use in interacting with others (family, colleagues) concerning having cancer were discussed. (vi) Plans for the future: patients were asked to allow themselves to think about the future and to make future plans; obstacles and fears regarding doing so, and ways to overcome them, were discussed. Results of the RCT showed that at least 2 months after cancer treatment, significantly fewer participants were severely fatigued in the CBT group compared with the UC group [14].

Despite finding that the CBT intervention proved to be effective in reducing fatigue, the results of our study also implied that some participants in the UC group managed fatigue very well without a specific intervention for fatigue. Based on the finding that 65% of the patients in the UC group were not severely fatigued both before the start of cancer treatment (T1) and 2 months after cancer treatment was finished (T2), we conclude that these patients may not need a fatigue intervention. Therefore, it is not unreasonable to assume that about the same percentage of the CBT group could have recovered spontaneously from fatigue and may thus have been overtreated. Therefore, an important question is who would benefit most from our CBT intervention. In other words, what are the indicators for CBT for fatigue during cancer treatment? To answer these questions, it is important to identify factors that moderated the effectiveness of CBT.

Although several RCTs demonstrated the effectiveness of a psychosocial intervention for fatigue during cancer treatment, there is a lack of interaction models of fatigue in controlled intervention studies. Using linear regression analysis, Armes *et al.* [5] identified mood disturbance and comorbid disorders as confounders of fatigue. Cohen and Fried [11] found that treatment with chemotherapy predicted less change in fatigue.

The first aim of this study was to explore which baseline factors moderated the effect of our CBT intervention on fatigue measured 2 months after cancer treatment. Besides baseline characteristics such as age, sex, and type of cancer treatment, we explored whether any of the secondary outcomes of our RCT, such as functional impairments, psychological distress and quality of life before the start of cancer treatment, moderated the effect of CBT on fatigue.

Long-term effects of psychosocial interventions specifically for fatigue during cancer treatment are seldom demonstrated [4]. Of the eight psychosocial intervention studies demonstrating effectiveness for fatigue during cancer treatment, only two RCTs demonstrated long-term effectiveness at 4 and 7 months of follow-up [5,11]. The other six studies had no follow-up assessment at all, or only a short follow-up period of about 4 weeks postintervention. To our knowledge, there is no RCT that examined the effect of a psychosocial intervention for fatigue during cancer treatment beyond 7 months of follow-up. Therefore, the second aim of this study was to determine if the effect of CBT for fatigue during curative cancer treatment would be maintained after a year of follow-up. It was hypothesised that at 1-year follow-up, participants in the CBT group would be significantly less fatigued compared with the UC group.

## Materials and methods

### Patients and procedure

#### Sample

Patients were recruited after being diagnosed with a primary tumour and scheduled to receive treatment with curative intent. Participants had to be between 18 and 75 years old. Exclusion criteria were as



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follows: comorbidity that could cause fatigue; receipt of psychiatric or psychological treatment in the preceding 3 months; and unable to speak, read or write Dutch. Patients were not included in the study if they reported severe fatigue for several years or indicated seeking treatment for pre-existing chronic fatigue. Because this intervention study was aimed at fatigue in patients who would receive treatment with curative intent, patients exhibiting disease progression or recurrence during the study were excluded. To minimise exclusion and dropout during the study, patients with lung or head and neck cancers were not included.

Patients were recruited from the Radboud University Nijmegen Medical Centre and six regional hospitals from November 2005 through August 2007. The ethics committees from all seven hospitals gave their approval for the study. Informed consent was obtained from all participating patients.

#### Design and procedure

Eligible patients who agreed to participate completed the baseline assessment (T1) before the start of cancer treatment and were subsequently randomised to one of the three conditions: BNI, CBT or UC. The procedures for recruitment [16] and randomisation [14] are described in detail elsewhere. The short-term follow-up assessment (T2) took place 6 months after T1 and at least 2 months after cancer treatment was finished. Thus, participants who received surgery, chemotherapy or radiotherapy more than 4 months after T1 were assessed 2 months after these treatments were finished. The long-term follow-up assessment (T3) was completed 1 year after T2. Between T2 and T3, participants were asked to complete the Checklist Individual Strength (CIS) at home each month.

### Instruments

Demographic, medical and cancer treatment characteristics were gathered from all participating patients by self-report questionnaire. Information on the type of malignancy was provided by the patient's physician. The instruments used to assess the secondary outcomes in our RCT were used in this study for the exploratory moderator analyses.

*The CIS* [17,18] consists of four subscales: fatigue severity (eight items), concentration problems (five items), decreased motivation (four items) and decreased activity (three items). Each item on the fatigue severity subscale is scored on a seven-point Likert scale. The CIS was completed at T1, T2 and T3 and 11 times (monthly) between T2 and T3. The CIS is a well-validated instrument [19,20] sensitive to detect change and was used in previous research investigating fatigue in patients with cancer [21–24]. Scores on the fatigue severity subscale of the CIS (CIS-fat) range from 8 to 56. A score of 35 or higher indicates severe fatigue, and a score between 27 and 34 indicates heightened fatigue.

*The Health Survey Short Form-36 (SF-36)* was used to assess functional impairment in different domains with eight multi-item scales: physical functioning, social functioning, role limitations due to physical health problems, role limitations due to emotional problems, bodily pain, vitality, general health perceptions and general mental health. The Dutch language version of the SF-36 has proven to be a practical, reliable, and valid instrument in the general population and in chronic disease populations [25].

*The Quality of Life Questionnaire of the European Organisation for Research and Treatment of Cancer (EORTC-QLQ-C30) version 3.0* contains five functioning scales (physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning), three symptom scales (fatigue, pain, nausea and vomiting) and one scale assessing global quality of life. The EORTC-QLQ-C30 is an internationally validated questionnaire [26,27].

*The Symptom Checklist-90 (SCL-90)* is a 90-item questionnaire consisting of eight subscales: anxiety, agoraphobia, depression, somatisation, obsessive–compulsive behaviour, interpersonal sensitivity, hostility and sleeping problems. The total score on the SCL-90 was used to measure psychological distress. The SCL-90 has good reliability and discriminant validity [28].

### Statistical method

SPSS, version 16.0 (SPSS Inc, Chicago, IL), was used for all data analyses.

One significant difference (marital status) was found between the three study groups at baseline. Marital status was thus used as a covariate in all analyses.

This study was powered to demonstrate effectiveness of interventions at T2 [14] and at T3 but not powered for moderator analyses. Powering for moderator analyses was not possible, because no moderators could be hypothesised beforehand. The moderator analyses were exploratory.

#### Moderator analysis

Two steps were taken to investigate which factors moderated the effect of CBT on fatigue. First, using Pearson correlations, it was tested if fatigue, quality of life, functional impairments and psychological distress in several domains at T1 significantly correlated with fatigue severity at T2. Second, linear regression analysis was performed to test for significant interactions. The method of Aiken and West was chosen to test for interactions [29]. With this method, potential multicolinearity can be greatly reduced by centering variables. Two dummy



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variables representing the intervention variable were entered in the first block. In addition, Z-scores for significantly correlated factors at T1 were entered in the first block. Z-scores of these factors at T1 multiplied by study condition were entered in the second block. Fatigue severity at T2 was the dependent variable.

#### Long-term effect of cognitive behaviour therapy

To examine the long-term effect of CBT, we performed analysis of covariance (ANCOVA) with fatigue severity as the dependent variable. Baseline scores were entered as covariates, and study condition was used as a fixed factor. Contrast analyses were performed to compare the intervention groups (level 2 and 3) against UC (level 1). Intention-to-treat analysis was used. A two-sided $p < 0.05$ was considered significant. To avoid overestimation of intervention effects, we replaced missing data on fatigue by the mean fatigue score of the UC group.

## Results

In total, 395 eligible patients with cancer were approached, and 155 refused to participate. The flow of participants through each stage of the study is illustrated in Figure 1. The recruitment procedure and the flow of participants through the study until T2 are described in more detail elsewhere [16]. After T2, 10 ineligible participants were excluded. When ineligible patients are randomised mistakenly into a trial, their data can be excluded post-randomisation without risking bias [30]. These participants no longer met the eligibility criteria because of, for example, disease progression or cancer recurrence during the study (Figure 1). In total, the number of participants in this study was 210: 69 in the BNI group, 73 in the CBT group and 68 in the UC group. Baseline characteristics are described in Table 1. There were no significant baseline differences between the three study groups except for marital status. More participants in the BNI group were married compared with the UC ($p = 0.008$).

Dropout in this study was low. Two participants did not complete both T2 and T3, and an additional four participants did not complete T3. Thus, 208 participants completed T2 and 204 completed T3.

Not all participants completed the T1 assessment before the start of cancer treatment because of the short time span between the diagnosis and start of treatment. Of the total group ($n = 210$), 27% of the participants were assessed after surgery or start of hormone therapy, but always before beginning adjuvant chemotherapy or radiotherapy. Of the 208 participants, 156 completed T2 6 months after T1. Fifty-two participants, who received cancer treatment for a longer period than 6 months, completed T2 2 months after cancer treatment was finished.

Most participants (88%, $n = 185$) completed all monthly fatigue assessments between T2 and T3 or missed one assessment at most. The median number of monthly assessments completed was 11. Eight percent of the participants ($n = 17$) did not complete any of the monthly fatigue assessments.

### Moderator analysis

Results of the linear regression analysis showed that the interaction between CBT and the EORTC-QLQ-C30 cognitive functioning subscale score was significant (Table 2). Specifically, patients in the CBT group who reported more impaired cognitive functioning at T1 had less fatigue at T2 compared with the UC group. CIS-fat scores ($p = 0.810$), SCL-90 total or subscale score (all $p \geq 0.194$) and SF-36 subscale score (all $p \geq 0.139$) at baseline did not significantly interact with CBT on fatigue at T2.

### Long-term effect of cognitive behaviour therapy

Results of the ANCOVA showed no significant differences between the CBT and UC groups on fatigue at T3 (Table 3). Thus, the effect of CBT on fatigue was not maintained at 1-year follow-up.

Because fatigue was assessed monthly, exploratory analyses were performed to investigate how long the effect of CBT was maintained after T2. Results of these ANCOVA analyses and the differences between the UC group and the CBT intervention are shown in Table 3. At the sixth and seventh month post-T2 assessments, a significant overall effect was found on fatigue. Until the seventh month, the difference between the CBT and the UC groups had a $p$-value smaller than 0.100, indicating a trend. The mean monthly fatigue scores for the CBT and UC groups are also illustrated in Figure 2. This figure demonstrates that throughout the year between the T2 and T3 assessments, fatigue in the CBT group remained lower than the UC group. Although fatigue had roughly a parallel course until the seventh month, after this point, the differences between the CBT and the UC group disappeared. The difference between the BNI and the UC group on fatigue was not significant at T3 or any of the monthly assessments (all $p = 1.000$).

## Discussion

The first aim of this study was to determine who would benefit the most from CBT for fatigue during curative cancer treatment, that is, identify moderating factors. Our results showed that self-reported impairments in cognitive functioning before the start of cancer treatment moderated the effect of CBT on fatigue. Thus, participants who experienced more concentration and memory problems benefited more from CBT for fatigue. No other moderators of CBT including psychological distress, global quality of life, fatigue,



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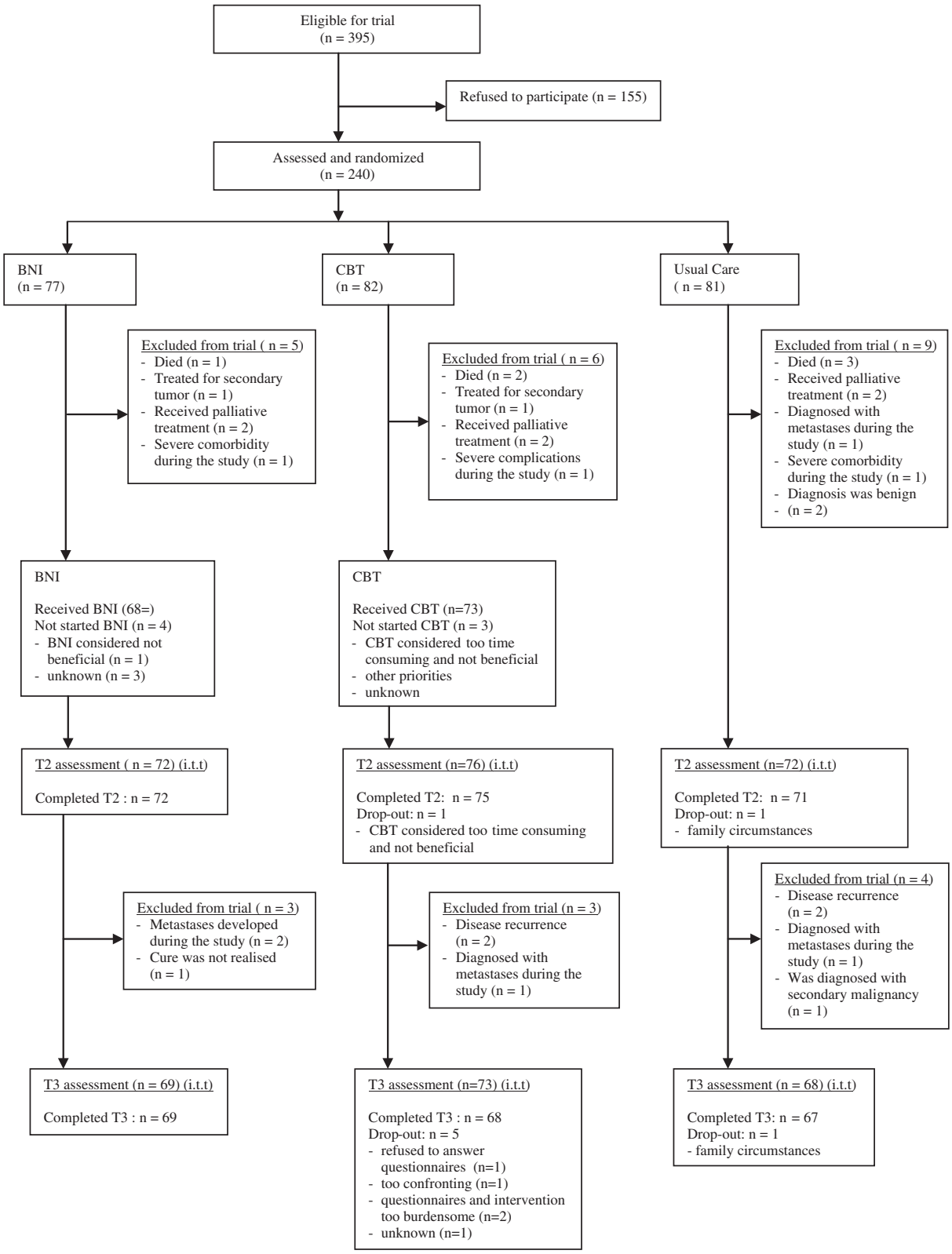


**Figure 1.** Consort diagram. CBT, cognitive behaviour therapy; BNI, brief nursing intervention; i.t.t., intention to treat

pain, nausea and vomiting or status in other domains of functioning could be identified in this study.

This exploratory study was a first step to determine clinical indications for CBT specifically aimed at fatigue during curative cancer treatment. Currently, there are no other studies that determined which factors moderated the effect of a specific intervention for fatigue during cancer treatment. Although some intervention studies identified some factors influencing fatigue, such as receipt of chemotherapy, these factors were not moderators of CBT for fatigue. There could be other moderators for CBT for fatigue that were not found in this exploratory study. Severe fatigue before the start of cancer treatment could be the first indicator for CBT, because fatigue at T1 correlated significantly with



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**Table 1.** Baseline characteristics for the three study groups

| | | Total ($n = 210$) | | BNI ($n = 69$) | | CBT ($n = 73$) | | UC ($n = 68$) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Characteristics** | | *n* | % | *n* | % | *n* | % | *n* | % | *p*-value |
| Sex | Male | 74 | 35 | 26 | 38 | 26 | 36 | 22 | 32 | 0.805 |
| | Female | 136 | 65 | 43 | 62 | 47 | 64 | 46 | 68 | |
| Age (years) | Mean (SD) | 56.5 (10.9) | | 57.2 (10.1) | | 55.6 (11.6) | | 56.9 (11.1) | | 0.629 |
| Education (1 = low to 7 = high) | Mean (SD) | 3.99 (1.71) | | 4.30 (1.87) | | 3.97 (1.61) | | 3.69 (1.61) | | 0.109 |
| Marital status | | | | | | | | | | |
| Married/cohabiting | | 169 | 81 | 62 | 90 | 58 | 80 | 49 | 72 | 0.031 |
| Other status | | 41 | 19 | 7 | 10 | 15 | 20 | 19 | 28 | |
| Diagnosis[a] | | | | | | | | | | |
| Breast cancer | | 102 | 49 | 34 | 49 | 35 | 48 | 33 | 49 | 0.780 |
| Prostate cancer | | 49 | 23 | 19 | 28 | 15 | 21 | 15 | 22 | |
| Other tumours | | 59 | 28 | 16 | 23 | 23 | 31 | 20 | 29 | |
| Gastrointestinal | | 27 | | 7 | | 8 | | 7 | | |
| Urogenital | | 15 | | 2 | | 7 | | 5 | | |
| Gynaecological | | 12 | | 6 | | 3 | | 3 | | |
| Lymphomas | | 6 | | 1 | | 3 | | 2 | | |
| Sarcoma | | 3 | | 0 | | 1 | | 1 | | |
| Melanoma | | 1 | | – | | – | | 1 | | |
| Thyroid carcinoma | | 2 | | – | | 1 | | 1 | | |
| Treatment type[b] | | | | | | | | | | |
| Surgery | | 193 | 94 | 63 | 91 | 70 | 97 | 63 | 93 | 0.311 |
| Chemotherapy | | 62 | 30 | 20 | 29 | 25 | 35 | 17 | 25 | 0.414 |
| Radiotherapy | | 123 | 59 | 40 | 58 | 44 | 60 | 39 | 57 | 0.933 |
| Hormone therapy | | 64 | 31 | 22 | 32 | 20 | 29 | 22 | 32 | 0.871 |

BNI, brief nursing intervention; CBT, cognitive behaviour therapy; UC, usual care; T1, baseline assessment; T3, follow-up assessment.
[a]Two patients were diagnosed with both bladder and prostate cancer and were categorised as other tumours. One was assigned to the control group and the other to CBT.
[b]The total is more than 100%, because several combinations of treatment regimes were given to patients.

**Table 2.** Results of linear regression analyses, with significant moderators for the effect of CBT on fatigue

| Independent variables | *B* | SE | *β* | *p*-value |
|---|---|---|---|---|
| *Step 1* | | | | |
| Constant | 21.99 | 1.02 | | 0.000 |
| Condition CBT | –6.48 | 2.07 | –0.228 | 0.002 |
| Condition BNI | –2.48 | 2.07 | –0.087 | 0.234 |
| Z-score CIS-fat | 5.93 | 0.95 | 0.433 | 0.000 |
| Z-score EORTC-QLQ-C30 CF | –0.41 | 0.94 | –0.030 | 0.666 |
| *Step 2* | | | | |
| Constant | 22.27 | 1.01 | | 0.000 |
| Condition CBT | –6.46 | 2.06 | –0.228 | 0.002 |
| Condition BNI | –2.92 | 2.08 | –0.102 | 0.161 |
| Z-score CIS-fat | 5.53 | 0.952 | 0.404 | 0.000 |
| Z-score EORTC-QLQ-C30 CF | –0.55 | 1.08 | –0.041 | 0.611 |
| Z-score EORTC-QLQ-C30 CF × CBT | 4.77 | 2.20 | 0.175 | 0.031 |

$R^2 = 0.026$ for step 1; $\Delta R^2 = 0.251$ for step 2. A two-sided $p$-value < 0.1 was considered significant.
BNI, brief nursing intervention; CBT, cognitive behaviour therapy; CIS-fat, subscale fatigue severity of the Checklist Individual Strength; EORTC-QLQ-C30 CF, quality of life questionnaire subscale cognitive functioning.

fatigue at T2. Because there is also a group of participants who were severely fatigued at T2 but not at T1, we subsequently compared this group with participants who were not severely fatigued at T1 and T2. Making this comparison with patients for the UC and the BNI groups revealed that poorer general mental health and somatisation before the start of cancer treatment might be indicators for CBT.

In this study, the long-term effect of CBT for fatigue during curative cancer treatment was also investigated. Results showed that after 1-year follow-up (T3), no significant difference was found between the CBT and UC groups on fatigue. This result raised the question of how long the effect of CBT intervention on fatigue was maintained. Subsequently, the monthly fatigue assessments were studied. These analyses demonstrated a trend until



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**Table 3.** Means and standard deviation for fatigue at the monthly and T3 assessments, mean differences between the intervention and usual care groups and *P*-values for the ANCOVAs

| Assessment | Groups | *n* | Mean (SD) | *F* | Overall *P*-value | Mean difference | *p*-value[a] |
|---|---|---|---|---|---|---|---|
| CIS-fat 1 | UC | 62 | 25.0 (14.3) | 2.677 | 0.071 | | |
| | CBT | 64 | 21.6 (12.6) | | | 4.6 | 0.080 |
| CIS-fat 2 | UC | 62 | 25.0 (13.8) | 1.443 | 0.239 | | |
| | CBT | 64 | 22.5 (13.3) | | | 3.7 | 0.274 |
| CIS-fat 3 | UC | 59 | 27.3 (13.0) | 2.441 | 0.090 | | |
| | CBT | 63 | 23.1 (13.4) | | | 4.8 | 0.088 |
| CIS-fat 4 | UC | 61 | 26.4 (13.0) | 2.730 | 0.068 | | |
| | CBT | 63 | 22.3 (13.1) | | | 4.8 | 0.065 |
| CIS-fat 5 | UC | 61 | 25.6 (12.9) | 2.148 | 0.120 | | |
| | CBT | 63 | 22.2 (13.0) | | | 4.1 | 0.162 |
| CIS-fat 6 | UC | 60 | 24.4 (13.1) | 4.627 | 0.011 | | |
| | CBT | 62 | 20.0 (12.8) | | | 5.0 | 0.069 |
| CIS-fat 7 | UC | 60 | 24.0 (12.6) | 4.266 | 0.015 | | |
| | CBT | 62 | 20.1 (13.4) | | | 4.7 | 0.096 |
| CIS-fat 8 | UC | 60 | 23.9 (13.4) | 1.616 | 0.202 | | |
| | CBT | 62 | 21.2 (13.3) | | | 3.4 | 0.378 |
| CIS-fat 9 | UC | 60 | 23.6 (13.2) | 0.456 | 0.635 | | |
| | CBT | 61 | 22.1 (13.7) | | | 2.0 | 1.000 |
| CIS-fat 10 | UC | 60 | 23.7 (13.7) | 0.228 | 0.797 | | |
| | CBT | 61 | 23.3 (14.9) | | | 0.9 | 1.000 |
| CIS-fat 11 | UC | 58 | 23.0 (13.4) | 1.290 | 0.278 | | |
| | CBT | 60 | 20.6 (12.7) | | | 3.1 | 0.476 |
| T3 | UC | 67 | 24.2 (14.7) | 1.273 | 0.282 | | |
| | CBT | 68 | 22.0 (13.5) | | | 3.0 | 0.472 |

CBT, cognitive behaviour therapy; UC, usual care; CIS, Checklist Individual Strength; T1, baseline assessment; T2, follow-up assessment.
[a]*p*-values of contrast analyses. The first *p*-value is the difference between the brief nursing intervention and UC; the second *p*-value is the difference between the CBT and UC. *p*-values <0.100 indicated a trend.

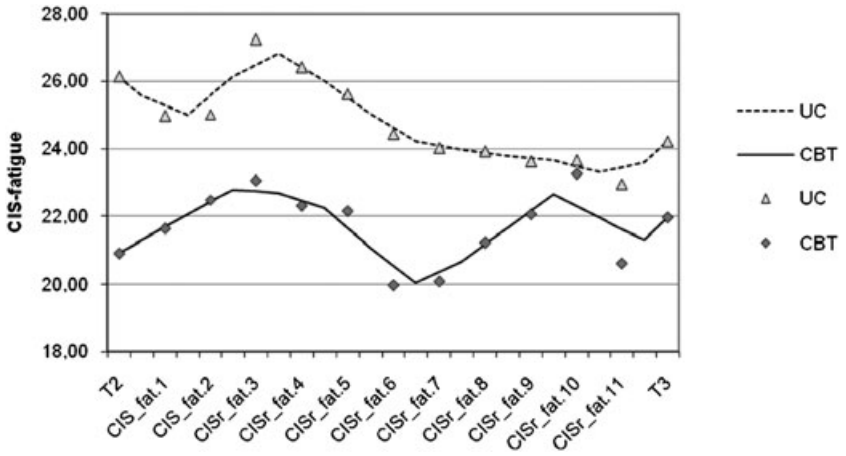


**Figure 2.** Mean monthly fatigue scores from T2 to T3. CIS-fatigue, fatigue severity; UC, usual care; CBT, cognitive behaviour therapy; T2, postintervention assessment; T3, 1-year follow-up assessment

7 months postintervention, but thereafter, the positive effect of CBT on fatigue disappeared totally.

One reason why the effect of CBT for fatigue could not be maintained for longer than 7 months postintervention could be explained by the fact that fatigue may decline naturally after cancer treatment is finished [31]. Second, it was probably more difficult to demonstrate a long-term effect because we overtreated our patients, and this weakened the effects of our intervention. With a larger sample size, the long-term effect of CBT on fatigue might become significant. Clinically, it is probably more important that CBT should be offered to the patients who have the highest chance to benefit from CBT for fatigue. To our knowledge, there is only one intervention RCT that has demonstrated a long-term effect on fatigue at 7 months of follow-up [5]. An important difference between this study and our RCT is that in this study, patients were only included when they reported significant fatigue. These results support our idea that severe fatigue might be a potential indication for CBT.

Our study had some limitations. First, the study was not powered for a moderator analysis or powered to determine how long the effect of the CBT intervention was maintained. In order to power for these types of analyses, many more patients



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would be required to participate. Therefore, concentration and memory problems should not be taken as firm indications for CBT for fatigue, because our analyses could only be exploratory.

Second, it should be noted that cognitive functioning was assessed using a questionnaire, the EORTC-QLQ-C30. The subscale consists of two items in which patients are asked if they experience difficulties with concentrating and remembering. Scores on questionnaires assessing cognitive impairments are often inconsistent with neuropsychological test scores. Furthermore, it has been demonstrated that fatigued breast cancer survivors also have higher self-reported concentration and memory problems [32]. So an interpretation of our finding could be that patients with more concentration and memory problems benefit more from CBT because they are more severely fatigued. The correlation between fatigue and both of these self-reported complaints measured at baseline (T1) was rather high ($r = 0.448$).

Because of the short time span between diagnosis and treatment, 27% of the patients were not treatment naïve at the T1 assessment. However, 73% were treatment naïve, and all patients were assessed before beginning adjuvant cancer treatment. The fact that about a quarter of our sample was not treatment naïve at T1 most likely did not influence our results, because no significant difference was found between cancer treatment naïve patients and patients assessed before adjuvant therapy on fatigue.

Finally, not all participants volunteered to complete the monthly fatigue assessments between T2 and T3. This might raise the question of whether participants who completed the monthly assessments differed in their level of fatigue compared with participants who did not complete the monthly fatigue assessments. However, no significant difference on fatigue was found at T2 and T3 between participants who completed the monthly fatigue assessments and participants who completed none of the monthly assessments.

Despite these limitations, this exploratory study revealed some important insights relevant for future studies and practice. Patients who reported more concentration and memory problems before the start of cancer treatment benefited the most from CBT for fatigue. In the future, it is important to avoid overtreatment with CBT for fatigue. If CBT for fatigue during cancer treatment can be indicated for a specific risk group, the intervention will have a better chance to demonstrate solid long-term effectiveness.

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## References

1. Prue G, Rankin J, Allen J, Gracey J, Cramp F. Cancer-related fatigue: a critical appraisal. *Eur J Cancer* 2006;**42**:846–863.
2. Servaes P, Verhagen C, Bleijenberg G. Fatigue in cancer patients during and after treatment: prevalence, correlates and interventions. *Eur J Cancer* 2002;**38**:27–43.
3. Gielissen MFM. General discussion. What is known about postcancer fatigue? A literature review *Fatigue in Cancer Survivors: From Assessment to Cognitive Behavior Therapy*. Ponsen & Looijen B.V.: Wageningen, 2007; 131–164.
4. Goedendorp MM, Gielissen MF, Verhagen CA, Bleijenberg G. Psychosocial interventions for reducing fatigue during cancer treatment in adults. *Cochrane Database Syst Rev* 2009: CD006953.
5. Armes J, Chalder T, Addington-Hall J, Richardson A, Hotopf M. A randomized controlled trial to evaluate the effectiveness of a brief, behaviorally oriented intervention for cancer-related fatigue. *Cancer* 2007;**110**:1385–1395.
6. Barsevick AM, Dudley W, Beck S, Sweeney C, Whitmer K, Nail L. A randomized clinical trial of energy conservation for patients with cancer-related fatigue. *Cancer* 2004; **100**:1302–1310.
7. Montgomery GH, Kangas M, David D, *et al*. Fatigue during breast cancer radiotherapy: an initial randomized study of cognitive-behavioral therapy plus hypnosis. *Health Psychol* 2009;**28**:317–322.
8. Ream E, Richardson A, Alexander-Dann C. Supportive intervention for fatigue in patients undergoing chemotherapy: a randomized controlled trial. *J Pain Symptom Manage* 2006;**31**:148–161.
9. Yates P, Aranda S, Hargraves M, *et al*. Randomized controlled trial of an educational intervention for managing fatigue in women receiving adjuvant chemotherapy for early-stage breast cancer. *J Clin Oncol* 2005;**23**:6027–6036.
10. Godino C, Jodar L, Duran A, Martinez I, Schiaffino A. Nursing education as an intervention to decrease fatigue perception in oncology patients. *Eur J Oncol Nurs* 2006; **10**:150–155.
11. Cohen M, Fried G. Comparing relaxation training and cognitive-behavioral group therapy for women with breast cancer. *Res Soc Work Prac* 2007;**17**:313–323.
12. Forester B, Kornfeld DS, Fleiss JL. Psychotherapy during radiotherapy: effects on emotional and physical distress. *Am J Psychiatry* 1985;**142**:22–27.
13. Spiegel D, Bloom JR, Yalom I. Group support for patients with metastatic cancer. *Arch Gen Psychiatry* 1981; **38**:527–533.
14. Goedendorp MM, Peters ME, Gielissen MF, *et al*. Is increasing physical activity necessary to diminish fatigue during cancer treatment? Comparing cognitive behavior therapy and a brief nursing intervention with usual care in a multicenter randomized controlled trial. *Oncologist* 2010; **15**:1122–1132.
15. Given CW, Given B, Azzouz F, Kozachik S, Stommel M. Predictors of pain and fatigue in the year following diagnosis among elderly cancer patients. *J Pain Symptom Manage* 2001;**21**:456–466.
16. Goedendorp MM, Gielissen MFM, Verhagen CAH, Peters MEJW, Bleijenberg G. Severe fatigue and related factors in cancer patients before the initiation of treatment. *Br J Cancer* 2008;**99**:1408–1414.
17. Vercoulen JHMM, Alberts M, Bleijenberg G. De checklist individual strength (CIS). *Gedragstherapie* 1999;**32**:131–136.
18. Vercoulen JHMM, Swanink CMA, Fennis JFM, Galama JMD, van der Meer JWM, Bleijenberg G. Dimensional Assessment of Chronic Fatigue Syndrome. *J Psychosom Res* 1994;**38**:383–392.
19. Beurskens AJHM, Bultmann U, Kant I, Vercoulen JHMM, Bleijenberg G, Swaen GMH. Fatigue among working

people: validity of a questionnaire measure. *Occup Environ Med* 2000;**57**:353–357.
20. Dittner AJ, Wessely SC, Brown RG. Fatigue among working people: validity of a questionnaire measure. *J Psychosom Res* 2004;**56**:157–170.
21. Gielissen MFM, 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.
22. Servaes P, van der Werf S, Prins J, Verhagen S, Bleijenberg G. Fatigue in disease-free cancer patients compared with fatigue in patients with Chronic Fatigue Syndrome. *Support Care Cancer* 2001;**9**:11–17.
23. Servaes P, Verhagen S, Schreuder HW, Veth RP, Bleijenberg G. Fatigue after treatment for malignant and benign bone and soft tissue tumors. *J Pain Symptom Manage* 2003;**26**: 1113–1122.
24. Servaes P, Verhagen S, Bleijenberg G. Determinants of chronic fatigue in disease-free breast cancer patients: a cross-sectional study. *Ann Oncol* 2002;**13**:589–598.
25. Aaronson NK, Muller M, Cohen PDA, *et al*. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998;**51**:1055–1068.
26. Aaronson NK, Ahmedzai S, Bergman B, *et al*. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;**85**:365–376.
27. Aaronson NK, Bullinger M, Ahmedzai S. A modular approach to quality-of-life assessment in cancer clinical trials. *Recent Results Cancer Res* 1988;**111**:231–249.
28. Arrindell WA, Ettema JHM. *SCL-90, Handleiding Bij Een Multidimensionele Psychopathologie-Indicator*. Swets & Zeitlinger B.V.: Amsterdam, 1983.
29. Aiken LS, West SG *Multiple Regression: Testing and Interpreting Interactions*. Sage Publications, Inc.: Newbury Park, 1991.
30. Fergusson D, Aaron SD, Guyatt G, Hebert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ* 2002;**325**:652–654.
31. Donovan KA, Small BJ, Andrykowski MA, Munster P, Jacobsen PB. Utility of a cognitive-behavioral model to predict fatigue following breast cancer treatment. *Health Psychol* 2007;**26**:464–472.
32. Servaes P, Verhagen CA, Bleijenberg G. Relations between fatigue, neuropsychological functioning, and physical activity after treatment for breast carcinoma: daily self-report and objective behavior. *Cancer* 2002;**95**:2017–2026.



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