Fatigue in cancer survivors from assessment to cognitive behaviour therapy

Marieke Gielissen

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Chapter 1

General introduction

General introduction

Earlier and more accurate diagnosis and improved observation and treatment have resulted in an increased number of people that has been successfully treated for cancer. In the Netherlands, it is expected that from 2000 to 2015 the number of cancer survivors will increase from 366.000 to 692.000. This means that in fifteen years' time the number of cancer survivors will have almost doubled.[1] Despite the fact that these persons have been cured from cancer, many survivors still face distressing physical, emotional and social consequences as a result of their illness and/or treatment. For these persons cancer must be managed as a chronic disease.

One of the long-term problems cancer survivors face is postcancer fatigue. Fatigue as a side-effect during cancer treatment attracted considerable research attention in the past decennia.[2-4] Fatigue is now recognized as one of the most common and distressing side effects of cancer treatment, occurring among patients undergoing surgery, radiation, chemotherapy and stem cell transplantation. Fatigue persists for months or years after completion of curative treatment in a substantial minority of the cancer survivors.[1-2,5-8] Interest in the problem of postcancer fatigue is growing among clinicians and researchers, and is consistent with a greater awareness of the importance of quality of life as an outcome in oncology.

Postcancer fatigue is a multidimensional concept with several modes of expression. It decreases a patient's ability to perform common daily activities by affecting mood, decreasing concentration and attention, and limiting physical activity. As such, postcancer fatigue has an enormous detrimental effect on quality of life.[1-2,9-10]

Up to now, the nature of the underlying pathophysiology of somatically unexplained postcancer fatigue remains unclear. Hypotheses have been proposed about increased proinflammatory cytokine activity and dysregulation in hypothalamic-pituitary-adrenal axis responsiveness, however, contradictory findings still exist.[3]

Expert Centre Chronic Fatigue

The Expert Centre Chronic Fatigue is a multidisciplinary collaboration of internists, virologists, neurologists, neurophysiologists, neuroscientists, oncologists and psychologist from several departments of the Radboud University Nijmegen Medical Centre. The Expert Centre has focussed on the study of chronic fatigue syndrome since 1990.[11-14] During the years the research extended to chronic fatigue in several other specific patients groups.[12,15-18] Since 1996 research is conducted on the subject of postcancer fatigue.[19] These studies dealt with the natural presence and course of fatigue and made clear that fatigue long after curative treatment for cancer is a severe problem for at least a quarter of the cancer survivors. The relation between postcancer fatigue and initial disease and treatment characteristics was investigated. No associations were found, except that patients who did not have had adjuvant treatment at all, and for whom surgery was without complications, seemed to experience persistent postcancer fatigue less often than other survivors.[8]

Complaints of severe fatigue were associated with considerable limitations in daily life, for instance in the areas of work, household activities, social interactions or recreation and pastime. Results of a longitudinal study with regard to the association between fatigue severity and psychological and physical variables indicated that low self-efficacy, elevated feelings of anxiety, serious limitations in role functioning, low sense of optimism and somatisation were associated with the persistence of the fatigue complaints.[19]

Postcancer fatigue: precipitating and perpetuating factors

Because no relationship has been found between the majority of former disease and treatment characteristics and postcancer fatigue,[2,3,5,8,20-22] we believe it is useful to make a distinction between precipitating factors and perpetuating factors of fatigue after cancer. The assumption is that cancer itself and/or cancer treatment may have triggered fatigue (precipitating factors), but other factors are responsible for persistence of fatigue complaints (perpetuating factors). Based on the literature, own studies[19] and our clinical experience a cognitive behavioural intervention was developed based on factors assumed to play a role in the perpetuation of the fatigue, such as poor or inappropriate coping skills, a heightened fear of a recurrence of the cancer, dysfunctional fatigue-related cognitions, dysregulatory sleep-wake cycles, dysregulatory activity patterns, and insufficient social support and interactions. Cognitive behaviour therapy (CBT) is a general form of psychotherapy directed at changing condition-related cognitions and behaviours. CBT appeared to be effective in conditions such as panic disorder, depression, obsessive-compulsive disorder, irritable bowel syndrome and chronic fatigue syndrome.[14,23-24] CBT is directed at cognitions and behaviours relevant for each specific disorder, which implies that CBT for postcancer fatigue is not the same as CBT for depression, or CBT for chronic fatigue syndrome. An important part of this dissertation is concerned with the evaluation of CBT for postcancer fatigue, such as the treatment protocol, the efficacy and the long term results.

Outline of the dissertation

This dissertation consists of nine chapters. The longitudinal study described in *Chapter 2* investigated the course of fatigue during a two-year period. This chapter reports on whether fatigue is a persistent problem, and whether persistent fatigue is related to former treatment modalities. In addition, predictors of postcancer fatigue were studied.

The results from Chapter 2 and previous studies of the Expert Centre Chronic Fatigue[19] revealed several perpetuating factors of persistent postcancer fatigue. This made it possible to develop a CBT-treatment protocol aimed at these factors. The treatment protocol of this intervention is presented in *Chapter 3*. The protocol encompasses six modules that coincide with the six factors assumed to perpetuate the symptoms of fatigue. The rationale of each module is discussed, followed by the relevant assessment instrument and the proposed course of action. For purposes of illustration, each module ends with a case example.

The efficacy of CBT for fatigue in cancer survivors was investigated in a randomized-controlled trial where the effects of the therapy were compared with a waiting list condition. The results of CBT on fatigue severity, functional impairment and psychological well-being

are reported in *Chapter 4*.
The long term effects were examined in cancer survivors who completed CBT and are described in *Chapter 5*. Furthermore, possible predictors of recovery at follow-up are reported in this chapter.
Servaes et al (2003)[8] found that patients with less intensive treatment were less at risk for persistent fatigue. A stem cell transplantation (SCT) is the opposite; it is a highly aggressive and demanding medical intervention. So, the main objective of *Chapter 6* was to investigate the prevalence of fatigue in this population. In addition, we analysed the relationship between medical variables and postcancer fatigue and if the model of perpetuating factors of postcancer fatigue derived from previous studies in cancer survivors without SCT, was applicable in SCT survivors as well.
To get a better understanding of the nature of (postcancer) fatigue, *Chapter 7* and *Chapter 8* are focussed on the use of novel measurements of fatigue. Studies on (postcancer) fatigue demonstrate the enormous influence of fatigue, like a low quality of life, many impairments in daily life, diminished concentration, depression, anxiety etc. Since fatigue has such a profound effect on many aspects of quality of life, it would also be valuable to know which impact fatigue has in a patients' life, the suffering due to fatigue. In *Chapter 7* we assess in a simple, graphic way the burden of suffering due to fatigue with the Pictorial Representation of Illness Measure (PRISM) in different fatigued patient groups.
Until now studies on (postcancer) fatigue use instruments to measure fatigue in a quantitative way, like fatigue severity. However, patients often describe their fatigue in different ways, with different words. To assess different perceptions of fatigue, we developed an adjective checklist, the Fatigue Quality List (FQL). *Chapter 8* reports about the development and psychometric testing of this instrument.
Finally, *Chapter 9* entails a general discussion, titled: What is known about postcancer fatigue? A literature review. The results of the studies presented in the preceding chapters will be placed into the perspective of the existing literature of postcancer fatigue. Furthermore, directions for future research will be discussed.

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Chapter 2

The course of severe fatigue in disease-free breast cancer patients: a longitudinal study

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ABSTRACT

We investigated whether fatigue is a persistent problem, and whether persistent fatigue is related to former treatment modalities. In addition, we studied the predictors of persistent fatigue.

At baseline (n=150, mean time since cancer treatment = 29 months) patients were asked to fill out several questionnaires on psychological, physical, social, cognitive and behavioral aspects (Ann Oncol 2002; 13: 589-598). During the two years after baseline patients were asked to fill out monthly a fatigue questionnaire (CIS-fatigue). Hundred-twenty-one patients completed the study, 10 dropped out and 19 had a disease recurrence.

Twenty-four percent of the patients experienced persistent severe fatigue complaints during the 2-year observation period. Persistent fatigue seemed to be related to the duration of former treatment but unrelated to type of surgery, type of adjuvant therapy and time since treatment finished. High anxiety, high impairment in role functioning and low sense of control over fatigue symptoms at baseline were predictors of persistent fatigue.

Fatigue appears to be a persistent problem for a quarter of a sample of disease-free breast cancer patients during a 2-year period. The predictors of persistent fatigue found in this study can be helpful for the development of interventions to reduce post-treatment fatigue.

INTRODUCTION

Fatigue is a well-known problem of cancer patients during active treatment. The malignancy itself, the treatment and its side effects like anemia all have impact on fatigue. Many quality of life instruments use the complaint fatigue as an important independent factor to differentiate between more or less harmful interventions or to measure the clinical importance of expensive supportive treatments like additional use of erythropoietin. When the patient has been cured, cancer treatment is stopped and the hemoglobin level has been normalized, it is expected that all complaints subside within a reasonable period of time.

However, based on cross-sectional studies, we may conclude that fatigue is a frequent complaint in former cancer patients even up to ten years after successful treatment for cancer.[1-5] So far, most longitudinal studies that have been published focused on fatigue complaints in cancer patients while they were undergoing active treatment for cancer[6-9] and in the year after completion of treatment.[10-13] Few longitudinal studies have been performed in which fatigue is examined over a longer period of time in cancer survivors.[14-17] In none of these studies the course of fatigue has been investigated.

In a previous cross-sectional study we investigated and discussed the prevalence and correlates of severe fatigue in a group of disease-free breast cancer patients.[18] Results indicated that severe fatigue was a problem for nearly 40 percent of a sample of 150 breast cancer survivors who completed cancer treatment a mean of 29 months earlier, compared to 11% in a matched sample of women without a cancer history. Fatigue was measured with a multidimensional assessment method. Based on previous research in fatigued patients with several chronic diseases, this method has identified nine dimensions, namely fatigue severity, psychological well-being, functional impairment in daily life, sleep disturbance, physical activity, neuropsychological impairment, social functioning/ social support, self-efficacy and causal attributions.[19] These dimensions appeared to be relatively independent, meaning that each dimension uniquely contributed to the description of a patient. A regression analyses on the cross-sectional data indicated that depression, physical inactivity, the need to sleep and rest during the day and the tendency to attribute fatigue symptoms to the breast cancer experience, contributed significantly to the severity of fatigue.[18]

The present longitudinal study focuses on the follow-up of this same cohort of women during a two-year period. During these two years, patients filled out every month a fatigue questionnaire. We will try to answer three questions in a prospective way:

1. Is severe fatigue a persistent problem in disease-free breast cancer patients long after treatment for cancer?
2. Is persistent fatigue related to former treatment modalities?
3. To what extent are psychological well-being, functional impairment, sleep disturbances, physical activity, neuropsychological functioning, social functioning, social support, self-efficacy and causal attributions able to predict persistent fatigue?

Furthermore, we will exploratory describe the course of fatigue for those patients that had a disease recurrence during the two years of our study.

METHODS

Sample

In order to select a relatively homogeneous group of patients for this study, patients had to be premenopausal and younger than 50 years by time of primary diagnosis. All these patients have been treated according to the same protocol, the Comprehensive Cancer Center East for premenopausal breast cancer patients. At the baseline assessment,[18] patients had completed treatment for breast cancer a minimum of 6 months earlier and had no evidence of disease recurrence. During the two years of this study patients went to their own oncologist for medical follow-up. Patients with a disease recurrence during this two-year period were not included in the analyses to answer the three research questions, but were described separately.

Recruitment procedure

Patients were recruited from one university hospital and 6 regional hospitals. All patients who met the eligibility criteria at the university hospital and at three regional hospitals, were initially informed about the study by mail with an introductory letter from their oncologist. At the other three regional hospitals, patients were informed by their oncologist during control-visits. In the following week, patients were contacted by telephone by the psychologist-researcher (P.S.). Those patients who agreed to take part in the study were invited to our department of the Radboud University Nijmegen Medical Center for a baseline measurement.[18] After this baseline assessment, patients filled out a fatigue questionnaire at the end of every month for a two-year period. The ethics committee of all participating hospitals agreed with this study.

Measurement

At the baseline measurement we investigated all nine dimensions by validated questionnaires. Furthermore, patients performed two standardized tests to assess neuropsychological functioning. In addition, they were asked to fill out a daily Self Observation List and to wear an actometer during a period of 12 days at home and to fill out a fatigue questionnaire (Checklist Individual Strength) at the end of every month, during a two-year period.

All measures are mentioned below. For a more extensive description of the measures we refer to the articles in which the baseline data of the present study are described.[18,20]

Fatigue severity has been measured by the fatigue severity subscale (CIS-fatigue) of the Checklist Individual Strength (CIS).[19,21] The CIS-fatigue consists of 8 items and each item is scored on a 7-point Likert scale. A score of 35 or higher on the subscale fatigue severity indicates severe feelings of fatigue.[19] A score between 27 and 35 indicates heightened experience of fatigue.[22] Because patients filled out the CIS at the end of every months during the two years of our study we calculated a mean CIS-fatigue score over 24 months, which we refer to as the ‘persistent fatigue score’. Patients with a persistent fatigue score of 35 or higher are referred to as persistently severely fatigued.

Psychological well-being has been measured with the Beck Depression Inventory for primary care (BDI-pc),[23] the Spielberger Trait Anxiety Inventory (STAI),[24] the Rosenberg Self Esteem Scale (RSE),[25] the Symptom Checklist (SCL-90),[26] and the emotional functioning subscale of the Quality of Life Questionnaire- C30 of the European Organisation for Research and Treatment of Cancer (QLQ- C30).[27]

Functional impairment has been measured with the subscales home management, work, and recreation and pastimes from the Sickness Impact Profile (SIP)[28] and the role functioning subscale of the QLQ- C30. In addition, hours of work (outside the home and household activities) are registered in the Self Observation List.

Sleep disturbances have been measured with the Groninger Sleep Quality Scale (GSQS).[29] In the present study we decided to delete two items because these items strongly overlap with fatigue complaints (GSQS-2; Cronbach's alpha = 0.87). Furthermore, the sleep/rest subscale of the SIP and the sleep subscale of the SCL were used. Finally, quality of sleep is registered daily in the Self Observation List.

Physical activity has been measured with the physical functioning subscale of the QLQ-C30, the mobility and ambulation subscales of the SIP. In addition, physical activity is registered once a day in the Self Observation List. Finally, actual physical activity has been measured with the actometer.[30,31]

Neuropsychological functioning has been measured with the cognitive functioning subscale of the QLQ-C30 and the alertness behavior subscale of the SIP. Furthermore, actual neuropsychological functioning is measured by the Complex Reaction Time task (CRT)[32] and the Symbol Digit subtest of the WAIS.[33]

Social functioning and Social support have been measured with the social functioning subscale of the QLQ-C30, the social interaction subscale of the SIP and the van Sonderen Social Support Inventory (SSL).[34]

Self efficacy has been measured with the Self Efficacy Scale (SES). The SES consisted of five questions that measured sense of control with respect to fatigue.[35,36]

Causal attributions with regard to fatigue complaints have been measured with the Causal Attribution List (CAL). This questionnaire consists of 9 items divided over two subscales, psychological (e.g. ruminate, sleep problems) and breast cancer related attributions (e.g. surgery for breast cancer, adjuvant therapy for breast cancer).

Statistical analysis

Data analysis was performed using SPSS (version 8.0). Paired sample *t*-tests were performed to analyze differences between baseline and follow-up percentages of severe fatigue. *T*-tests, and general linear model (GLM)- general factorial have been performed to test differences between groups. Pearson correlations between the persistent fatigue score and the baseline measures were used as preparatory analyses in order to examine the contribution of the baseline measures to persistent fatigue. Those measures that correlated highest with the persistent fatigue score were used as independent variables in a linear regression analyses (enter-method).

RESULTS

Description of the sample

At baseline, 150 disease-free breast cancer patients participated in this study. Numbers and reasons for non-participation have been described in our previous publication.[18] From these 150 participating patients, 10 patients dropped out for several reasons during the two-year period of this study (e.g. taking part in research takes too much time, family circumstances). Furthermore, 19 women had a disease recurrence during the two-year period. Hundred-twenty-one patients thus completed the study. Compliance with respect to the completion of the monthly fatigue questionnaires was high. Fifty-six percent of the patients (n=68) returned all 24 monthly questionnaires. Twenty-seven percent of the patients (n=33) returned 20 to 23 questionnaires, and 17 percent returned 16 to 19 questionnaires (n=20). There was no difference in the number of monthly questionnaires returned by patients with or without persistent fatigue complaints (respectively an average of 22.0 (s.d.= 3.0) vs 22.3 (s.d.= 3.0), P =0.680)

Information on baseline demographic and medical characteristics of the patients can be found in Table 1. A division has been made between those women who stayed disease-free, those who had a disease recurrence during our study and those who dropped out for other reasons. The only significant difference between the three groups is that the first group is older than the third group.

Research questions

Is severe fatigue a persistent problem in disease-free breast cancer patients long after treatment?

For the total group of disease-free breast cancer patients the mean CIS-fatigue score at baseline was 28.9 (s.d.=13.5), and at follow-up 25.0 (s.d.=13.2) (P <0.001). The correlation between baseline and follow-up CIS-fatigue scores is 0.65 (P <0.01). Both the mean baseline and follow-up CIS-fatigue scores are significantly higher than the mean scores of a matched group of healthy women without a cancer history (CIS-fatigue 19.4 (s.d.= 11.0)).[18] The number of severely fatigued disease-free breast cancer patients was 47 (39%) at baseline. In addition, 21 patients (17%) experienced heightened fatigue. At follow-up, the number of severely fatigued patients was 28 (23%) and 26 patients experienced heightened fatigue (22%).

Table 1

Baseline demographic characteristics and medical characteristics

	Disease-free breast cancer patients N=121		Patients with a tumor relapse N=19		Drop-outs for other reasons N=10	
Mean age	46.7 (SD 5.9)		43.3 (SD 6.2)		41.8 (SD 8.3)	
Marital status						
married	106	88%	16	84%	8	80%
unmarried	4	3%	2	1%	1	10%
divorced	8	7%	1	5%	1	10%
widowed	3	2%	-	-	-	-
Higher education (>= 12 years)	45	37%	8	42%	4	40%
Employment						
paid work outside home	75	62%	10	53%	7	70%
home management	106	88%	15	79%	7	70%
disablement insurance act	15	12%	1	5%	2	20%
Surgery						
mastectomy	78	65%	12	63%	5	50%
lumpectomy	43	35%	7	37%	5	50%
Adjuvant therapy						
no adjuvant therapy	18	15%	1	6%	-	-
only radiotherapy	24	20%	5	26%	2	20%
only chemotherapy	28	23%	4	21%	1	10%
radiotherapy and chemotherapy	51	42%	9	47%	7	70%
Duration of treatment (months)[1]	Mean 6 (SD 3)		Mean 6 (SD 3)		Mean 6 (SD 2)	
< 1 month	16	13%	-	-	2	20%
> 1 month, < 6 months	38	32%	12	63%	5	50%
> 6 months	67	55%	7	37%	3	30%
Time since treatment (months)[2]	Mean 30 (SD 18)		Mean 25 (SD 13)		Mean 26 (SD 18)	
between 6-12 months ago	12	10%	2	11%	1	10%
between 13-24 months ago	44	36%	10	52%	4	40%
between 25-36 months ago	26	22%	3	16%	1	10%
between 37- 48 months ago	17	14%	3	16%	3	30%
between 49-60 months ago	11	9%	-	-	1	10%
more than 60 months ago	11	9%	1	5%	-	-

1. defined as the period from the time of surgery until the end of adjuvant therapy
2. defined as the period from the end of adjuvant therapy until the day of the baseline measurement[1]

The percentage of women who experienced heightened or severe fatigue had thus decreased from 56 to 45 percent (*P* <0.01). In Table 2 we indicated the number (and percentages) of patients that were classified as severely, heightened or not fatigued at follow -up, on basis of their classification as severely, heightened or not fatigued at baseline. Almost half of the patients (49%) that were identified as severely fatigued at baseline were also identified as severely fatigued at follow-up. In addition, 28 percent of these patients was identified as heightened fatigued at follow-up. Furthermore, most patients (85%) that were identified as not fatigued at baseline were also identified as not fatigued at follow-up.

Table 2

Numbers (and percentages) of patients that were classified as severely, heightened or not fatigued at follow-up, on basis of their classification as severely, heightened or not fatigued at baseline

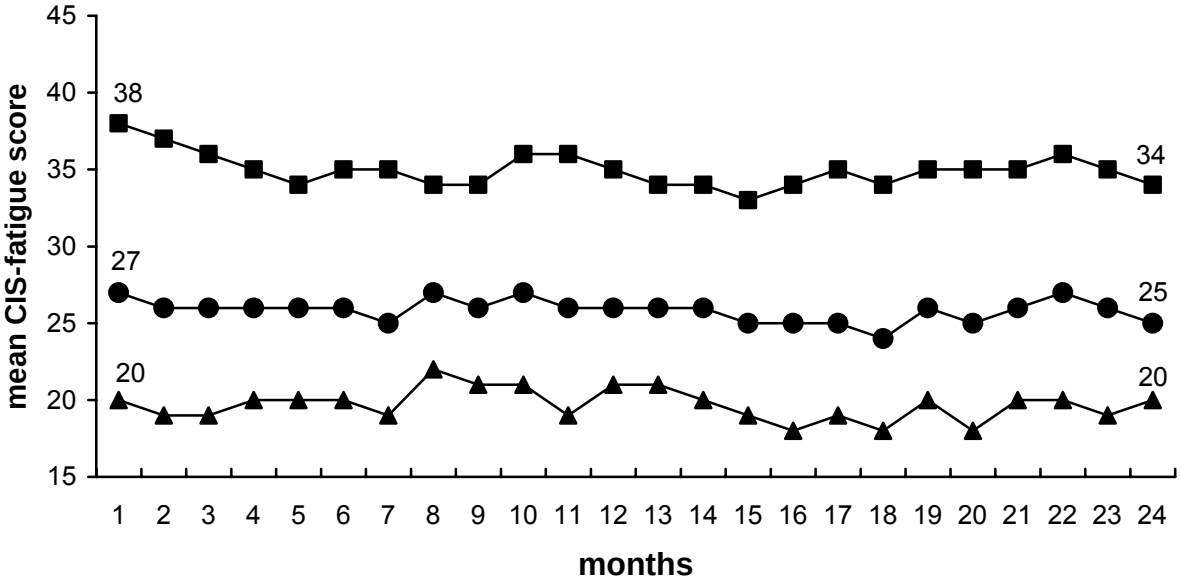
	n	percentage
severe fatigue at baseline (n=47)		
severe fatigue at follow-up	23	49%
heightened fatigue at follow-up	13	28%
no fatigue at follow-up	11	23%
heightened fatigue at baseline (n=21)		
heightened fatigue at follow-up	8	38%
no fatigue at follow-up	11	52%
severe fatigue at follow-up	2	10%
no fatigue at baseline (n=53)		
no fatigue at follow-up	45	85%
heightened fatigue at follow-up	5	9%
severe fatigue at follow-up	3	6%

The monthly CIS-fatigue scores of the total sample are depicted in Figure 1. In addition, the monthly CIS-fatigue scores are displayed for those women who were severely fatigued at baseline, and for those who were not severely fatigued at baseline. Results indicate that the monthly fatigue score dropped a little within a two-year period. For the total group of 121 disease-free breast cancer patients, the monthly fatigue score dropped from 27 at first measurement to 25 at last measurement. This descent is due to the descent of fatigue scores in patients who were severely fatigued at baseline. Their monthly fatigue score dropped from 38 to 34. Monthly fatigue scores of patients who were not severely fatigued at baseline remained equal.

The persistent fatigue score, which is the mean of all monthly fatigue scores, was 25.9 (s.d.= 11.1) for the total sample. Further, the number of patients with a persistent fatigue score of 35 or higher was 29 (24%). In addition, 25 patients (21%) had a persistent fatigue score between 27 and 35.

Figure 1

Mean CIS-fatigue scores over 24 months of the total group (n=121; — ●), patients who were severely fatigued at baseline (n=47; — ■) and patients who were not severely fatigued at baseline (n=74; — ▲)



Is persistent fatigue related to former treatment modalities?

The mean persistent fatigue score did not differ significantly for those patients who underwent mastectomy (24.8 (s.d.=11.6)) and those who underwent lumpectomy (28.1 (s.d.=10.4)) (*P* =0.130).

Also for patients with different types of adjuvant therapy the mean persistent fatigue score was not statistically different, although patients who did not receive any kind of adjuvant therapy at all had a relatively low persistent fatigue score. The mean persistent fatigue score was 28.2 (s.d.=11.4) for patients who received radiotherapy, 24.9 (s.d.=11.4) for patients who received chemotherapy, 27.1 (s.d.=11.1) for patients who received both radiotherapy and chemotherapy, and 21.7 (s.d.=10.5) for patients who did not receive adjuvant therapy (*P* =0.244). Patients that used tamoxifen during a two year period (n=11) had equal fatigue scores to patients that did not use tamoxifen. Their fatigue score were respectively 23.5 (s.d.=11.8) and 26.2 (s.d.=11.2) (*P* =0.436).

Furthermore, there appeared to be a relation between persistent fatigue and the duration of cancer treatment. The mean persistent fatigue score was 19.5 (s.d.=8.7) for patients who finished treatment within one month, 27.0 (s.d.=11.3) for patients who finished treatment within 6 months and 27.0 (s.d.=11.3) for patients who were treated for cancer for more than 6 months (*P* =0.045). Finally, we found no relation between persistent fatigue and time since treatment finished (*P* =0.997).

To what extent are psychological well-being, functional impairment, sleep disturbances, physical activity, neuropsychological functioning, social functioning, social support, self-efficacy and causal attributions able to predict persistent fatigue?

Results of the preparatory analyses indicated that within the different dimensions one or more baseline measures correlated significantly with the persistent fatigue score. In summary (highest correlations are described), women with higher persistent fatigue scores report more psychological distress (Trait anxiety (STAI) r =0.612, P <0.001), functional impairment (Role functioning (QLQ-C30), r = -0.537, P <0.001), sleep disturbances (Sleep (SCL) r =0.438, P <0.001), physical impairment (physical functioning (QLQ-C30) r = -0.477, P <0.001), neuropsychological impairment (Cognitive functioning (QLQ-C30) r = -0.514, P <0.001) and more problems with regard to social functioning and social support (social functioning (QLQ-C30) r = -0.444, P <0.001). Furthermore these women had a lower sense of control (self efficacy (SES) r = -0.489, P <0.001) and stronger psychological attributions with respect to their fatigue complaints (psychological attributions (CAL) r = -0.479, P <0.001).

The regression analyses (Table 3) showed that 51% of the persistent fatigue score was predicted by the baseline CIS-fatigue score. The other selected measures predicted an additional 9%. Apart from a high baseline CIS-fatigue score, high persistent fatigue was also predicted by low self-efficacy. Thus, less perceived control over symptoms predicted higher persistent fatigue. Because the CIS-fatigue score at baseline had the largest contribution to the prediction of the persistent fatigue score, a second regression analysis was performed without the baseline CIS-fatigue score. Fifty-three percent of the persistent fatigue score was

Table 3

Linear regression analyses to predict the persistent fatigue score (range 8-56); with baseline CIS-fatigue score (A) and without baseline CIS-fatigue score (B)

	A		B	
	Beta	**adj R^2**	**Beta**	**adj R^2**
Fatigue (CIS)	.377***	.510		
Trait anxiety (STAI)	.136		.324**	
Role functioning (QLQ-C30)	-.153		-.271**	
Sleep (SCL)	.053		.058	
Physical functioning (QLQ-C30)	-.085		-.140	
Cognitive functioning (QLQ-C30)	-.084		-.063	
Social functioning (QLQ-C30)	.103		.182	
Amount of negative interactions (SSL-N)	.022		-.005	
Self-efficacy (SES)	-.214**		-.303***	
Psychological attributions (CAL)	-.148	.090	-.156	.525
total adj R^2		.600		.525

* p < .05
** p < .01
*** p < .001

predicted by the selected measures. Higher persistent fatigue scores were significantly predicted by lower self-efficacy, more anxiety and more limitations in role functioning at baseline.

Description of the course of fatigue in those women who had a disease recurrence

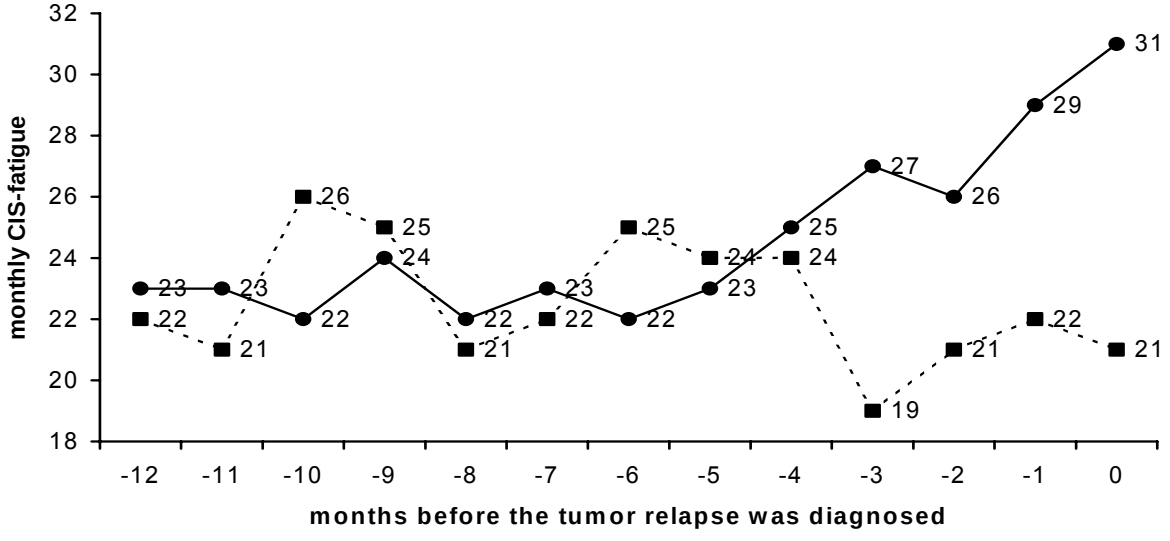
The mean CIS-fatigue score at baseline for those women who had a disease recurrence within the two year period of our study was 23.9 (SD 14.5) at baseline. Further, the number of severely fatigued patients at baseline was five (26%) and one patient (5%) experienced heightened fatigue.

In Figure 2 mean monthly fatigue scores are depicted for the 19 women who had a disease-recurrence during the study period. The CIS-fatigue scores rose from 23 (12 months before the diagnosis of a disease recurrence) to 31 in the month that the disease recurrence was diagnosed. Within the group of disease-free breast cancer patients who did not have a disease recurrence a matched 'control group' was constituted (n=19). The group with and without disease recurrence were matched on the baseline CIS-fatigue score. In addition, the two groups were comparable with respect to type of surgery, age, adjuvant therapy, duration of treatment and time since treatment. In figure 2 the mean monthly fatigue scores are depicted for this matched group. There was no clear rise of the monthly CIS-fatigue scores in this control group of persistent disease-free women. Their monthly CIS-fatigue score varied from 19 to 26.

Figure 2

Mean monthly fatigue scores for women who developed a tumor relapse (n=19; — ●) in the 12 months before the tumor relapse was diagnosed compared to a matched control group (n=19; - - - ■)

Tumor relapse: n=19 at time 0; n=16 at time –3; n=14 at time –6; n=11 at time –9; n=10 at time -12



DISCUSSION

The unique quality of this study lies in the fact that we studied fatigue in disease-free breast cancer patients during a longer period of time. Because of that we were able to take a closer look at the course of fatigue complaints and we were able to identify those patients that experienced persistent fatigue complaints.

Based on the monthly fatigue scores we concluded that severe fatigue is a persistent problem for 24% of a group of disease-free breast cancer patients. This is a decrease with respect to the baseline assessment, at which 38% of the disease-free breast cancer patients experienced severe fatigue 2.5 years after curative treatment ended.[18] Bower et al.[17] also found a decrease of patients with severe fatigue in a longitudinal study, namely from 35% (3.5 years after treatment) to 21% (6.3 years after treatment). In one of our previous publications a sample of patients with bone or soft tissue tumour were also assessed two times in a period of two years. In this sample of patients who finished cancer treatment with an average of 6 years ago (range 1 to 15 years), the percentage of severe fatigue remained about equal, namely 28% to 26%.[16] Hjermstad et al.[14] investigated disease-free cancer patients 16 years and 24 years after treatment for cancer. In this longitudinal study the percentage of fatigued cancer survivors also remained about equal, that is 25% to 28%. These results seem to suggest that fatigue complaints continue to decrease during the first 3 – 4 years after curative treatment. For about a quarter of the cancer survivors fatigue remains a continuous problem with profound effects on functional status, like role functioning, work, home management and recreation and pastimes.

The duration of severe fatigue was determined prospectively by calculating the mean CIS-fatigue score over the 24 months that patients filled out the fatigue questionnaire. Patients with a fatigue score of 35 or higher were referred to as ‘persistently severely fatigued’. We realize that this technique has some shortcomings, for example, a few months of very high fatigue might place a person in the ‘persistently severely fatigued’ category even if most of her monthly scores fell below the cut point of 35. Because of this shortcoming we additionally calculated the persistent fatigue score according to another approach. We calculated the percentage of times that scores fell above the cut-point of 35. However, this technique has some shortcomings as well. For example, a person that has many fatigue scores just under 35, will not be labeled as persistently fatigued, while this is probably untrue. In spite of the shortcomings of both techniques it is reassuring to know that the Pearson correlation between these differently obtained persistent fatigue scores turned out to be very high; 0.90 (P <0.000).

Most studies find no strong association between cancer treatments and fatigue in long-term cancer survivors.[5,37] However in the current study we found that patients who did not receive any kind of adjuvant therapy and who did not experience any kind of complications during treatment, i.e. those patients that completed treatment for cancer within one month, were at lower risk for persistent fatigue. A possible explanation for the low persistent fatigue scores in patients whose treatment duration was short may be due to the fact that they had not been subjected to the harmful effects of adjuvant therapy and/or multiple operations (and anesthetics) because of complications. In addition, for this group of patients the period of

great uncertainty had been limited and they had been spared many hours of traveling to and from the hospital, which can cause exhaustion as well. Some other studies also found evidence for the assumption that patients with more aggressive treatments are more at risk for persistent fatigue.[16,17,38]

Breast cancer patients often become menopausal as a result of chemotherapy. Menopausal symptoms seem to be both more prevalent and more severe in cancer survivors than in healthy women,[39,40] and can therefore be of influence on the persistent of fatigue. In a subgroup of 80 patients we measured with the self-observation list the intensity of hot flashes four times a day during a 12-day period. Patients with severe fatigue had a higher score than non-fatigued patients. This difference approached significance ($P < 0.071$).

Some studies suggest an association between fatigue and adjuvant hormonal therapy.[39,40] Patients in our study were treated for cancer according to the guidelines of that time and therefore only a minority of the breast cancer patients (n=11) was treated with tamoxifen. In this small group no differences in fatigue were found between patients with or without tamoxifen.

Due to the recruitment procedure it is possible that a selection bias exists in this study. In our previous publication about this cohort of breast cancer survivors, we looked at differences between responders and nonresponders with respect to background variables.[18] Reasons for non-participations were e.g. takes too much time, too emotional, problems with transport, too tired etc. Nonresponders (41%) did not differ from the responders with regard to age, type of surgery, radiotherapy and time since treatment completion. Nonresponders received chemotherapy less often: 41% compared with 66% (χ^2 tests; P <0.001). Therefore, duration of treatment was significantly lower for nonresponders (4 compared with 6 months for responders; P <0.001). Because of these differences it is possible that the responders experience more fatigue and the percentage of fatigue in breast cancer survivors might be worse than in reality. However, the percentages found in our studies were similar to percentages in other longitudinal and cross-sectional studies on fatigue in disease-free cancer patients.[14,16,17,41,42]

With respect to the relation between severe fatigue and disease recurrence it is important to note that at baseline severe fatigue was found both in patients who had a disease recurrence and in patients who remained disease-free. In our study the mean CIS-fatigue score and the percentage of severely fatigued patients at baseline were even lower in the group of patients who had a disease recurrence than in the patients that remained disease-free. In clinical practice severe fatigue complaints can thus not be interpreted as an indicator of a possible disease recurrence. However, there seems to be a rise of the fatigue score in the months preceding the diagnosis of the disease recurrence. Nevertheless, we should be careful in interpreting this finding because the group of women who had a disease recurrence is small.

In understanding off-treatment fatigue in disease-free cancer patients it is important to make a distinction between initiating factors and perpetuating factors of fatigue. This model appeared to be useful in patients with chronic fatigue syndrome (CFS),[35,36] but can be applied in fatigued cancer survivors too. We know that fatigue arises during the active treatment of cancer in nearly all patients. For about a quarter of the cancer survivors

persistent fatigue becomes an invalidating long lasting side effect of the cancer treatment.[5,14,17,37,42] Because almost no relations were found between initial disease- and treatment variables and off-treatment fatigue,[5,37] other factors seem to be responsible for the persistence of fatigue complaints.

In this study persistent fatigue was very well predicted by the questionnaires that we used to measure psychological well-being, functional impairment, sleep disturbances, physical activity, neuropsychological functioning, social functioning, social support, self-efficacy and causal attributions. With use of several selected baseline measures, the percentage of explained variance was 60 percent. Based on the results of the current study we might expect that low sense of control, anxiety and impairment might be important perpetuating factors.

In managing fatigue in cancer survivors exercise has been proposed in the literature as a useful strategy.[43-45] However, to our knowledge there have been no published randomised controlled intervention studies in which the main object was to reduce fatigue complaints in cancer survivors. For CFS patients, cognitive behavior therapy (CBT) has proven to be successful in reducing fatigue complaints.[36,46,47] CBT may also be a useful intervention in reducing postcancer fatigue. Servaes et al.[1,48] made clear that the perpetuating factors in former cancer patients differ from factors in the CFS model and interindividual differences are larger in fatigued cancer survivors than in CFS patients. Therefore, CBT for postcancer fatigue should be adapted to each individual cancer survivor and directed, among others, at the predictors of persistent fatigue found in this follow-up study.

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Chapter 3

Cognitive behaviour therapy for post-cancer fatigue: a treatment protocol

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Cognitieve gedragstherapie voor vermoeidheid na kanker: een behandelprotocol. TSG, tijdschrift voor gezondheidswetenschappen 2004; 6: 364-370

ABSTRACT

Fatigue during cancer treatment is a common complaint in cancer patients being treated with curative intent. Physically unexplained fatigue long after cessation of the clinical treatment (1 year or more) has only recently received attention. Research has shown that this postcancer fatigue tends to become chronic in an estimated 25% of all cancer survivors, with serious, associated implications for their daily lives. Clinicians generally have little to offer in terms of a remedy, especially due to the lack of somatic leads. Research conducted by our own institute and the literature have identified several factors assumed to play a role in the perpetuation of the fatigue, such as poor or inappropriate coping skills, a heightened fear of a recurrence of the cancer, dysfunctional fatigue-related cognitions, dysregulatory sleep-wake cycles, dysregulatory activity patterns, and insufficient social support and interactions. Cognitive behaviour therapy (CBT) targeting these so-called perpetuating factors has been found to reduce the symptoms of fatigue. In this report we present the treatment protocol for CBT specifically designed for the treatment of persistent postcancer fatigue.

INTRODUCTION

During their clinical treatment many cancer patients mention complaints of fatigue, with proportions of as high as 99% having been reported.[1, 2] In an estimated 25% of all cancer survivors the fatigue symptoms are sustained long (at least one year) after treatment completion and have become chronic without any apparent somatic causes.[3-7] Research has shown that this persistent, postcancer fatigue has serious consequences for the daily lives of these former cancer patients.[1-2]

For a proper understanding of chronic fatigue following successful curative cancer treatment we need to make a distinction between precipitating or initiating factors on the one hand and perpetuating factors on the other. Such a distinction has earlier been shown indispensable in studies into chronic fatigue syndrome (CFS).[8] That disease and treatment characteristics have been demonstrated to be unrelated to the severity of the postcancer fatigue argues in favour of making a similar distinction in this population.[1-3,5,9-11] In other words, the proposed precipitating factors for fatigue occurring during cancer treatment, i.e. the disease itself and its treatment, do no longer explain the persistent post-treatment fatigue. Although it is plausible to assume that the fatigue was originally educed by the treatment, over time other factors must have come into play causing the symptoms to be maintained.

Research and clinical experience have since shed more light on these perpetuating factors in cancer survivors. Thus, if a patient copes poorly with the diagnosis of cancer and the subsequent clinical treatment, the fatigue is likely to be sustained, as can happen when the disease-free patient suffers from a pervasive fear of a recurrence of the cancer.[5,10] Furthermore, all kinds of aggravating rather than alleviating fatigue-related thoughts and perceptions, henceforth referred to as cognitions, may be implicated, an example of which is catastrophising, which exacerbates existing symptoms.[12] A patient's deviant sleep-wake cycle may also affect the complaints and over- as well as inactivity – both often observed in former cancer patients – tend to worsen the fatigue.[1-2,10] Finally, cancer survivors often report the sensation of not being understood by their social environment, which feeling can additionally intensify their fatigue.[13]

It is the rationale of a cognitive behaviour therapy (CBT) specifically designed for the treatment of CFS that an intervention that addresses a patient's perpetuating factors will help reduce fatigue levels. The CBT approach has indeed been successfully applied in various CFS populations.[14-17] A comparison of the defining characteristics of chronically fatigued cancer survivors and patients diagnosed with CFS has enabled us to identify which aspects of the CFS treatment programme warranted modification before it could be applied in cancer survivors. A major, a priori distinguishing feature is that in postcancer fatigue there is a clear and for each patient similar time of onset, viz. in the course of the oncological treatment, which seems to point to the presence of a similar, precipitating factor. In CFS the point of onset is not always clear and, if known, tends to vary per patient. The fatigue-related attributions of the two patient groups are hence already quite dissimilar. Another essential difference is the greater variation in the dimensions of the fatigue in disease-free cancer patients.[19] The degree of physical activity among cancer survivors, for instance, tends to vary widely, whereas the activity levels in CFS patients are less heterogeneous. Also, relative to

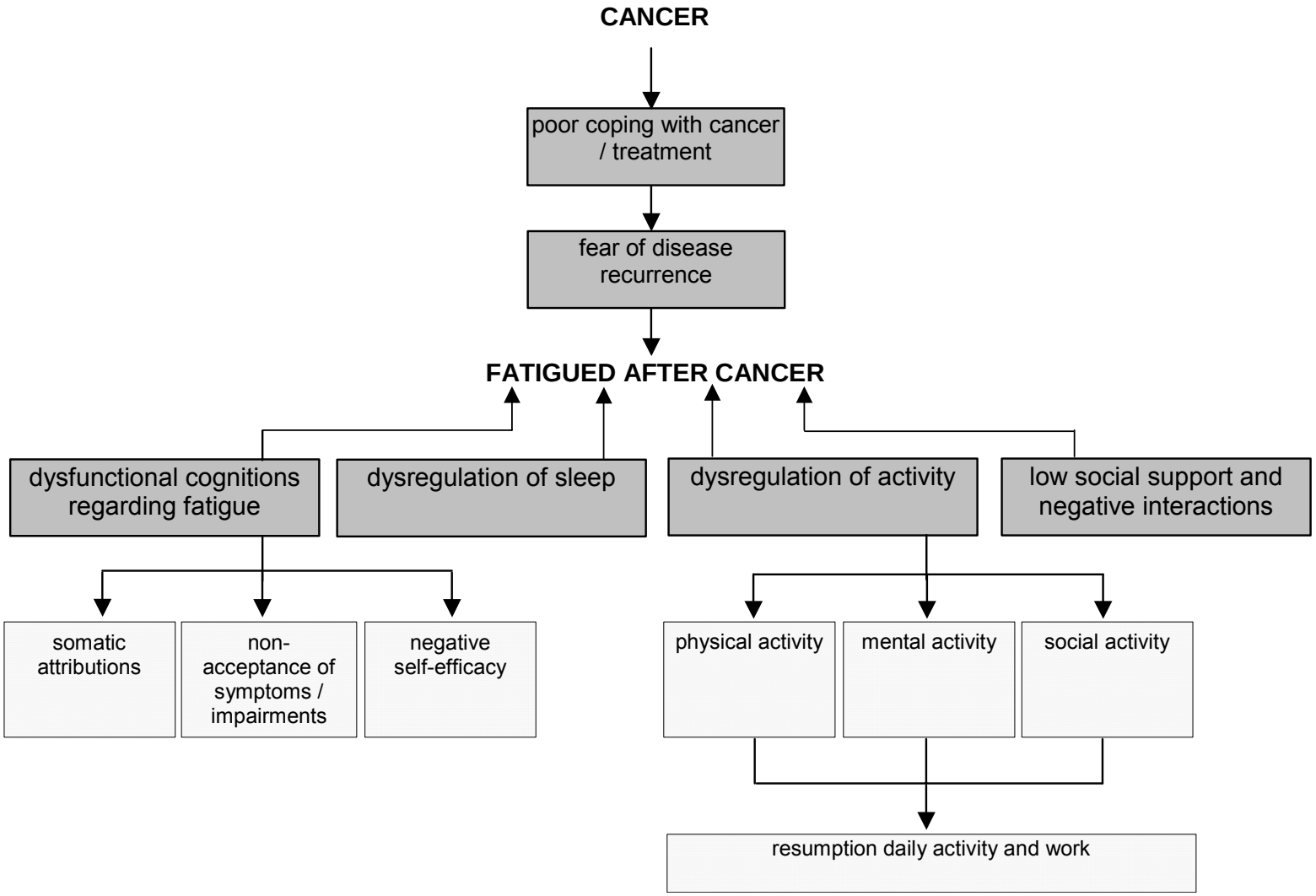
cancer survivors, CFS patients have been found to have higher fatigue scores, to experience more limitations in their daily functioning, to be less physically active, to report more intense pain and have a lower sense of control over their fatigue complaints.
On the strength of mentioned differences we concluded that a psychotherapeutic programme aimed at chronically fatigued, disease-free cancer patients clearly needed to differ on essential aspects and had to be far more tailored than CBT programmes targeting patients with CFS. The efficacy of such a newly-designed, individualised CBT approach for fatigued cancer survivors has recently been demonstrated in a randomised controlled trial (RCT).[20] The current report provides the protocol for the treatment. We will subsequently place the CBT into its proper perspective and conclude with directions for future research.

Patient-specific CBT for persistent postcancer fatigue

The treatment protocol encompasses six modules that coincide with the six factors assumed to perpetuate the symptoms of fatigue (see Figure 1). Note that these are not the same for each patient. To determine the key factors for each patient, in addition to an interview, the patient completes several assessment instruments. Based on the tools' norm scores it is determined whether the patient has a deviant or problem score. Subsequently, founded on the outcomes of the assessment instruments and the patient-therapist interview, a custom-built treatment plan is drawn up comprising only patient-relevant modules. The tailored programme hence aims at changing the patient's specific perpetuating factors.
At the start of the programme patients are given room to relate their story after which the therapist explains the treatment and treatment goals in general terms. Since severely fatigued cancer survivors often tend to attribute their complaints to their having had cancer or to the subsequent treatment they have undergone, in the first session each patient is explained the difference between precipitating (triggering) and perpetuating (maintaining) factors.[13] It is also opportune to inform the patient of relevant scientific studies: research has shown that medical factors such as cancer type and treatment type have no bearing on post-cancer fatigue. This may help patients to come to terms with the fact that, although the initial complaints started during and in relation to their medical treatment, they are now sustained by other factors. Next, the outcomes of the assessment instruments are discussed and the patient's individual treatment goals formulated. Throughout the programme the patient is given home assignments that are reviewed during the sessions.
In the protocol below the treatment modules are described in the order in which they are usually carried out (the masculin pronoun is used to denote both male and female patient). First, the rationale of each module is discussed, followed by the relevant assessment instrument and the proposed course of action. For purposes of illustration, each module ends with a case example. Preceding the module descriptions, the case histories on which these are based are given.

Figure 1

The six modules of the treatment protocol for postcancer fatigue



Two case histories

Case history Mr. O.

O. is a 38-year-old married man with two daughters (15 and 9 yrs) and a son (12 yrs). He is head of sales in a company manufacturing orthopaedic aids. O. was diagnosed with testicular cancer seven years ago for which he underwent surgery and four successive chemotherapy treatments. During the chemotherapeutic sessions the patient reported feeling progressively more fatigued. After treatment completion the fatigue did not abate and now, after several years, the patient still feels fatigued.

O. feels impeded by his fatigue. He has given up playing tennis and no longer tinkers with motorbikes. Since the previous year, instead of working fulltime, he has cut his hours to 80%. He has been seeing a psychologist with whom he has mainly discussed ways to cope with his fatigue. Although he appreciated the sessions, improvements were minimal. The fatigue persisted.

Case history Mrs. T.

T. is a 45-year-old woman who underwent surgery for ovarian cancer twice with subsequent chemotherapy five years ago. The patient first became fatigued in the course of the treatment. Rather than improving, after treatment completion she felt even more fatigued. The fatigue persisted. T. is married with two children aged 12 and 15 years. Her husband is a great source of support and frequently takes care of the family's evening meal and the daily shopping.

At the time, T. found the clinical treatment extremely taxing. Though earlier still active as a remedial teacher, due to the treatment and the fatigue she failed to manage working her usual (24) hours. She is now on full disability.

Module: Poor coping with cancer and cancer treatment

Rationale

Having developed cancer and having undergone treatment for the disease may both constitute traumatic events in a person's life. Coping with these events takes time. Clinical practice has shown that cancer survivors may need the entire first year following treatment end to do so. During this post-treatment period one should therefore not talk poor coping with cancer and cancer treatment. Only when the patient continues to be (pre)occupied with what has happened to him (long) after this period should poor coping patterns be considered. In this event, we may be dealing with so-called posttraumatic symptoms that sustain the fatigue.[21-22] Sometimes the deficient coping mechanisms and the accompanying fatigue are reactivated by events in the patient's immediate environment, for instance, upon learning that someone he knows has been diagnosed with cancer.

Assessment

The extent to which patients have coped with their cancer can be assessed with the Impact of Event Scale (IES).[23-24] The patient instructions are adjusted to accommodate for cancer and cancer treatment. The questionnaire consists of two subscales, i.e. intrusion and

avoidance. We take a high score on both subscales (>10 for each separate scale and > 20 for the combined scales) to be a sign that the patient has both heightened cognitions and feelings associated with his reliving the diagnostic and clinical treatment stages and displays marked avoidant behaviour. If this applies, the present module is indicated.

Procedure

The aim of the module is to help the patient give the facts of having had cancer and his cancer treatment their proper place in his life, thus taking away the need or urge to keep reliving or actively avoiding memories of the events. In order to reduce these propensities, the patient first needs to be exposed to the past events. To this end, the therapist and patient should go over the patient's experiences in terms of events and impact in great detail. Targeted writing assignments (e.g. having the patient write down his experiences) as well as tailored suggestions to talk about specific events with spouse or others close to the patient form part of the process.

Case example

During the first session O. discloses that he is often confronted with vivid memories of the moment he was told he had cancer. O.: "I was devastated. For quite a while I kept thinking I was going to die. I was afraid that the chemo would not work for me. My wife and relatives kept trying to lift my spirits. I didn't dare tell them how scared I was. When the chemo proved to take effect, everyone was relieved, including me. I no longer felt I could tell them how bad I was still feeling; I was getting well, was being cured, wasn't I? I keep thinking about it and it still distresses me. I can still see the doctor's face when he told me we were dealing with cancer. I don't talk about it with my wife; we're glad it's all over and I don't want to complicate things for her for no apparent reason."

Module: Excessive fear of disease recurrence

Rationale

Typically, feelings of anxiety in cancer survivors are higher than before the diagnosis, especially when a follow-up visit draws near. In some patients anxiety levels may be continually and excessively elevated. Their anxiety pertains to a fear of recurrence of their cancer with associated concerns about potential treatments and deteriorating condition, evolving into a fear of dying.[5,10,25]

Assessment

To gauge the patient's fear of disease recurrence we propose a modified version of the Cancer Acceptance Scale (CAS).[5, 9] It presents the patient with two statements: "I worry about the cancer returning" and "I am anxious about my health". Both are rated on a 4-point scale ranging from 'Does not apply to me at all' to 'Completely applies to me'. We take a total score of ≥ 5 to indicate undue fear of recurrence.

Procedure

The module aims at preventing the worries concerning a possible recurrence of the cancer from dictating the patient's life. Crucial to this part of the intervention is to identify and explicate the cognitions underlying the patient's fear. These can subsequently be weighed

against what the attending oncologist earlier told the patient about the likelihood of a recurrence. This reality check may help the patient put things into perspective. In addition, encouraging the patient to adopt cognitions relating to the patient's current situation may contribute to curbing his daily anxiety.

Case example

Mrs. T: "It is always there, in the background. I know I've always been a bit of a worrier, really, but when the thought that I might get cancer again enters my mind, I start to feel all panicky. The fear tends to crop up most when I'm thinking of my kids. It consumes me".

Module: Dysfunctional cognitions

Rationale

This module is concerned with various dysfunctional fatigue-related cognitions. Patients may be unable to accept their fatigue-induced impairments and refuse to adapt their life patterns to the new condition, hence exacerbating the symptoms. It is known from the literature that disease-free cancer patients suffering from severe fatigue more frequently revert to catastrophising as their coping strategy, i.e. they tend to have an excessively negative orientation towards their fatigue.[12] This coping style is also seen in people suffering from chronic pain.[26-27] Fatigue-related catastrophising cognitions sustain or even magnify the symptoms. Self-efficacy, reflecting the extent to which a patient feels or thinks he can or cannot control his symptoms, may also be implicated and appears pivotal in cancer survivors, in whom a low or negative self-efficacy has been related to increases in fatigue levels.[13] Similar findings have been reported for patients diagnosed with CFS and multiple sclerosis, in whom negative self-efficacy proved to directly affect the severity of the fatigue.[18]

Assessment

The Fatigue Catastrophising Scale, an adaptation of the Pain Catastrophising Scale, is used to evaluate the extent of catastrophising thoughts relating to fatigue.[28] The self-report questionnaire comprises three subscales, i.e. helplessness (6 items), magnifying (3 items) and ruminating (4 items), which are each answered on a 5-point scale. The latter two are used , Scores of 2 or higher are taken to reflect excessive magnifying and a score of or exceeding 7 unwarranted ruminating. Self-efficacy is assessed using the modified Self-Efficacy Scale (SES) for fatigue.[15,18] Its seven items are rated on a 4-point scale and scores of 19 or lower indicate negative self-efficacy. If one of the two scales yields a problem score, it is recommended to incorporate the module in the programme.

Procedure

The module's goal is to enable the patient to use more conducive and fatigue-reducing cognitions. By helping him to gain insight into the way catastrophising thoughts can exacerbate the complaints, the patient is motivated to replace these with more realistic and beneficial cognitions. Through Socratic dialogues unhelpful thoughts that tend to render the patient helpless can be modified into more appropriate, helpful cognitions that advance his self-reliance and self-efficacy.

Case example

T. relates all the things she has undertaken to divest herself of the fatigue. Mrs. T.: “I have tried everything there is to try. Nothing worked. I will never get rid it. I have no control over it whatsoever. I actually won’t be able to cope with it much longer”.

Module: Dysregulatory sleep-wake cycle

Rationale

The patient’s circadian pattern may have become disrupted by his keeping irregular bedtime and wake-up times, which may in turn have additionally provoked problems with falling asleep and sleep disturbances. Lying down or sleeping during the day may also lead to irregular or disturbed nocturnal sleeping patterns. Persisting sleep problems and irregular sleep patterns are common in cancer survivors and both tend to perpetuate the fatigue.[1,2]

Possibly, the dysregulations have been caused by coping difficulties or fears of disease recurrence. If so, these factors need to be addressed concurrently.

Assessment

To chart a patient’s circadian patterns use can be made of a Self-Observation List, a standardised journal the patients keeps for two weeks to record, among other aspects, his bedtime and get-up times and sleep quality.[13] The patient notes down his resting and sleeping times daily. When plotted in a bar chart the irregularities in the patient’s sleep-wake patterns are easily visualised (see Figure 2). By also having the patient record each morning how he has slept the night before, the quality of his sleep can be determined and problems identified. Response options include: I have slept well, I had trouble falling asleep, I had a restless sleep, I woke up early, I did not feel rested when I woke up. If the patient has problems sleeping or dysregulated sleep-wake cycles, the module is considered relevant.

Procedure

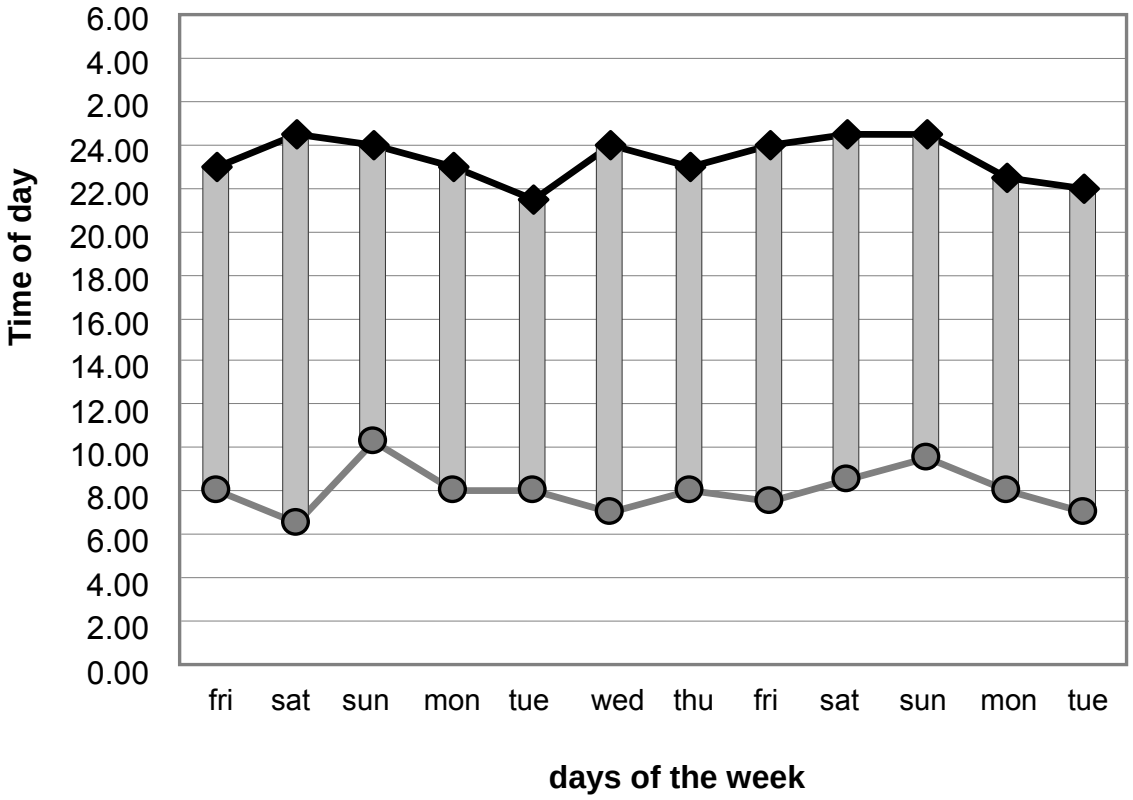
The module aims at establishing a consistent sleep-wake pattern with regular bedtime and wake-up times. This requires explaining the patient how he can (re)set his ‘biological clock’. It may be helpful to illustrate this by explaining the consequences of jetlag, working shifts or changing daylight saving times (shifts between ‘summer’ and ‘winter’ time). Introducing and encouraging adequate sleep-hygiene practices may also be opportune (e.g. the bed should be reserved for sleeping; it is advisable to adopt regular going-to-bed preparations; do not get up when you wake up at night).

Case example

T. goes to bed at variable times depending on how she is feeling. She usually gets up early in the morning on account of the children and then returns to bed. On the days she works (i.e. restricted hours and on a therapeutic basis), as soon as she comes home she lies down on the couch where she usually dozes off.

Figure 2

Self-Observation List: bed times (— ◆) and wake-up times (— ●) of 12 days



Module: Dysregulatory activities and return to work

Rationale

Especially in activity levels fatigued cancer survivors tend to show wide inter-individual differences.[13,19] Some are physically overactive; an overly active disease-free cancer patient tends to overtax himself continuously, with all the consequential physical and emotional adverse effects. Conversely, some patients will exhibit an excessively low activity pattern, reflected in an habitual lack of physical activity. Here, a fear that activity will aggravate the fatigue may be implicated or it may simply be a matter of habit. Both over and inactivity may perpetuate the symptoms of fatigue[10,29] Patients may also display excessively high or low activity patterns in their mental (reading, working at the PC, doing crosswords) and social activities (e.g. visiting or entertaining friends) that may both also affect their fatigue levels.

Assessment

An actometer is used to assess the patient's actual level of activity – to supplement his self-reported activity patterns (see below). The device has the size of a box of matches and is worn around the ankle for two weeks (day and night) to record the number of movements the

patient makes at five-minute intervals. With dedicated software various parameters can be computed and plotted. One of the crucial actometer variables in our treatment context is the mean daily physical activity across twelve days and nights: the higher the outcome score, the greater the overall extent of the activities the patient has displayed. Based on these mean day scores two problematic daily activity patterns can be distinguished: passive and relatively active.[13,15,29,30] In the two-week period the actometer is worn, the patient also rates (the extent of) his daily endeavours, comprising both physical and other activities, on the Self-Observation List. The current module is usually not indicated for patients with a mean actometer score ranging between 80 and 90

Procedure

It is the aim to first help the relatively active patient to establish a base level. By base level is meant that the patient reduces his level of physical (and possibly also mental and social) activities by learning to respect his limitations, and hereby adopting and sustaining a suitable personalised activity level that does not lead to excessive fatigue. The moment the patient has set his base level, the physical activity programs start. The patient selects a simple physical activity that can be performed every day (e.g. walking or cycling). The aim is to have the patient gradually and systematically increase the frequency or duration of this particular activity. The inactive patient starts immediately with the physical activity program. Intensifying or curbing specific activities will also raise the patient's (perceptions of his) capabilities in other areas. In subsequent stages the feasibility of a resumption of (paid) work and other desired activities should be considered for both patient types. To this end, the discrepancy between the patient's daily activity pattern and his preferred level needs to be established, after which activity-regulating schemes to reach the new goals are jointly set. If needs be, separate goals may be formulated to modify mental and social activity patterns. The patient thus learns to balance his activities, allowing him to perform his daily tasks and routines in an appropriate way, paving the way for a phased return to work.

Case example

T is an example of an inactive patient. T. needs to plan all her activities well ahead and reserves ample time to recover from them. She tries to prevent herself from becoming excessively fatigued because this will lead to failure in all other areas.

T: "I have many interests, but I restrain myself because if I don't, the fatigue will only get worse. If I need to be somewhere, for instance, I take extra time out to rest before I go, just to help me manage to get through it. That's also why I spend so much time lying on the settee. It is about the only thing that helps me to do the little I can, really. "

O. is an example of an overactive patient. O has periods that he tries to do everything. He brings his son to football and stays to view the match. He visits with his wife his daughter's dance performance. During and afterwards he feels awfully and exhausted. Sometimes if a friend asks him to play tennis, he does not want to say no. The next day he is not able to go to his work . But he says to himself "before I could do that, so now I also should be able to do that".

Module: low social support and negative interactions

Rationale

The extent of the social support disease-free cancer patients enjoy is positively related to their perceptions of quality of life.[31] Research of our group has shown that fatigued cancer survivors report more incidences of negative social interactions and that the discrepancy between the self-reported extent of their social interactions and the preferred level is larger than it is for their non-fatigued cancer survivors: most indicate needing more support than they currently receive.[13] Sometimes they crave the same attention and recognition they received while undergoing treatment even though for most people in their immediate vicinity these events are no longer relevant, which makes the fatigued former cancer patient feel neglected and ignored.

Assessment

We have gauged the patients' dimensions of social support with the 34-item Discrepancies subscale of the Sonderen Social Support Inventory (SSL-D).[32] The SSL-D measures the perceived discrepancy in actual and desired support, also denoted as insufficiency in supportive interactions. Total scores for the SSL-D range from 34 to 136. Scores exceeding 50 are seen as indicative of the current treatment module.[13,33]

Procedure

The module is directed at modifying the patients' excessive expectations regarding their social environment by promoting more realistic expectations, which are expected to reduce their negative cognitions and feelings vis-à-vis their social contacts. The patient's perceived insufficiency in supportive interactions is discussed. The patient is encouraged to adopt a different attitude towards his environment, abandoning any expectations of empathy and support where these are no longer relevant or reasonable. If these also pertain to the patient's spouse, inviting him or her to participate in this part of the programme is recommended. If indicated, time may be dedicated to enhancing the patient's capacity to assert himself.

Case example

O.: "At work they never talk about it anymore; it's as if it's never happened. They don't even know about my feeling so damned tired. They also act as if things are all back to normal even though they know full well why I'm working fewer hours. They expect me to attend each meeting, just like they do of the others. They obviously have no idea of what I've been through. They could ask me how I'm doing every once in a while, now couldn't they?!".

Treatment content and module frequency

The mean treatment duration for the 65 patients who completed the above-described CBT in our controlled trial was 11.8 (sd=4.4) hours divided over 12 sessions.[20] On average, three and a half hours were spent on general topics such as the session's introduction, discussion of the assessment outcomes, fine-tuning of expectations and joint goal setting.

In Table 1 we have listed per module the extent to which they contributed to the actual treatment of our sample of cancer survivors, i.e. the time (in terms of the percentage of total

treatment time) dedicated to the relevant module, the number of patients for whom the module had indeed become part of their tailored treatment and the percentage of sessions in which the topic of the module was raised.
Example how to read the table: 25% of total treatment time was spent on the module challenging the patient's cognitions, which was part of the final treatment protocols for all 65 patients, and this topic was raised in 49% of the total number of sessions.

Table 1

Module frequency of 65 patient who completed the treatment for postcancer fatigue

Modules	Time spent on the module (% of total treatment time)	Patients for whom the module was part of the treatment protocol (% / n)	% of sessions in which the module was raised
Poor coping with cancer	5%	63% (n=41)	12%
Fear of disease recurrence	3%	45% (n=29)	8%
Dysfunctional cognitions	25%	100% (n=65)	49%
Dysregulation of sleep	6%	86% (n=56)	36%
Dysregulation of activity	49%	100% (n=65)	71%
low social support	12%	86% (n=56)	25%

Treatment efficacy and relevance

As mentioned earlier, the efficacy of the proposed CBT was demonstrated in a randomised controlled trial in which we tested the programme in fatigued patients that had successfully completed curative treatment for various types of cancer: 76% of the patients no longer reported to be (severely) fatigued after CBT completion.[20]
The CBT is especially designed for fatigued cancer survivors for whom at least one year has elapsed since their clinical treatment and that patients presenting or diagnosed with comorbid psychological or psychiatric symptoms are excluded.
It is, of course, even more desirable to prevent people from developing post-cancer fatigue. Additional investigations are underway to explore the usefulness of the current CBT in preventing persistent fatigue in this population by offering the programme to patients immediately following or even during their curative clinical treatment.

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Chapter

4

The effects of cognitive behaviour therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behaviour therapy: a randomised controlled trial

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ABSTRACT

Persistent fatigue is a long term adverse effect experienced by 30% to 40% of patients cured of cancer. The main objective of this randomised controlled trial was to show the effectiveness of cognitive behaviour therapy (CBT) especially designed for fatigue in cancer survivors.

A total of 112 cancer survivors with somatically unexplained fatigue were allocated randomly to immediate cognitive behaviour therapy or to a waiting list condition for therapy. Both conditions were assessed two times, at baseline and 6 months later. The primary outcome variables were fatigue severity (Checklist Individual Strength) and functional impairment (Sickness Impact Profile). Data were analyzed by intention to treat.

Analyses were based on 50 patients in the intervention condition and 48 patients in the waiting list condition. Patients in the intervention condition reported a significantly greater decrease than patients in the waiting list condition in fatigue severity (difference, 13.3; 95% CI, 8.6 to 18.1) and in functional impairment (difference, 383.2; 95% CI, 197.1 to 569.2). Clinically significant improvement for the CBT group compared with the waiting list group was seen in fatigue severity (54% vs. 4% of the patients, respectively).

Cognitive behaviour therapy has a clinically relevant effect in reducing fatigue and functional impairments in cancer survivors.

INTRODUCTION

Current cancer treatments are increasingly effective in improving survival. However, with larger numbers of survivors a variety of long term adverse side effects have emerged. One of these adverse effects is persistent fatigue, which occurs in at least 30% to 40% of the cancer survivors, with profound effects on quality of life.[1-6]

The etiology of postcancer fatigue is unknown. Fatigue seems to be elicited during the treatment phase, but later there is no clear relationship between persistent fatigue and initial disease and cancer treatment variables.[1-3,7-8] Hypotheses have been proposed about increased proinflammatory cytokine activity and dysregulation in hypothalamic-pituitary-adrenal axis responsiveness[9-11]; however, contradictory findings exist.[2] At present, there is no somatic strategy in managing fatigue in cancer survivors.

We believe it is useful to make a distinction between precipitating factors and perpetuating factors of fatigue after cancer. The assumption is that cancer itself and/or cancer treatment may have triggered fatigue (precipitating factors), but other factors are responsible for persistence of fatigue complaints (perpetuating factors); for example, physical activity,[1,2,7] sleep quality,[1,2] cognitions related to fatigue,[4] the use of catastrophizing as coping strategy,[12] and fear of disease recurrence.[7,13]

Exercise is one of the few interventions suggested to decrease fatigue among cancer survivors,[14,15] but randomised controlled trials (RCTs) supporting this are absent.[16,17] The main objective of this RCT was to study the effectiveness of cognitive behaviour therapy (CBT), directed at perpetuating factors of postcancer fatigue. Our hypothesis is that fatigue severity and functional impairment will decrease significantly more in a group of patients assigned to CBT than in patients waiting for the therapy.

PATIENTS AND METHOD

Sample

Between December 2001 and September 2004, disease-free cancer patients with severe fatigue (score of 35 or higher on the Checklist Individual Strength [CIS], fatigue subscale) were recruited from outpatient clinics of medical oncology, urology, surgery, orthopedics, hematology and gynecology. Patients were screened by their physician on clinically relevant systematic diseases (eg, malnutrition, hemoglobin level, presence of hypothyroidism, and other physical co morbidities). If a physician was certain that the fatigue had no somatic cause, the patient was invited to participate. Patients completed curative treatment for cancer at least 1 year previously and had no evidence of disease recurrence at the time of participation. The minimum age at disease onset was 18 years, patients were no older than 65 years and had no current psychological or psychiatric treatment when participating in the study. The ethics committee of the hospital approved the study.

Design and procedure

We gave patients verbal and written information about the study and obtained informed consent before randomly assigning them to either the intervention condition (CBT) or the

waiting list condition. Random assignment was done by means of a sequence of labelled cards contained in sealed, numbered envelopes prepared by a statistical adviser. The envelopes were opened by the researcher (M.G.) in the presence of the patient. Both conditions were assessed two times, at baseline and six months later. Patients in the waiting list condition were informed beforehand that, if desired, they could start therapy after the second assessment.

Intervention

The rationale of the intervention was based on the model of precipitating and perpetuating factors. CBT was focused on six perpetuating factors (six modules) of postcancer fatigue, which were based on existing literature and experience in clinical practice. They involve insufficient coping with the experience of cancer, fear of disease recurrence,[7,13] dysfunctional cognitions concerning fatigue,[4,12] dysregulation of sleep,[1,2] dysregulation of activity,[1,2,7] low social support and negative social interactions.[4]

Because of the existence of large differences within the group of fatigued cancer survivors,[18] therapy was adapted to each individual. To determine which modules were necessary, each perpetuating factor was measured with specific questionnaires. If a patient had a score on one of these questionnaires indicating problems, the accessory module became part of the treatment, resulting in an individualized treatment protocol per patient. Notably, the therapy only varied in number of modules, but within each module the therapy is standardized. The number of sessions was determined by the number of modules used and whether the goal of the therapy was reached. Therapy sessions varied between 5 and 26 sessions (mean, 12.5 sessions; standard deviation [s.d.], 4.7 sessions) with a duration of 1 hour during a 6-month period. Patients were offered a maximum of two sessions during a 6-month follow-up period.

Three therapists with previous CBT experience with patients with chronic fatigue (eg, patients with chronic fatigue syndrome [CFS], neuromuscular diseases, and other chronic diseases) treated the patients. The therapists were trained in the use of instruments to determine which module should be included in the therapy. Therapists were also trained in instrument application. Role-playing was an important part of this training. The therapists were supervised throughout the study by one author (G.B.). During supervision, it was discussed how the relevant module should be applied to a particular patient.

To give some insight into cognitive and behavioural techniques used in the therapy, we illustrate briefly how the six perpetuating factors were challenged during CBT.[19]

<u>Insufficient coping with the experience of cancer</u>

A patient can continue to be occupied with the period of being diagnosed or treated for cancer (similar to a patient with a post traumatic stress disorder). By means of talking, or writing about this experience (which we would refer to as exposure), the patient will acquire better coping skills.

<u>Fear of disease recurrence</u>

The therapist helps the patient to formulate explicit words to describe the thoughts of fear of disease recurrence. These thoughts are challenged against reality (reality testing). In this

way, daily unhelpful thoughts about the possibility of a recurrence are reduced and put into perspective.

Dysfunctional cognitions concerning fatigue

Dysfunctional cognitions relate to a variety of ideas, including a patient's idea of lack of control over symptoms ("I cannot do anything about it, I am helpless"), unhelpful attributions ("The chemotherapy caused the fatigue"), and dysfunctional cognitions about fatigue, such as catastrophizing ("This fatigue is awful, I can't stand it"). These cognitions are disputed and more helpful ways of thinking are taught. Explaining the distinction between precipitating and perpetuating factors can also help reduce dysfunctional cognitions.

Dysregulation of sleep

An irregular sleep-wake rhythm can perpetuate fatigue. To restore the biologic rhythm, patients are encouraged to adhere to fixed bedtimes and wake-up times and are discouraged from sleeping during the day.

Dysregulation of activity

Some patients experience fluctuating periods of activity with subsequent periods of rest during a longer period. Others avoid activity because they are concerned that activity increases fatigue; consequently, they are physically inactive. For patients with fluctuating activity levels, a base level should be established by alternating rest and activities to prevent bursts of activity. Once the patient has set a base level, the physical activity program started, usually twice a day, starting with 5 to 10 minutes of an activity such as walking or cycling. The activity is increased by 1 minute a day each time the activity is performed (ending at a maximum of 120 minutes per day). The inactive patient will start the activity program immediately. Gradually, physical activities are replaced by other activities.

Low social support and negative social interactions.

If a patient still has unrealistic expectations of others (eg, expecting that others still recognize him or her as a patient who has experienced something terrible) or perceives a discrepancy between actual support and desired support, the therapist helps to instil more realistic expectations toward the patient's social support group.

Assessment

Primary outcome variables

Fatigue severity was measured by the fatigue severity subscale of the CIS.[20-22] The subscale consists of eight items, each scored on a 7-point Likert scale (range, 8 to 56 points), in which the patient is asked about fatigue in the 2 weeks preceding the assessment. Based on research with CFS patients, a score of 35 or higher indicates severe fatigue.[20] The questionnaire has been used in cancer survivors,[4,13,18] and showed good reliability, discriminative validity, and sensitivity to change.[21,23-24]

Functional impairment was measured by the Sickness Impact Profile-8 (SIP-8). The SIP-8 consists of eight subscales: home management, mobility, alertness behaviour, sleep/rest, ambulation, social interactions, work, recreation and pastimes. A total score was calculated by addition of the weights of items (range, 0 to 5.799). This widely used measure has good reliability and content validity.[25]

Secondary outcome variable

Psychological distress was measured by the Symptom Check List 90 (SCL-90). The scale consists of 90 items scored on a 5-point Likert scale. The total score ranges from 90 to 450. The SCL-90 has good reliability and discriminating validity.[26]

Clinically Significant Improvement

There has been growing recognition that the clinical importance of a treatment effect is not equivalent to the statistical effect. The following questions can be addressed regarding this issue. First, is the amount of change in fatigue that has occurred after CBT large enough to be considered meaningful? Second, are patients comparable with a normative group with respect to their fatigue after CBT? A patient was classified as showing clinically significant improvement if both criteria were met. A meaningful change was calculated with the reliable change index.[27] The method of normative comparison was used in answering the second question.[28]

A patient's own opinion about improvement is another possible approach in investigating the clinical importance of a treatment effect. Self-rated improvement was measured on the second assessment by one specific question: patients indicated whether they had completely recovered, felt much better, had the same complaints or had become worse compared with the baseline assessment.[23-24,29]

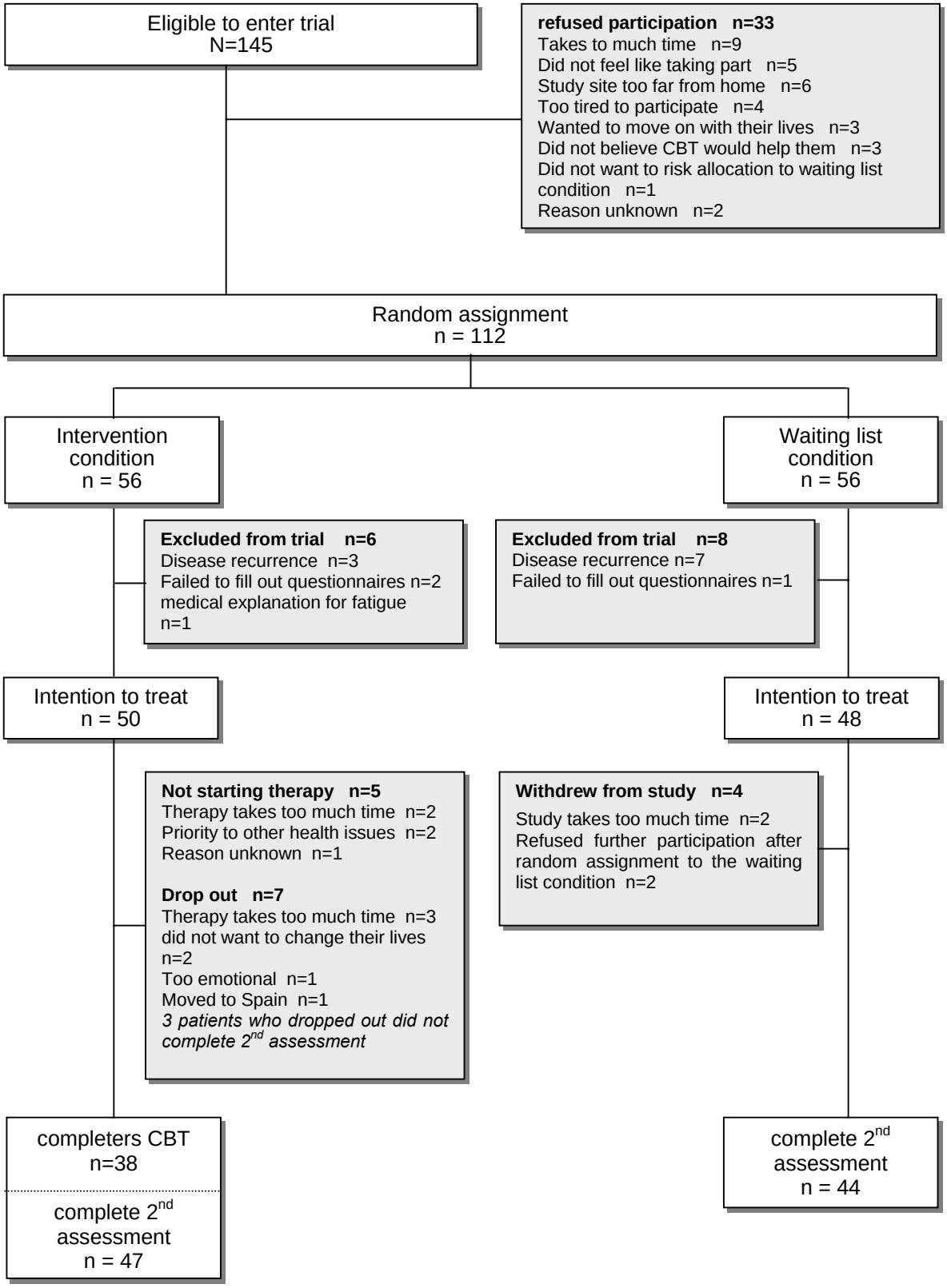
Statistical analysis

Power calculations showed that 49 patients were needed in each condition assuming a significance of 5% (two-tailed), power of 85%, and a dropout rate of 20%, in detecting a clinically relevant change of 8 points on the primary outcome variable (CIS-fatigue).[4,18, 20] Data analyses were performed using SPSS, version 12.1 (SPSS Inc, Chicago, IL). Analyses were conducted on an intention-to-treat basis and the last observation was carried forward if data were missing. Independent samples *t* test and χ^2 tests were performed testing baseline differences between the two conditions. If a significant difference was present, the baseline assessment was used as a covariate in additional analyses.

Differences between the two conditions on the amount of change in the outcome variables were calculated with analyses of variance on change from baseline to 6 months, with 95% CIs. A patient was defined as having a clinically significant improvement if he or she had a reliable change index more than 1.96 and decreased to a normal range (defined as any score < 1 s.d. above the mean of a normative group).[23-24,27-28] The normative group consisted of 93 nonfatigued breast cancer survivors (mean age, 46.4 years; s.d.= 6.3[4]). Normal range was defined as less than 30.4 on CIS-fatigue and less than 643 on SIP-8-total. Patients who reported "I have completely recovered" or "I feel much better" on self-rated improvement were also seen as clinically significant improved. χ^2 tests were used to analyze the differences between the proportions of patients meeting these criteria for clinically significant improvement.

Figure 1

Trial profile (CBT, cognitive behaviour therapy)



RESULTS

Trial profile

Figure 1 shows the trial profile. Of the 145 patients who met the eligibility criteria, 33 refused to take part (23%). There were no differences on baseline characteristics (demographic characteristics, disease and cancer treatment characteristics, or fatigue severity) between participants and nonparticipants (data not shown).

Fifty-six patients were allocated to both conditions. After random assignment, 14 ineligible patients were excluded from the trial.[30] Intention-to-treat analyses were based on 50 patients in the intervention condition and 48 patients in the waiting list condition. Five patients did not start treatment and seven patients dropped out of treatment. In the intervention condition, 47 patients had a complete second assessment. After baseline assessment, four patients in the waiting list condition withdrew from the study. For these missing data, the last observation was carried forward (7%; n=7). No differences in baseline characteristics (demographical characteristics, disease and cancer treatment characteristics, and the outcome variables) were found among those who completed treatment (n=82) and the total number of patients who did not start treatment, who dropped out of treatment or withdrew from the study (n=16; data not shown).

Baseline comparison

Table 1 demonstrates baseline demographic, disease and cancer treatment characteristics, and the outcome variables in both conditions. Compared with the intervention condition, patients in the waiting list condition underwent chemotherapy more often and had less psychological distress.

Effect of intervention

Patients in the intervention condition reported a significantly greater decrease in fatigue severity (difference, 13.3; 95% CI, 8.6 to 18.1), in functional impairment (difference, 383.2; 95% CI, 197.1 to 569.2), and in psychological distress (difference, 21.6; 95% CI, 12.7 to 30.4) than patients in the waiting list (Table 2).

Clinically significant improvement

The proportion of patients with clinically significant improvement on fatigue severity, functional impairment, and self-rated improvement was significantly higher in the intervention condition than in the waiting list condition (Table 3).

Table 1

Baseline characteristics of study participants. Values are means (sd) unless stated otherwise

Characteristics	Cognitive behaviour therapy (n=50)	Waiting list (n=48)
Age: years	44.6 (9.9)	45.3 (10.3)
Male / Female : n	27 / 23	23 / 25
Education: (1=low to 7=high)	4.4 (1.6)	4.3 (1.7)
Marital status : % (n)		
married / cohabiting	82% (41)	86% (41)
unmarried	12% (6)	8% (4)
divorced	4% (2)	6% (3)
widowed	2% (1)	-
Employment : % (n)*		
work outside home	54% (27)	56% (27)
voluntary work	14% (7)	8% (4)
full disablement insurance act	28% (14)	29% (14)
partial disablement insurance act	24% (12)	33% (16)
sick leave	10% (5)	4% (2)
school	4% (2)	6% (3)
Cancer diagnosis : % (n)		
mamma carcinoma	30% (15)	31% (15)
testicular cancer	24% (12)	27% (13)
haematological cancer	20% (10)	13% (6)
other solid tumors	26% (13)	29% (14)
Treatment type : % (n)*		
surgery	78% (39)	88% (42)
chemotherapy	60% (30)	85% (41)**
radiotherapy	54% (27)	48% (23)
Duration of cancer treatment : months	6.5 (6.8)	7.1 (6.0)
Time since cancer treatment : years	5.5 (4.3)	4.6 (3.4)
Primary outcome variables***		
fatigue severity	47.6 (6.5)	47.3 (6.9)
functional impairment	1029.6 (504.9)	860.7 (485.5)
Secondary outcome variable***		
psychological distress	143.6 (39.9)	130.1 (23.5)**

* percentages do not add up to 100% because more options are possible

** the difference is significant at P <.05 level between the two conditions

*** high scores reflects a high level of fatigue, more functional impairments, and high psychological distress

Table 2

Effect of cognitive behaviour therapy on fatigue severity, functional impairment and psychological distress analyzed on the basis of intention-to-treat

Condition *	0 months	6 months	Treatment effect (95% CI)**	p-value
Fatigue severity				
CBT	47.6 (6.5)	29.0 (14.9)	13.3 (8.6 to 18.1)	.000
WL	47.3 (6.9)	42.1 (9.6)		
Functional impairment				
CBT	1029.6 (504.9)	607.4 (578.9)	383.2 (197.1 to 569.2)	.000
WL	860.7 (485.5)	821.7 (524.3)		
Psychological distress				
CBT	143.6 (39.9)	123.2 (36.3)	21.6 (12.7 to 30.4)	.001
WL	130.1 (23.5)	131.2 (28.9)		

* cognitive behaviour therapy (CBT), n=50; waiting list condtion (WL), n=48 (n=46 for functional impairment and psychological distress).

** difference in improvement between intervention and control group. In analyzing differences, baseline psychological distress and chemotherapy were used as covariates.

Table 3

Clinically significant improvement at 6 months in fatigue severity, functional impairment, and self rated improvement by treatment group

	6 months % (n) improved	Treatment effect (95% CI)**	p-value
Fatigue severity*			
CBT	54% (27)	0.50 (0.34 to 0.65)	.000
WL	4% (2)		
Functional Impairment**			
CBT	50% (25)	0.32 (0.14 to 0.51)	.001
WL	18% (18)		
Self rated improvement***			
CBT	66% (33)	0.45 (0.27 to 0.63)	.000
WL	21% (10)		

* reliable change index > 1.96 and cutoff score of Checklist Individual Strength-fatigue < 30.4

** reliable change index > 1.96 and cutoff score of the Sickness Impact Profile-8 total < 643

*** answer of 'yes' to statement, 'I have completely recovered' or 'I feel much better but still experience some symptoms'

DISCUSSION

This study is the first RCT in managing postcancer fatigue. The results show that CBT is successful in treating fatigue in cancer survivors. CBT was more effective than remaining on a waiting list in reducing fatigue severity, functional impairment, and psychological distress. Moreover, treatment resulted in a greater proportion of patients with clinically significant improvement in these variables and self-reported improvement.

The model of precipitating and perpetuating factors is also used in patients with CFS.[23-24,31] However, it is important to note that there are differences between patients with CFS and cancer survivors with fatigue.[18] Therefore, CBT for fatigue also is different for both patient groups. For cancer survivors, there is a distinct starting point of fatigue complaints, namely the period in which they were diagnosed and treated for cancer. For patients with CFS, the onset differs per patient and often is unknown. This suggests automatically that the attributions relating to the cause of the fatigue are different for both groups. In addition, there is a difference in perpetuating factors. Dealing with fear of disease recurrence and coping with the experience of cancer are important factors in CBT of fatigued cancer survivors and are not present in CBT for CFS. Intraindividual differences are larger in fatigued cancer survivors than in CFS patients, especially for physical activity.[18] Therefore, CBT for cancer survivors is tailored more to the individual, unlike CBT for CFS.

The dropout rate in this study was slightly higher than assumed in the power calculation. In the CBT condition the dropout rate was 24%; in the waiting list condition, the dropout rate was only 8%. However, many patients who dropped out were willing to attend for the assessment. At the second assessment only 7% of the total group had missing data. Because analyses were conducted on an intention-to-treat basis and the last observation was carried forward if data were missing, the dropout rate will not weaken our findings.

Although the normative group used in analyzing clinically significant improvement were all female cancer survivors and were slightly older than the patients in the present study, it is a more adequate control group than healthy controls. Servaes et al[4] demonstrated that in general, these breast cancer survivors with non-severe fatigue were comparable to a healthy control group, with the exception of functional impairment. The cancer and/or the cancer treatment seem to be responsible for permanent impairments and therefore comparison with nonfatigued cancer survivors is more appropriate.

Our study was limited to patients no older than age 65 years, whereas almost 50% of the cancer will be diagnosed after this age. Furthermore, the study was performed with frequently diagnosed tumours. Replication of this study is necessary for older cancer survivors and survivors with other diagnoses.

Controlled follow-up was not possible in this RCT because patients in the waiting list were offered CBT immediately after the second assessment. Therefore, future research should give more insight into the long-term effects of CBT. Another limitation of this study is the omission of an attention placebo control group. Previous studies showed no effect of an attention placebo group on fatigue in CFS patients.[24,32] However, as described herein, there are differences between CFS patients and fatigued cancer survivors. Therefore, we can not rule out that mere attention for the patient has contributed to the outcome.

For a medical specialist it is difficult to treat postcancer fatigue when a somatic explanation is excluded. However, with a growing number of cancer survivors and given the substantial adverse physical, psychosocial, and economic consequences of postcancer fatigue, rehabilitation is critical. Even more desirable would be to prevent postcancer fatigue by intervening during cancer treatment. Additional investigation is needed to demonstrate the usefulness of CBT just after or during cancer treatment in preventing persistent fatigue.

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Chapter 5

Cognitive behaviour therapy for fatigued cancer survivors: Long term follow-up

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ABSTRACT

An earlier randomised controlled trial demonstrated the positive effects of cognitive behaviour therapy (CBT), especially designed for fatigued cancer survivors in reducing fatigue, functional impairments and psychological distress. In the current prospective study, we were able to examine the long term effect of CBT in patients who completed the therapy. Predictors of fatigue severity at follow-up were exploratory investigated.

Sixty-eight patients who completed CBT were assessed at pretreatment, post-treatment and at follow-up (mean follow-up 1.9 years (s.d.=1.0), range 0.5 – 4 years). To analyse possible predictors of treatment outcome a linear regression (enter) was carried out.

Improvements on fatigue severity, functional impairment and psychological distress after CBT appeared to remain stable during the follow-up period. Patients who were not fatigued anymore at follow-up were not different from a reference group of non-fatigued cancer survivors. The explorative regression analysis showed that fatigue severity, psychological distress and somatic attributions at pretreatment contributed to persistent fatigue severity at follow-up.

CBT especially designed for postcancer fatigue, is successful in reducing fatigue and functional impairment in cancer survivors. Moreover, these positive effects were maintained at about 2 years after finishing CBT.

INTRODUCTION

Fatigue is a common and distressing side effect of cancer treatment.[1,2] Unfortunately, fatigue persists in patients for even years after completion of curative treatment. At least a quarter of the cancer survivors suffer from postcancer fatigue, with profound effects on quality of life.[1-6]
Although research on postcancer fatigue has increased in the last decennia, there are only a few randomised controlled trials (RCTs) investigating the management of postcancer fatigue. Until now, 6 RCT's have investigated the effect of an intervention on fatigue, measured as a primary or secondary outcome. Two were pilot studies and found no effect on fatigue.[7,8] No effect was found investigating a lifestyle physical activity intervention,[7] and the second study found no effect of yoga.[8] Two studies investigated the effect of exercise in cancer survivors. Both studies used fatigue as a secondary outcome and showed beneficial effects.[9-10] The fifth study found that acupuncture was a more effective method to improve fatigue compared with acupressure or sham acupressure.[11] None of these RCTs includes follow-up assessments. In the last RCT cognitive behaviour therapy (CBT), especially designed for postcancer fatigue, appeared to be highly effective.[12] The rationale of this intervention was based on the model of precipitating and perpetuating factors. Fatigue seems to be elicited during the treatment phase, but later on there is no clear relationship between persistent fatigue and initial disease and cancer treatment variables.[1-3,13,14] The assumption is that the cancer itself and/or the cancer treatment may have triggered fatigue (precipitating factors), but other factors are responsible for persistence of fatigue complaints (perpetuating factors). Cognitive behaviour therapy for postcancer fatigue is focused on these perpetuating factors. The RCT consisted of two conditions, the intervention condition (6 months of CBT) and waiting list condition (6 months). Patients in the intervention condition reported a clinically relevant decrease compared to patients in the waiting list condition in fatigue severity, functional impairment and psychological distress. Patients in the waiting list condition were informed beforehand that, if desired, they could start therapy directly after the waiting period of 6 months.
In this current study, the long-term effect of CBT will be investigated in patients who were involved in this former study and received CBT, including patients in the intervention condition and patients who had been treated after the 6-month waiting list. Furthermore, we will exploratory investigate predictors of fatigue severity at follow-up.

METHODS

Sample

Between December 2001 and September 2004, six departments of the Radboud University Nijmegen Medical Centre participated in the recruitment of patients for this study. Cancer survivors who experienced severe fatigue (score of 35 or higher on the Checklist Individual Strength, fatigue subscale), were recruited from the outpatient clinics of medical oncology, urology, surgery, orthopaedic, haematology and gynaecology. During follow-up visits in the hospital fatigued survivors were screened by their physician on clinically relevant systematic diseases (eg, malnutrition, haemoglobin level, presence of hypothyroidism, and other physical comorbidities). If a physician was certain that the fatigue had no somatic cause, the

patient was invited to participate. Patients completed curative treatment for cancer at least 1 year ago and had a minimal age at disease onset of 18 years. At time of participation patients had no evidence of disease recurrence and patients were not older than 65 years. Patients with current psychological or psychiatric treatment were excluded. The ethics committee of the hospital approved the study.

Intervention

Cognitive behaviour therapy was focused on six perpetuating factors of postcancer fatigue, which were based on existing literature and experience in clinical practice. They involve (1) insufficient coping with the experience of cancer, (2) fear of disease recurrence,[13,15] (3) dysfunctional cognitions concerning fatigue,[16,17] (4) dysregulation of sleep,[1,2] (5) dysregulation of activity,[1,2,13] (6) low social support and negative social interactions.[16]

Each perpetuating factor became a module in the therapy protocol. Because of the existence of large differences within the group of fatigued cancer survivors,[18] therapy was adapted to each individual. To determine which modules were necessary, each perpetuating factor was measured with specific questionnaires. If a patient scored problematic on one of these questionnaire, the accessory module became part of the treatment, resulting in an individualized treatment protocol per patient. It is important to realise that the therapy only varied in number of modules, but within each module the therapy is standardised. The number of sessions was determined by the number of used modules and by reaching the goal of the therapy.

Three therapists with previous CBT experience in patients with chronic fatigue treated patients who started directly with CBT as well as patients who started CBT after the waiting list period. For a more detailed description of the intervention see Gielissen et al.[12]

Assessment (Appendix A)

Patients were asked to complete questionnaires at the Expert Centre Chronic Fatigue of the Radboud University Nijmegen Medical Centre, pretreatment and post-treatment. Additionally, a package of questionnaires was sent by mail to all patients 6 months after the last patient finished CBT.

<u>Outcome measures</u>

Fatigue severity was measured by the fatigue severity subscale of the Checklist Individual Strength (CIS).[19-21] The questionnaire has been used in cancer survivors,[4,12,15,16,18] showed good reliability, discriminative validity and sensitivity to change.[12,20,22,23]

Functional impairment was measured by the Sickness Impact Profile-8 (SIP-8). This widely used measure has good reliability and content validity.[24,25]

Psychological distress was measured by the Symptom Check List 90 (SCL-90), which has good reliability and discriminating validity.[26,27]

Perpetuating factors

Coping with the experience of cancer was measured with the Dutch version of the Impact of Event Scale (IES), which measures the extent to which a subject is currently occupied with the coping process after a major event (in this study the diagnose and treatment for cancer).[28-30]

Fear of disease recurrence was measured by two items of the Cancer Acceptance Scale (CAS).[15]

Cognitions related to fatigue. Self-efficacy was measured with the Self-Efficacy Scale (SES)[15,16,23,31] and somatic related attributions with regard to fatigue complaints were measured with the Causal Attribution List (CAL).[16]

Sleep disturbances was measured with the sleep/rest subscale of the SIP-8 ,and the insomnia subscale of the Quality of Life Questionnaire-C30 (QLQ-C30).[32]

Physical activity was measured with the physical functioning and role functioning subscale of the QLQ-C30. Furthermore, physical activity was measured with the subscales home management, work, and recreation / pastimes from the SIP.

Social functioning was measured with the van Sonderen Social Support Inventory (SSL).[33]

Statistical analysis

Data analyses were performed using SPSS (version 12.1). Independent samples *t*-test and Chi-squared tests were performed testing differences between the intervention condition and the waiting list condition.

In the current study, the data collected at the end of the 6-month waiting period were used as pretreatment measurements. Comparison of the results of the pretreatment, post-treatment and follow-up assessments were carried out by GLM repeated measures analysis. Furthermore, GLM multivariate analysis was performed testing the differences between different follow-up periods and with a reference group. In a previous study of our research group 93 non-fatigued breast cancer patients were identified and used in this study as reference group (CIS-fatigue < 35; mean age, 46.4 years; s.d.=6.3).[16]

Mann-Whitney *U*-tests were used testing the differences between patient who did not accept CBT after the 6-month waiting list period and patients who completed CBT.

McNemar tests were used to analyse the differences between the proportions of patients who did not meet the criteria for severe fatigue (CIS-fatigue < 35) anymore at post-treatment and follow-up.

To analyse possible predictors of treatment effects a linear regression (enter) was carried out, with fatigue severity at the last follow-up assessment as dependent variable. Pearson correlations between fatigue severity at follow-up and the six perpetuating factors were used as preparatory analyses to examine the contribution of these factors to fatigue severity. Those measures that correlated significant with the fatigue severity at follow-up were used as independent variables in the logistic regression analyses. Correlations between the six perpetuating factors were tested on multicollinearity ($r < 0.9$).

RESULTS

Sample

Figure 1 shows the trial profile. The controlled data are described in Gielissen et al.[12] In this current study, we used the pooled data of both conditions. In the intervention condition, 38 patients completed CBT of whom 36 had a follow-up assessment. Forty-four patients completed the 6-month waiting list period and were offered CBT. Thirty-two patients accepted and completed the therapy and the follow-up assessment. There were no significant differences between patients in the intervention condition and waiting list condition on demographic and medical characteristics (Table 1). In addition, no significant differences were found on the outcome variables at pretreatment (fatigue severity *P* =0.052; functional impairment *P* =0.210; psychological distress *P* = 0.300) and post-treatment (fatigue severity *P* =0.582; functional impairment *P* =0.118; psychological distress *P* =0.346). Furthermore, the number of CBT sessions in both conditions were equal (12.5 (s.d.=4.7) vs 12.4 (s.d.=4.6), *P* =0.853). Because no differences were found, the data of both conditions were pooled (Table 1). Furthermore, we compared patients who did not accepted CBT after the 6-month waiting list period (n=12) with patients who completed CBT (n=68). There were no differences in the pretreatment assessment on fatigue severity (*P* =0.205), functional impairment (*P* =0.925) and psychological distress (*P* =0.671). Seven of the 12 patients who did not accept CBT after the waiting list period, completed the follow-up assessment

Long-term effect

The mean length of time between completion of therapy and follow-up assessment was 1.9 years (s.d.=1.0) with a range of 6 months to 4 years. The median was 2.0 years. The time interval between completion of therapy and follow-up assessment varied because patients entered the study at various times and started treatment at different moments.

Information about the outcome variables at the three assessments are listed in Table 2. Scores of fatigue severity, functional impairment and psychological distress significantly decreased at post-treatment and follow-up assessment compared with the pretreatment assessment. Additionally, the means on all outcome measures remained stable between post-treatment and follow-up. Compared with the reference group, patients in this study were significantly more fatigued at follow-up assessment, but had the same level of functional impairment and psychological distress. The follow-up period of patients who did not accept CBT (n=7) was comparable with the follow-up period of patients who completed CBT (1.5 years (s.d.=0.8), *P* =0.145). Patients who did not accept CBT were significantly more fatigued, had more functional impairments and higher psychological distress at follow-up compared to patients who accepted CBT (Table 2).

Eighty-one percent (n=55) of the patients did not meet the criteria of severe fatigue at post-treatment (CIS-fatigue < 35). At follow-up this percentage of non-fatigued patients was 71% (n=48, *P* =0.118). Compared with the non-fatigued reference group (Table 2), the patients who were not fatigued after CBT (n=48) had the same level of fatigue (19.9; s.d.=8.4, *P* =0.842), the same level of functional impairment (271.0; s.d.=292.7, *P* =0.476) and a significantly lower level of psychological distress (106.3; s.d.=14.4, *P* =0.042).

Figure 1

Trial profile

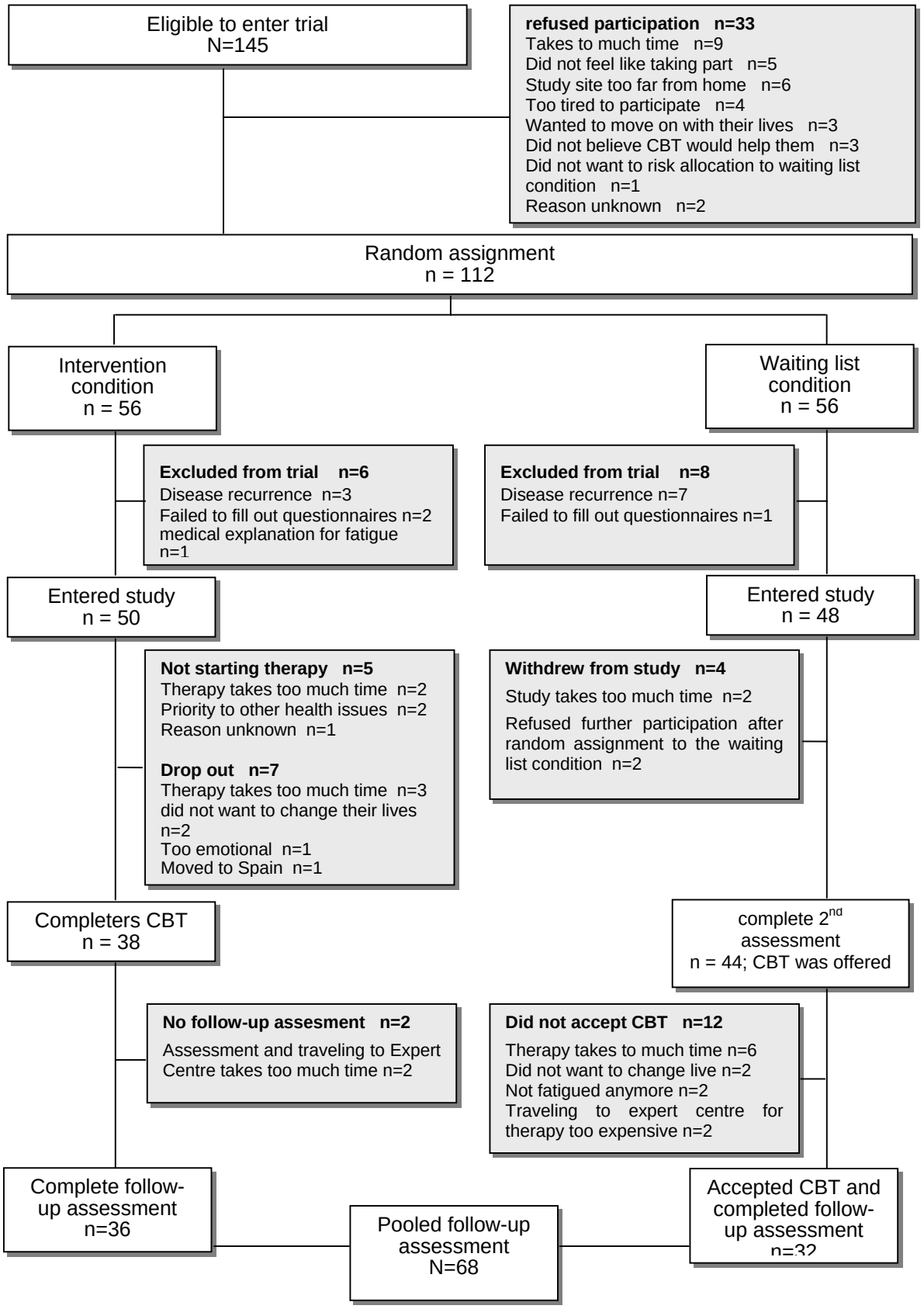

Table 1

Characteristics of study participants. Values are means (s.d.) unless stated otherwise

	CBT (n=36)	Waiting list (n=32)	Pooled group (n=68)
Age : years	43.8 (10.3)	43.9 (10.3)	43.8 (10.2)
Male / Female : n	19 / 17	16 / 16	35 / 33
Cancer diagnosis : % (n)			
mamma carcinoma	36% (13)	25% (8)	31% (21)
testicular cancer	33% (12)	25% (8)	29% (20)
haematological cancer	17% (6)	16% (5)	16% (11)
other solid tumors	14% (5)	34% (11)	24% (16)
Treatment type : % (n)*			
surgery	75% (27)	81% (26)	78% (53)
chemotherapy	70% (24)	84% (27)	75% (51)
radiotherapy	53% (19)	44% (14)	49% (33)
Duration of cancer treatment: months	6.6 (7.1)	7.3 (6.3)	6.9 (6.7)
Time since cancer treatment : years	5.2 (4.0)	5.1 (3.6)	5.1 (3.8)

* percentages do not add up to 100% because more options are possible

There were no significant differences between the cognitive behaviour therapy (CBT) and waiting list condition.

Table 2

Means (s.d) of CBT-completers (n=68) at pretreatment, post-treatment and follow-up, a reference group of non-fatigued cancer survivors and non-accepters of CBT at follow-up assessment

	A pre-treatment	**B** post-treatment	**C** follow-up	**D** reference values (n=98)	non-accepters CBT at follow-up (n=7)
Fatigue Severity	45.3 (7.7)[b,c,d]	24.3 (10.9)[a,d,]	26.9 (13.1)[a,d,e]	19.6 (8.4) [a,b,c]	40.3 (14.8)*
Functional impairment	937.1 (530.4)[b,c,d]	415.1 (438.6)[a,]	429.8 (483.2)[a,e]	309.5 (333.4)[a]	842.9 (302.2)*
Psychological well-being	138.5 (35.6)[b,c,d]	113.6 (25.5) [a,]	119.3 (37.1)[a]	113.2 (20.3)[a]	138.6 (39.8)

a: significantly different from pretreatment assessment (p <0.05)
b: significantly different from post-treatment assessment (p <0.05)
c: significantly different from the follow-up assessment (p <0.05)
d: significantly different from the reference group (p < 0.05)
* significantly different from follow-up assessment of CBT-completers

Short versus Long-term follow-up

As there is a considerable range in the duration of the follow-up, we investigated whether the treatment outcome differed between patients with a shorter and a longer follow-up period. Patients were divided into four groups: patients who completed CBT between 6 months and 1 year ago (n=15), between 1 and 2 years ago (n=21), between 2 and 3 years ago (n=20), between 3 and 4 years ago (n=12). Post hoc analyses showed no significant differences on change scores (pretreatment scores - / - follow-up scores) between the four-follow-up period on fatigue severity, functional impairment and psychological distress (Table 3). Furthermore, correlations between time since CBT and fatigue severity (r = - 0.067, P =0.585), functional impairment (r =0.216, P =0.077) and psychological distress (r = 0.141, P =0.251) were low and nonsignificant.

Table 3

Change scores (pretreatment scores - / - follow-up scores) at different follow-up points

	A 6 months – 1 year (n=15)	**B** 1 year – 2 years (n=21)	**C** 2 years – 3 years (n=20)	**D** 3 years – 4 years (n=12)
Fatigue severity	16.3 (13.0)	20.4 (13.1)	15.8 (12.2)	21.8 (11.9)
Functional impairment	507.1 (358.3)	557.2 (473.5)	473.5 (501.5)	476.3 (351.1)
Psychological well-being	26.0 (19.5)	18.9 (21.0)	11.3 (38.7)	24.3 (14.4)

There were no significant differences on change scores between the four-follow-up periods

Predictors

Results of the preparatory analyses indicated that fatigue at follow-up was significantly correlated with fatigue severity (CIS-fatigue, r = 0.354, P =0.003), psychological distress (SCL90-total, r = 0.398, P =0.001), somatic related attributions (CAL, r = 0.293, P =0.015) and insufficiency in social interactions (SSL-D, r = 0.316, P =0.009) at pretreatment. These variables were used as independent variables in the linear regression analysis. Table 4 summarise the regression analysis. Somatic attributions contributed almost significantly (P = 0.050) to fatigue severity at follow-up. Furthermore, a trend was seen for pretreatment fatigue severity (P =0.064) and psychological distress (P =0.074).

Table 4

Linear Regression (enter) to predict fatigue severity at follow-up (n=68)

	Dependent variable CIS-fatigue at follow-up	
Independent variables (pretreatment measurements)	Beta	p-value
Fatigue (CIS-fatigue)	.373	.064
Psychological distress (SCL90-total)	.087	.074
Dysfunctional cognitions (somatic-CAL)	1.803	.050
Social insufficiency (SSL-D)	.086	.422

CAL=Causal Attribution List; CIS=Checklist Individual Strength; SCL=Symptom CheckList; SSI=Social Support Inventory. Adjusted R^2 = 0.222

DISCUSSION

The results of the present study indicate that the positive results of CBT especially designed for fatigued cancer survivors were maintained at follow-up. Fatigue severity, functional impairment and psychological distress remained stable in patients who completed CBT after almost a mean follow-up period of 2 years. Furthermore, we could not find any difference between patients with a short- and a long-term follow-up. Therefore, even after 4 years the positive effect of CBT remained.

Patients who were allocated to the 6-month waiting list, were offered CBT directly after the second assessment. Therefore, the long-term effect was investigated with an uncontrolled design. Nevertheless, patients who were recovered at follow-up were comparable with a reference group of non-fatigued cancer survivors. Additionally, we investigated a small group of patients who did not accept CBT after the waiting list period. These patient did not improve over time on fatigue severity, functional impairment and psychological distress. Because of the small sample size, we should be careful in interpreting these results. Patients could have improved regardless of the followed treatment. It would increase the impact of our findings if future studies could prove the long-term superiority of CBT over natural course in fatigued cancer survivors. Another reason why it is difficult to draw firm conclusions is that follow-up data were not available of all patients who participated in the previous RCT.

The explorative regression analysis showed a trend that patients with more fatigue, higher psychological distress and stronger somatic attributions at pretreatment were more fatigued at the follow-up assessment. Fatigued cancer survivors have the tendency to attribute their fatigue complaints to the cancer itself and/or cancer treatment.[16] However, research on postcancer fatigue fails to show such relationship, which makes this a false attribution.[1-3,13,14] In the current model of postcancer fatigue, we assume that fatigue originates in the

diagnostic and treatment stage; however, there is no clear relationship between fatigue long after curative treatment and the initial disease and cancer treatment characteristics. Because somatic attributions still proved to contribute to fatigue at follow-up in this study, it seems that this aspect has received not enough attention during the CBT. If a patients continues to think that the cancer itself and/or cancer treatment is responsible for the experienced fatigue, the chance on recovery is lowered. It is possible that (further) education on postcancer fatigue for professionals working in cancer care, can increase the chance of improvement with CBT. Somatic attributions in fatigued cancer survivors can be reinforced by inaccurate information delivery about the cause of postcancer fatigue. Therefore, education should be aimed particularly on the model of precipitating and perpetuating factors.

Furthermore, indications were found that patients with high psychological distress, had a worse treatment outcome. Extreme high scores on the SCL90 total score (>200) are indicative for psychiatric comorbidity.[27] Five patients in our sample met this criterion. All five patients remained fatigued after CBT. When deleting these cases, the trend of psychological distress as contributor to fatigue at follow-up disappeared in the regression analysis (P = 0.776). Therefore, fatigued cancer survivors with high scores on psychological distress (probably indicative of psychiatric comorbidity) proved to have hardly any chance to improve with CBT for postcancer fatigue. However, results from the regression analyses should be regarded as exploratory and interpreted with caution.

Most studies on postcancer fatigue do not find an association between fatigue and cancer type.[1,2,34] In the current study we did not find a significant difference in fatigue severity at baseline between the different types of cancer (P =0.821). There was also no difference in effect of CBT on fatigue severity (P =0.983). However, our study was limited to patients with rather frequently diagnosed tumours. Therefore, replication is necessary in survivors with other cancer types.

The long term follow results of our study shows that the positive effects of CBT especially designed for postcancer fatigue are maintained even years after treatment. Until now, no other interventions have been published with comparable good results on postcancer fatigue on the long term.

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Appendix A

Patients were asked to complete questionnaires at the Expert Centre Chronic Fatigue of the Radboud University Nijmegen Medical Centre, pre-treatment and post-treatment

Questionnaires		Response format	Example questions
Fatigue Severity	Checklist Individual strength – Subscale Fatigue Severity (8 items)	7 point Likert scale * range 8 – 56 * a score of 35 indicates severe fatigue	* I feel tired * I am rested * Physically I feel exhausted
Functional impairment	Sickness Impact Profile – 8 • Home management (10 items) • Mobility (10 items) • Alertness behaviour (10 items) • Sleep/ Rest (7 items) • Ambulation (12 items) • Social interactions (20 items) • Work (8 items) • Recreation and pastimes (8 items)	patients can mark a box behind each statement. * a total score is calculated by addition the weights of items * range 0 - 5799	* I am not doing any of the house cleaning that I would usually do (hm) * I am not going out to visit people at all (si) * I walk shorter distances or stop to rest often (amb) * I react slowly to thing that are said (alert) * I have difficulty doing activities involving concentration and thinking (alert)
Psychological distress	Symptom Check List 90 (90 items) • Anxiety (10 items) • Agoraphobia (7 items) • Depression (16 items) • Somatisation (12 items) • Obsessive-compulsive behaviour (9 items) • Interpersonal sensitivity (18 items) • Hostility (6 items) • Sleep (3 items)	5 point Likert scale * range 90 – 450	During the past 7 days about how much were you distressed or bothered by: * Feeling fearful (anx) * Feeling of worthlessness (depr) * Numbness or tingling in parts of your body (som) * Feeling that people are unfriendly or dislike you (int.sens) * Nervousness or shakiness inside (anx)

Appendix A. continued

Questionnaires		Response format	Example
Coping with the experience of cancer	Impact of Event Scale • Intrusion (7 items) • Avoidance (8 items)	6-point Likert Scale * range 13 – 52	* I had dreams about it (intr) * I tried not to think about it (avoid) * I tried not to talk about it (avoid)
Fear of disease recurrence	Cancer Acceptance Scale	4-point Likert Scale * range 2 – 8	* I am worried about a tumour relapse * I am anxious about my health
Cognitions related to fatigue	Self Efficacy Scale (7 items)	4-point Likert Scale * range 7 – 28	* Whatever I do, I cannot change my complaints * I think I could positively influence my fatigue
	Causal Attribution List – subscale somatic attribution (4 items)	4-point Likert Scale * range 4 – 16	* Do you think your complaints have to do with the anti-cancer treatment?
Sleep disturbance	SIP-8 – subscale Sleep / Rest EORTC QLQ-C30 – subscale Insomnia (1 item)	 4-point Likert Scale	* I sleep more during the day * Have you had trouble sleeping?
Physical activity	EORTC QLQ-C30 – subscale physical functioning (5 items) EORTC QLQ-C30 – subscale role functioning (2 items) SIP-8 – Home management SIP-8 – Work SIP-8 – Recreation and Pastimes	Yes / No; range 5 – 10 4-point Likert; range 2 - 8 patients can mark a box behind each statement.	* Do you have trouble waling a long walk? * Has your physical condition interfered with your family life? * I am not doing any of the clothes washing * At work, I make more mistakes than usually * I am doing fewer community activities
Social functioning	Van Sonderen Social Support Inventory • SSL-I: amount of social support (34 items) • SSL-D: insufficiency of supporting interactions (34 items) • SSL-N: amount of negative interactions (7 items)	4-point Likert Scale * range 34 – 136 * range 34 – 135 * range 7 - 28	* Do you experience friendliness and sympathy in your contacts with other people? * Do you talk problems over with other people?

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Chapter
6

The experience of severe fatigue in long term survivors of stem cell transplantation

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ABSTRACT

Literature suggests that cancer survivors with more aggressive treatments are more at risk for postcancer fatigue. In this study, we investigated the prevalence of fatigue after completion of stem cell transplantation (SCT). Furthermore, we studied if medical variables are associated with fatigue and if the model of perpetuating factors of postcancer fatigue derived from previous studies in cancer survivors, without SCT, is applicable in SCT survivors.

Ninety-eight patients treated with autologous or allogeneic SCT filled out several questionnaires. Medical characteristics were obtained from the medical charts. All patients had to be in persistent complete remission for at least 1 year.

Thirty-five per cent of the patients experienced severe fatigue. The percentage of patients with severe fatigue remained stable during the years after transplantation. Several psychosocial factors, but no medical factors, were associated with fatigue. The model of perpetuating factors appeared to be applicable.

Contrary to cancer survivors without SCT, we found no decrease in fatigue complaints during the first years after SCT. Cognitive behaviour therapy (CBT) is a general form of psychotherapy directed at changing condition-related cognitions and behaviours. CBT especially designed for postcancer fatigue, aimed at perpetuating factors, can also be used to manage fatigue in cancer survivors treated with SCT.

INTRODUCTION

Stem cell transplantation (SCT) is a potentially curative treatment for various malignant diseases. Results are improving in the course of time and this has led to reduced morbidity and an increased life expectancy. Therefore, the number of patients surviving a SCT is growing during the last decennia. Because SCT is a highly aggressive and demanding medical intervention, significant concerns related to the long-term well-being of SCT survivors have been voiced. Generally speaking, most patients seemed to have reached an acceptable level of functioning during the first year after transplant.[1-5] However, there seems to be a subgroup of patients who experience ongoing problems following transplantation.[6] One of these problems is persistent fatigue.[3,4,7-9]

More research has been done in the field of postcancer fatigue in cancer survivors who were not treated with a SCT. Fatigue seems to be a problem for about a quarter of these patients long after curative treatment for cancer, with profound effects on quality of life.[10,11] Furthermore, it seems that patients with more aggressive treatments are more at risk for persistent fatigue.[12-14] However, little is known about the aetiology of persistent fatigue and at this moment, persistent fatigue is unexplainable by somatic factors. Fatigue seems to be elicited during the treatment phase, but later on there is no clear relationship between persistent fatigue and initial disease and cancer treatment variables.[10,11,15-17] Therefore, we think it is useful to make a distinction between precipitating factors and perpetuating factors of fatigue after cancer. The assumption is that cancer itself and/or cancer treatment may have triggered fatigue (precipitating factors), but other factors are responsible for the persistence of fatigue complaints (perpetuating factors).[13,18,19]

In a previous study we found cognitive behaviour therapy (CBT) especially designed for fatigued cancer survivors effective in reducing fatigue and impairment.[18] The rationale of this intervention was based on the model of precipitating and perpetuating factors. The intervention was focused on six perpetuating factors of post-cancer fatigue: (1) insufficient coping with the experience of cancer, (2) fear of disease recurrence,[13,16] (3) dysfunctional cognitions concerning fatigue,[19,20] (4) dysregulation of sleep,[10,11] (5) dysregulation of activity,[10,11,16] (6) low social support and negative social interactions.[19]

However, in this last study none of the patients included were treated with a SCT. Therefore we conducted this study, to answer to following research questions:

1. What is the prevalence of severe fatigue in patients after successful SCT?
2. Is the model of precipitating and perpetuating factors found in other cancer survivors also applicable in cancer survivors treated with a SCT?
   (a) Is there a relationship between past and/or current medical characteristics and fatigue severity?
   (b) Are the same perpetuating factors, that play a role in persistent fatigue after curation for solid tumours, involved in fatigue after successful SCT?

METHODS

Patients

This study involved all patients who were treated at the age of eighteen or older with an autologous or an allogeneic SCT between 1981 and 2003 at the Department of Haematology of the Radboud University Nijmegen Medical Centre. Diagnoses included were acute myeloid or lymphatic leukaemia in first complete remission (CR1), chronic myeloid leukaemia in first chronic phase (CP1), non-Hodgkin's lymphoma in CR1. The conditioning regime included total body irradiation. All patients had to be in persistent complete remission for at least 1 year after SCT.

Graft versus host disease (GVHD) is a frequent complication of an allogeneic SCT in which the engrafted donor cells attack the patient's organs and tissue. Acute GVHD was classified as grade I-IV according to Glucksberg et al.[21] and chronic GVHD as limited or extensive following the Shulman criteria.[22] Patients with severe GVHD after allogeneic SCT (i.e. grade III and IV, acute GVHD or extensive chronic GVHD) may experience many acute and chronic medical problems, are treated with several drugs and other therapies, which may influence an unstable clinical balance and may provoke fatigue. Therefore, these patients were excluded from this study.

Anaemia is a well known physical factor that can cause fatigue. Therefore, all patients with a haemoglobin (Hb) concentration of 10 g/dl and lower were not eligible for this study.

Recruitment procedure

All patients that underwent SCT since 1981 could be identified by a database that was set up at the research centre of the Department of Haematology. Inclusion and exclusion criteria were checked according to the data of the most recent clinical check-up. All patients were sent a package of questionnaires and an informed consent form, together with a letter of their physician, explaining the purpose of the study. Patients were asked to fill out and send back the questionnaires together with the informed consent to the Expert Centre Chronic Fatigue. The ethics committee of the hospital approved the study.

Demographic and medical characteristics

The demographic characteristics like age, gender, marital status, education and employment were gathered by self-report.

Characteristics of the medical history of patients were obtained from the medical chart and consisted of type of diagnosis, type of transplantation, time since transplantation, grade of GVHD, duration of hospitalization during SCT and number of hospitalizations for complications after SCT. Additionally, we acquired information about current medical characteristics from the medical chart, like comorbidity, medication use, Hb concentration and body mass index (BMI) at time of participation in the study.

Questionnaires

Fatigue severity was measured by the 'fatigue severity' subscale (CIS-fatigue) of the Checklist Individual Strength (CIS),[23-26] consisting of 8 items designed to measure fatigue severity during the previous 2 weeks. Each item was scored on a 7-point Likert scale. High scores indicated a high level of fatigue. A CIS-fatigue score equal or higher 35 was used to identify severe fatigue.[19,23] The questionnaire has been used in cancer survivors,[13,18,19,27,28] showed good reliability, discriminative validity and sensitivity to change.[18,22,29,30]

Coping with the experience of cancer was measured with the Dutch version of the Impact of Event Scale. This 15 item scale consists of two subscales (intrusion: 7 items and avoidance: 8 items) on a 6-point Likert Scale and measures the extent to which a subject is currently occupied with the coping process after a major event (in this study the diagnose and treatment for cancer). High scores are indicative for intrusively experienced ideas, images, feelings or bad dreams about the event and avoidance of unpleasant feelings or memories of the event.[31-33]

Fear of disease recurrence was measured by two items of the Cancer Acceptance Scale (CAS) scored on a 4-point Likert Scale.[13] The items are (1) I am worried about a tumour relapse, (2) I am anxious about my health. High scores are indicative of a high level of fear.

Cognitions related to fatigue. Self-efficacy was measured with the Self-Efficacy Scale (SES), consisting of five questions, which measured sense of control in relation to fatigue complaints.[13,19,30,34] Cancer-related attributions with regard to fatigue complaints were measured with the Causal Attribution List (CAL),[19] consisting of 4 items (cancer, SCT, radiation therapy, chemotherapy). For each item, patients were asked to indicate their opinion regarding the cause of their fatigue complaints on a 4-point scale (1 = not at all applicable to 4 = very applicable). Internal reliability of this questionnaire was good, with a Cronbach's alpha coefficient 0.95.

Sleep disturbances was measured with the sleep/rest subscale of the Sickness Impact Profile (SIP-8),[35,36] and the insomnia subscale of the Quality of Life Questionnaire-C30 (QLQ-C30),[37] with higher values reflecting an increased presence of symptoms.

Physical activity was measured with the physical functioning and role functioning subscale of the QLQ-C30, with higher scores representing a better level of physical/role functioning. Furthermore, physical activity was measured with the subscales home management, work, and recreation and pastimes from the SIP, with high scores reflecting more functional impairments

Social functioning was measured with the social functioning subscale of the QLQ-C30 and the social interaction subscale of the SIP.

Statistical analysis

Data analyses were performed using Statistical Package for Social Science (SPSS; version 12.1). Descriptive statistics were used for description of the sample. Chi-square, independent samples *t*-tests and analyses of variance general linear model (GLM) have been performed to test differences between groups. Pearson correlations were used to investigate the association between fatigue severity (CIS-fatigue) and medical characteristics. Furthermore,

Pearson correlations between fatigue severity and the six perpetuating factors were used as preparatory analyses to examine the contribution of these factors to fatigue severity. Those measures that correlated highest with the fatigue severity score were used as independent variables in a linear regression analyses (enter-method). Correlations between the six perpetuating factors were tested on multicollinearity ($r < 0.9$).

Table 1

Demographic and medical characteristics (n=98)

	cancer survivors treated with a SCT
Age	45.3 (10.9)
	range 19.0 – 67.3
Gender	
male	57 (58%)
female	41 (42%)
Marital status	
married / cohabiting	77 (79%)
unmarried	17 (17%)
divorced	2 (2%)
widowed	2 (2%)
Higher education (≥ 12 years)	34 (35%)
Employment	
work outside home	54 (54%)
study	6 (6%)
disablement insurance act	26 (26%)
partial disablement insurance act	7 (7%)
sick leave	3 (3%)
no work	4 (4%)
Primary diagnosis	
acute leukaemia	70 (72%)
chronic leukaemia	21 (21%)
lymphoma	7 (7%)
Transplantation	
allogeneic	79 (81%)
autologous	19 (19%)
Time since transplantation (years)	9.3 (5.5)
	range 1.0 – 21.5

Abbreviation: SCT = stem cell transplantation

RESULTS

Response

Hundred twenty-four patients met the eligibility criteria and were asked to participate in this study. Ultimately, the questionnaires were filled out and returned by 98 patients (79%). Reasons for non-participation (n=26) were: too emotional to participate (n=6), did not feel like taking part because they had no complaints at the moment (n=3), bad concentration and therefore not able to fill out the questionnaires (n=1) and unknown (n=16). Non-participants did not differ from the participants with regard to demographic characteristics (data not shown), except for age. Non-participants were significant younger compared with the participants (40.5 (s.d.=8.9) vs 45.3 (s.d.=10.8); *P* =0.038). Information about demographic, disease and treatment characteristics of the participants are listed in Table 1.

Research questions

What is the prevalence of severe fatigue in patients after successful SCT?

The mean CIS-fatigue severity score of the total sample was 26.9 (s.d.=14.0). Thirty-four patients (35%) met the cutoff criteria for severe fatigue (CIS-fatigue ≥ 35), whereas an additional 12 patients (12%) had heightened fatigue scores (CIS-fatigue between 27 and 35). There were no differences in fatigue severity between male (27.6, s.d.=14.0) and female cancer survivors (25.9, s.d.=14.2, *P* =0.558), younger (24.7, s.d.=12.6) and older survivors (29.0, s.d.=15.1, *P* =0.125) (median 45.7 years), married/cohabiting (27.0, s.d.=14.0) and unmarried/divorced/widowed survivors (26.5, s.d.=14.3, *P* =0.880) and survivors with lower and higher education, respectively 27.7 (s.d.=14.9) and 26.0 (s.d.=12.2) (*P* =0.552)

Is there a relationship between past and/or current medical characteristics and fatigue severity?

Medical History

Diagnose and transplantation: No significant difference was seen in mean fatigue score between patients who were diagnosed with acute leukaemia, chronic leukaemia or lymphoma and between patients who were treated with allogeneic transplantation or autologous transplantation (Table 2).

Time since transplantation: To investigate the relationship between fatigue severity and time since transplantation, the total sample has been divided into four groups: patients who were treated with a SCT between 1 and 5 years ago (n=32), between 5 and 10 years ago (n=19), between 10 and 15 years ago (n=30) and more than 15 years ago (n=17). Mean fatigue scores and percentages of severe fatigue for these four groups are shown in Table 3. No statistically significant differences were found in mean fatigue scores and in percentages of severe fatigue. In addition, the correlation between the CIS-fatigue score and time since transplantation proved to be very low and non-significant (Figure 1).

GVHD: From the medical charts, we obtained for each patient the maximum GVHD grade after transplantation. As described in the Methods section, patients with severe GVHD were excluded. There were no differences in the mean fatigue score between patients who experienced no GVHD after transplantation, or who suffered from grade I or grade II.

Table 2

The association of fatigue with medical characteristics (medical charts)

	n	Mean CIS-fatigue (s.d.)	P-value
Diagnosis			
acute leukaemia	70	27.3 (13.9)	
chronic leukaemia	21	27.8 (14.2)	0.733
lymphoma	7	22.9 (16.0)	
Transplantation			
allogeneic	79	27.6 (13.9)	0.285
autologous	19	23.8 (14.4)	
Graft vs Host Disease			
absent	36	26.8 (13.8)	
grade I	34	29.4 (14.5)	0.562
grade II	9	24.4 (12.4)	
Duration of hospitalization SCT			
≤ 5 weeks	51	27.3 (13.4)	0.471
> 5 weeks	47	26.5 (14.8)	
Hospitalizations after SCT for complications			
0 hospitalizations	55	24.7 (12.5)	
1 hospitalization	26	28.9 (15.9)	0.181
> 1 hospitalization (range 2 – 7)	17	31.1 (15.2)	
Co morbidity at the time of participation			
(7 missings)			
yes	38	31.7 (14.9)	0.018
no	53	24.7 (12.7)	
Medication at the time of participation			
no medication	51	25.8 (13.5)	
medication but no antibiotics and/or beta blocker	17	29.9 (14.8)	0.174
antibiotics	11	35.8 (14.9)	
beta blocker	9	26.6 (13.7)	
Hb concentration at the time of participation			
= normal concentration	78	26.7 (14.1)	0.814
< normal concentration	20	27.6 (14.0)	
BMI at the time of participation			
normal BMI	53	25.0 (12.6)	0.156
> or < normal BMI	45	29.1 (15.4)	

Abbreviations: BMI = body mass index; CIS= Checklist Individual Strength; SCT= stem cell transplantation

Table 3

Mean CIS-fatigue scores and percentages of fatigue for patients who finished SCT within a different time period

	n	Mean CIS-fatigue (s.d.)*	% of severe fatigue **
Time since transplantation			
between 1 and 5 years ago	32	27.5 (12.3)	41
between 5 and 10 years ago	19	28.4 (14.2)	32
between 10 and 15 years ago	30	25.4 (14.5)	30
more than 15 years ago	17	26.7 (16.9)	35
total	98		

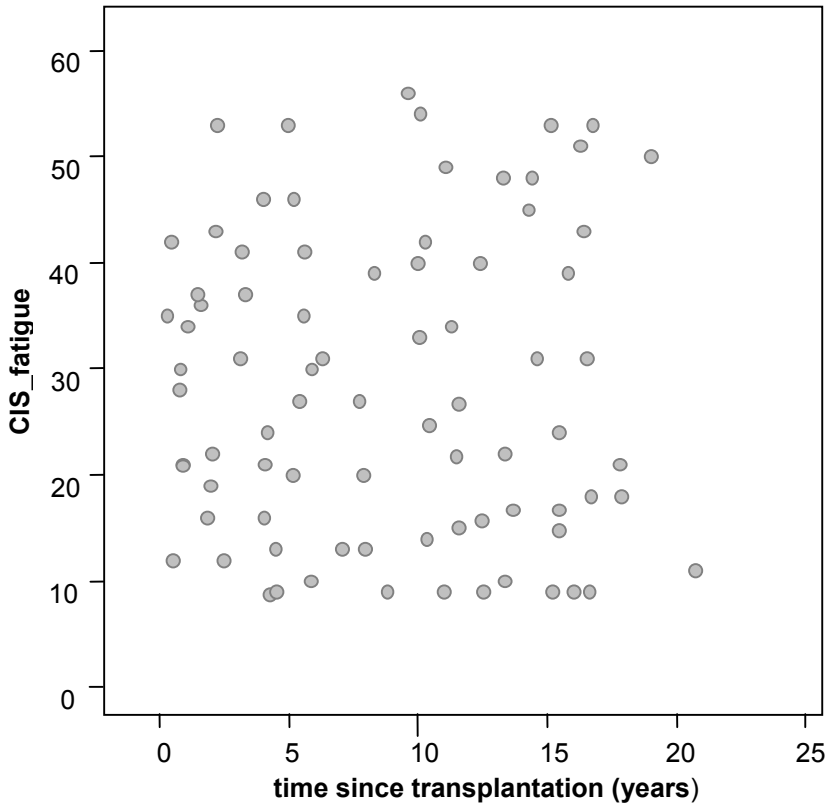
Abbreviations: CIS = Checklist Individual Strength; GLM = general linear model; SCT = stem cell transplantation.

* analyses of variance (GLM), P=0..901

** chi-square, P =0.832

Figure 1

The association of time since treatment with fatigue severity (CIS-fatigue); *r* = - 0.080, *P* = 0.434



Hospitalization and complications: To analyse the association between post-cancer fatigue and the duration of hospitalization during the transplantation, the group was divided into two groups based on the median time of hospitalization (5 weeks). No difference in mean fatigue scores of the two groups was found. Furthermore, the correlation between the fatigue score and total days of hospitalization was nonsignificant (r = 0.046, P =0.652).
Owing to complications, 44% of the patients (n=43) had been re-admitted after the SCT (n=5 abdominal pain; n=9 nausea/vomiting/diarrhoea; n=21 fever; n=9 respiratory insufficiency/ failure, n=7 Herpes Zoster; n=11 other complications). No difference was found between the mean fatigue score of patients who had no complications after transplantation, patient who had been hospitalized once, and patients who had been hospitalized more than one time. Additionally, post-treatment fatigue was not related to the number of hospitalizations and to the number of days of hospitalization due to complications (respectively, r = 0.128, P = 0.208; r = 0.043 P =0.676).

Current medical characteristics

Comorbidity: Patients with comorbidity at the time of participation (n=38) were significantly more fatigued than patients without comorbidity (n=53; P = 0.018) (Table 2). The group of patients with comorbidity was divided in three subgroups:

(a) comorbidity that possibly can cause fatigue (n=10; four hepatitis C, four hypertension with use of a beta blocker, two recurrent respiratory infections);
(b) comorbidity possibly caused by the SCT (n=13, six iron overload, five good controlled hypothyroidism (normal levels of thyroid stimulating hormone (TSH) and Free T4 at the time of participation in the study) , two postherpetic neuralgia);
(c) remaining comorbidities (n=15, five diabetes mellitus, six hypercholesterolemia, two epilepsy, one haematuria, one gout).

Within these three groups, mean fatigue scores were, respectively, 33.9 (s.d.=14.7), 33.2 (s.d.=15.0) and 28.9 (s.d.=15.5) and were not significantly different (P =0.662).
Medication use: We investigated medication use by patients at the moment of participation in the study. There was no significant difference between postcancer fatigue in patients

(a) without medication (n=51)
(b) with antibiotics (n=11),
(c) with beta blocker (n=9),
(d) with other medication (n=17).

Hb concentration: To test the association between postcancer fatigue and the Hb concentration at the moment of participation, two subgroups were identified based on the normal distribution of Hb concentration of the WHO.[38,39] No difference was seen in the mean fatigue score between patients with a normal Hb concentration (n=78: men 13.6 – 17.2 g/dl ; women 12 – 15 g/dl) and patients with a low Hb concentration (n=20: men < 13.6 g/dl ; women < 12 g/dl). Additionally, the correlation between fatigue severity and Hb concentration was non-significant (r = -0.024, P =0.813)
BMI: Based on WHO standards, BMI was categorized as underweight (BMI < 18.5), normal weight (BMI = 18.5-24.9), overweight (BMI = 25-29.9) and obese (BMI ≥ 30).[40] To analyse

the association between post-cancer fatigue and the weight of patients at the time of participation, the total group was divided into two groups. Patients with a normal weight (n=53) and patients with underweight, overweight and obese patients (n=43).There was no difference in fatigue severity between these two groups. Additionally, the correlation between fatigue severity and BMI was low and non-significant (r = 0.098, P =0.338).

Are the same perpetuating factors, that play a role in persistent fatigue after curation for solid tumours, involved in fatigue after successful SCT?

In Table 4, comparisons have been made between fatigued cancer survivors (CIS ≥ 35) and non-fatigued cancer survivors (CIS < 35) with regard to the six perpetuating factors.

Table 4

Comparisons between severely fatigued cancer survivors (CIS-fatigue ≥ 35) and non-fatigued cancer survivors (CIS-fatigue < 35) long after SCT

	Nonfatigued n=64	Severe fatigued n=34	p-value	Correlation: CIS_fatigue
Coping with the experience of cancer	7.6 (10.6)	16.5 (16.1)	0.004	0.380**
Impact of event scale				
Fear of disease recurrence				
Cancer Acceptance Scale	12.7 (3.3)	16.8 (4.9)	0.000	0 .454**
Dysfunctional cognitions				
Self-Efficacy (SEQ)	22.3 (3.6)	17.4 (3.3)	0.000	- 0.639**
Cancer related attributions (CAL)	11.1 (4.0)	14.7 (1.9)	0.000	0.599**
Sleep disturbances				
Sleep / Rest (SIP)	20.5 (36.9)	85.1 (76.4)	0.000	0.550**
Insomnia (QLQ-C30)	13.0 (21.1)	29.4 (35.5)	0.021	0.407**
Dysregulation of physical activity				
Home management (SIP)	32.0 (66.9)	93.3 (70.6)	0.000	0.514**
Recreation and pastimes (SIP)	30.1 (53.6)	91.7 (71.7)	0.000	0.518**
Work (SIP)	61.7 (125.0)	149.5 (157.0)	0.001	0.358**
Physical functioning (QLQ-C30)	91.8 (13.7)	71.8 (13.7)	0.000	- 0.614**
Role functioning (QLQ-C30)	94.5 (11.2)	57.8 (30.5)	0.000	- 0.675**
Social functioning				
Social functioning (QLQ-C30)	90.4 (18.3)	71.1 (25.4)	0.000	- 0.472**
Social interactions (SIP)	52.1 (92.7)	150.3 (136.1)	0.000	0.544**

Abbreviations: CAL = Causal Attribution List; CIS = Checklist Individual Strength; QLQ-C30 = Quality of Life Questionnaire-C30; SES = Self-Efficacy Scale ; SIP = Sickness Impact Profile.

** p < 0.01

Results were consistent; patients experiencing severe fatigue had more difficulties in coping with the experience of cancer, more fear of disease recurrence, more dysfunctional cognitions, sleep disturbances, less physical activity and low social functioning. Furthermore, all measurements correlated significantly with the fatigue severity score.
The highest correlations were used as independent variables in a linear regression analyses. There was no multicollinearity between the six perpetuating factors entered in the regression analyses. Results of the regression analyses (Table 5) indicated that insufficient coping with the experience of cancer, fear of disease recurrence, low self-efficacy, sleep disturbances and low role functioning contributed significantly to fatigue severity. In total, 68% of the variance of fatigue severity was explained by the six perpetuating factors.

Table 5

Linear Regression (enter) to predict fatigue severity

Independent variables	Dependent variable: CIS-fatigue severity	
	Beta	P-value
Coping with the experience of cancer (IES)	0.172	0.016
Fear of disease recurrence (CAS)	0.175	0.034
Dysfunctional cognitions (SES)	- 0.243	0.002
Sleep disturbances (SIP- sleep / rest)	0.215	0.007
Dysregulation of physical activity (QLQ-C30- role functioning)	- 0.376	0.000
Social functioning (SIP – social interactions)	0.005	0.958
Total R^2 (adjusted)	0.679	

Abbreviations: CIS = Checklist Individual Strength; IES = Impact of Event Scale; CAS = Cancer Acceptance Scale; SES = Self-Efficacy Scale; SIP = Sickness Impact Profile; QLQ-C30 = Quality of Life Questionnaire-C30;

DISCUSSION

In this study, 35% of a group of patients experienced severe fatigue long after finishing SCT (mean = 9.3 years). The percentage cancer survivors with severe fatigue remained stable during the years after transplantation, even after more than 15 years.
Cross-sectional studies investigating the prevalence of fatigue (all not including patients who were treated with a SCT) showed that the percentage of cancer survivors with severe fatigue decreases during the years after treatment: this was 38% after 2.5 years,[19] 30% after 3 year,[41] 37% after 4 years,[42] 26% after 12 years,[43] 16% after 12 years.[44] The course of fatigue was also investigated in four longitudinal studies, measuring the prevalence of fatigue in cancer survivors two times at different time points. Bower et al.[12] found a decrease of 35% (3.5 years after treatment) to 21% (6.3 years after treatment) and Servaes et al.[27] found a decrease of 38% (2.5 years after treatment) to 23% (4.5 years after treatment). In the two

other longitudinal studies the percentage of patients with severe fatigue remained equal, 28% (6 years after treatment) to 26% (8 years after treatment).[12] Hjermstad et al.[15] investigated disease-free cancer patients 16 years and 24 years after treatment for cancer. In this longitudinal study the percentage of fatigued cancer survivors was respectively, 25% to 28%. These results seem to suggest that fatigue complaints continue to decrease during the first 3–4 years after curative treatment and remains a persistent problem for about a quarter of the cancer survivors. However, in the current study we investigated the course of fatigue, and we found no decrease of fatigue even up to 15 years after completing SCT. So it seems that in patients after a SCT the percentage of fatigue remains high. This finding is in agreement with the assumption that patients with more aggressive treatments are more at risk for persistent fatigue.[12-14, 45]

The respondent sample consist of almost 80% of the patients who were treated for acute leukemia in CR1, non-Hodgkin lymphoma in CR1 and chronic leukemia's in CP1. The population of (A)SCT patients from the Department of Haematology of the Radboud University Nijmegen Medical Centre does not differ from other Dutch and European centres for (A)SCT.[46] Our study involved patients who were 18 years or older at the time of (A)SCT and who had to be in persistent CR for at least 1 year after (A)SCT. Patients with acute GVHD grade III or IV and/or extensive GVHD were excluded and this was also true for patients with a Hb concentration of 10 g/dl at the time of inclusion. This is given in the Methods section. The exclusion of patients with severe acute or sever chronic GVHD and the exclusion of patients with a haemoglobin level of less than 10.0 g/dl may result in a respondent sample with relatively more patients who are less prone to fatigue than the general population after (A)SCT. This means that the impressive number of patients that experienced severe fatigue will be even higher in a general (A)SCT population.

We found no associations with fatigue severity and characteristics of the medical history. Owing to shorter time in protective isolation, fewer treatment-related side effects and no risk of GVHD, the assumption has been uttered that patients with allogeneic SCT have more late effects than patients with a autologous SCT. However, the literature is ambiguous on this point.[1, 47-50] Concerning fatigue, Hjermstad et al.[1] also found no differences between the two types of transplantation. However, similar to their studies, the small number of patients in our autologous group implies that chance findings cannot be ruled out.

Because in this study the focus was on fatigue with no somatic cause, we excluded beforehand patients with medical problems that could possible cause fatigue, like GVHD-grade of III and IV and Hb concentration of 10 g/dl and lower. This could be the reason why no relation between fatigue severity and somatic characteristics were found.

Thirty-eight of the 98 patients (39%) had a medical comorbidity besides persistent fatigue. Patients with a medical comorbidity scored higher on fatigue severity compared with patients without a medical comorbidity. However, no differences were found in fatigue severity between the different kinds of medical comorbidity (comorbidity that possibly can cause fatigue, comorbidity possibly caused by the SCT and the remaining comorbidities). Because of the relatively small numbers of patients in the different groups, an actual difference cannot be ruled out fully.

The model of perpetuating factors derived from previous studies in cancer survivors, not undergoing transplantation, appears to be applicable in SCT cancer survivors as well. Persistent fatigue was well predicted by the supposed perpetuating factors: insufficient coping with the experience of cancer, fear of disease recurrence, dysfunctional cognitions concerning fatigue, dysregulation of sleep and dysregulation of activity. In total, 68% of the variance of fatigue severity was explained by the six factors. Only impairment in social functioning did not contribute significantly to fatigue severity. Servaes et al.[19] demonstrated that severely fatigued cancer survivors experienced more negative interactions and insufficiency of supporting interactions than those who were not fatigued. No significant difference was found in the frequency of supporting interactions. So, it seems that the experienced insufficiency and negative interactions have more influence on fatigue severity than impairment in social functioning as measured in this study. Additionally, these results suggests that in the absence of clear medical causes, the CBT especially designed for fatigued cancer survivors after conservative treatment, can also be used in the management of fatigue after SCT.

The strength of this paper is characterized by an underlying theoretical perspective of postcancer fatigue, the model of precipitating and perpetuating factors. However, it could be argued that the factors do not perpetuate fatigue, but represent, for example, psychosocial consequences of stress. Furthermore, the study is cross-sectional and limits our ability to draw conclusions about the course of post-cancer fatigue in patients following a SCT. For definitive conclusions, a longitudinal design would be more appropriate.

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Chapter
7

Pictorial Representation of Self and Illness Measure (PRISM) in patients suffering from severe fatigue: a useful tool in research and clinical practice

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ABSTRACT

In this study we want to get a better understanding of suffering associated with fatigue by using a simple, graphic instrument: the Pictorial Representation of Illness Measure (PRISM). In this study four research questions were investigated:

(1) Is suffering, as measured with the PRISM, a separate dimension of chronic fatigue?
(2) Is there a difference in suffering between patient groups experiencing chronic fatigue?
(3) Is it possible to discriminate within a patient between the suffering due to an illness and the suffering due to fatigue?
(4) Does suffering diminish following a treatment for chronic fatigue?

Three samples, 60 chronic fatigue syndrome patients, 82 cancer survivors experiencing severe fatigue complaints and 68 fatigued patients with various neuromuscular disorders were assessed on dimensions of fatigue, disease specific characteristics and with the PRISM.

Correlations found with dimensions of fatigue were not to the extent that the PRISM could be seen as a parallel test. Furthermore, the three patient groups displayed different profiles in the correlations of the PRISM with the dimensions of fatigue. Discrimination of suffering due to fatigue or due to cancer was possible in the sample of the fatigued cancer survivors. Finally, suffering diminished following successful therapy of chronic fatigue.

The present study offers encouraging data for the use of the PRISM as a tool in fatigue research and clinical practice.

INTRODUCTION

Fatigue is a complaint experienced differently among persons and occurs both in health and in illness. In healthy individuals fatigue seems to be a protective, sometimes even a pleasant regulatory response to physical or psychological stress. For people with a disease chronic fatigue becomes a disabling and life- and activity limiting experience.[1-5] Therefore, fatigue is a concept with several modes of expression. Our research group has focused on the study of chronic fatigue for years now and has identified nine dimensions of chronic fatigue, namely fatigue severity, functional impairment associated with the fatigue, the level of physical activity, psychological distress, sleep disturbances, concentration problems, social functioning and social support, self-efficacy and causal attributions.[1,2] These dimensions appear to be relatively independent, meaning that each dimension uniquely contributes to the experience of fatigue. Based on these dimensions a multidimensional assessment method has been developed. However, since fatigue has such a profound effect on many aspects of quality of life, it would also be valuable to know which impact fatigue has in a patients' life, the suffering due to fatigue. This is a concept that is not included in the present multidimensional assessment method.

Suffering is a multi-faceted experience which reflects the patients' perception and appraisal of his illness in everyday life.[6] It implies that what causes suffering in one patient may not do so in another, whereas they have symptoms in the same degree. For one patient an illness may not be seen as the most important aspect of his life. If there are other aspects in his life which are more important to him than his illness, these are likely to moderate the impact of the illness, and so the suffering. Because suffering is a complex and elusive symptom without a precise definition, it is difficult to assess.

However, recently a novel instrument was developed by Büchi et al. that aims to assess the perception of suffering caused by an illness.[7] This instrument is called the Pictorial Representation of Illness Measure (PRISM). It measures in a simple, graphic way the burden of suffering due to illness or due to a symptom. To date five studies have been carried out supporting validity and reliability of the PRISM.[7-10] The first study showed that the PRISM task was simple to administer and well accepted by patients. Furthermore, significant correlations were found with a variety of physical and psychological measurements.[7] The usefulness of the PRISM in the clinical practice was demonstrated by discussing three case vignettes.[8] The third study presented supporting evidence of reliability, validity and sensitivity to change in 714 patients with a variety of chronic physical illnesses.[9] Furthermore, validity aspects were provided of the PRISM used in a self-administered paper-pencil format within a sample of 333 patients suffering from vitiligo.[10]

In this study we want to get a better understanding of suffering associated with fatigue, in three different patients groups; patients with chronic fatigue syndrome, fatigued cancer survivors and fatigued and non-fatigued patients with a neuromuscular disorder. Four specific research questions were investigated:

1. Is suffering, as measured with the PRISM, a separate dimension of chronic fatigue?
2. Is there a difference in suffering between the three patient groups experiencing chronic fatigue?

3. Is it possible to discriminate within a patient between the suffering due to an illness and the suffering due to fatigue?
4. Does suffering diminish following the treatment of chronic fatigue?

METHODS

Patients

Patients in this study were all patients participating in scientific studies conducted by the Expert Centre Chronic Fatigue of the Radboud University Nijmegen Medical Centre. For a more detail description of the patients groups we refer to the original studies

Sixty patients with *chronic fatigue syndrome* (CFS) were included in this study (mean age 36.1 (s.d.=12.1); female 67%). Chronic fatigue syndrome is characterised by persistent or relapsing unexplained fatigue, of new or definite onset and lasting for at least six months. The fatigue is not the result of an organic disease or ongoing exertion, rest does not alleviate it, and there is substantial limitation of occupational, educational, social and personal activities as a result of the fatigue.[11] All 60 patients were treated with cognitive behaviour therapy (CBT) at our department.[12] Multidimensional assessments at pre- and post treatment were available (a period of 6 months).

The second patient group consisted of 82 fatigued *cancer survivors* (mean age 44.7 (s.d.=10.2; female 48%). Fatigue is a problem for many cancer patients during the active phase of their disease. After successful treatment of the cancer fatigue complaints return to a normal level in most patients within several months. However, in at least 30-40% of the survivors severe fatigue persists even years after successful cancer treatment has ended and has profound negative effects on self-care abilities and quality of life.[3,13] The 82 patients described in this paper participated in a randomised controlled trial studying the effectiveness of CBT especially designed to reduce chronic fatigue in cancer survivors.[14] Patients were randomly allocated to the intervention condition (n=41) and the waiting list condition (n=41). Multidimensional assessments were made pre- and post treatment (a period of 6 months).

The third sample consisted of 68 fatigued patients who participated in a study assessing the prevalence of fatigue in various *neuromuscular disorders* (mean age 42.7 (s.d.=10.0); female 43%), namely: facioscapulohumeral muscular dystrophy (FSHD), a myogenic disorder; adult-onset myotonic dystrophy (MD), a multisystem disorder; and hereditary motor and sensory neuropathy type I (HMSN), a neurogenic disorder.[15] Multidimensional assessments were made, at baseline and after a period of 18 months.[5]

Materials

The PRISM task[7]: Patients were shown a A4 shaped paper with a yellow fixed disk at the bottom-right hand corner (diameter 6 cm) and were asked to imagine that the paper represents his/her life as it is at the moment. The disk represents the subjects' self. A red detachable disk (diameter 4 cm) was used to represent the fatigue. Subjects were asked : 'where would you put fatigue to reflect its importance in your life at this moment?'. In the sample of the fatigued cancer survivors and the patients with a neuromuscular disorder the PRISM+ was used, meaning that a second blue detachable disk (diameter 4 cm) was used to

represent the illness. Subjects were asked: 'where would you put cancer/neuromuscular disorder to reflect its importance in your life at the moment?'. The PRISM was quantified in measuring the distance between the disks centres and the centre of the self disk, called the Self-Illness Separation (SIS). A smaller distance indicates a greater burden of suffering. The SIS values, called SIS-fatigue and SIS-Illness, ranged from 0 to 27 cm. In the sample of the fatigued cancer survivors the PRISM+ was also used in a qualitative way. After putting the disks on the paper patients were asked to explain why they put the 'fatigue disk' and 'cancer disk' at the position where they had done. A note of these comments was made by the researcher (MG).

Questionnaires: Elements of eight dimensions of fatigue were measured with valid and reliable measures. The dimension 'causal attribution' was omitted in this study because different questionnaires were used in the three samples, making comparisons between the three groups impossible.

Fatigue severity was measured by a subscale of the Checklist Individual Strength (CIS-fatigue) consisting of 8 items. Each item was scored on a 7-point Likert scale. High scores indicated a high level of fatigue severity. Based on research with CFS patients, a score of 35 or higher on the subscale fatigue severity indicated severe feelings of fatigue.[1,16-18] The questionnaire has also been used in cancer survivors[3,13,14] and patients with chronic diseases.[2,5]

Functional impairment was measured with the 'physical functioning' subscale of the SF-36, consisting of 10 items. Each item was scored on a 3-point Likert scale. High scores indicated good physical functioning.[19-21]

Physical activity was measured with the subscale ambulation from the Sickness Impact Profile-8 (SIP-8), consisting of 12 items. High scores indicated more limitations in the domain of ambulation.[22-24]

Psychological distress was measured with the total score of the Symptom Checklist (SCL-90), consisting of 90 items. Each item was scored on a 5-point Likert scale. High scores indicated a high level of psychological distress.[25]

Sleep disturbance was measured with the sleep-rest subscale of the SIP-8, consisting of 7 items. High scores indicated more sleep disturbances.

Experienced *concentration problems* were measured with the concentration subscale of the CIS, consisting of 5 items. A high score indicated a high level of problems with regard to concentration.

Impairment of *social functioning* was measured with the social interaction subscale of the SIP-8, consisting of 20 items. High scores indicated more problems in social functioning.

Self Efficacy was measured with the Self Efficacy Scale (SES). The SES consisted of 7 questions that measure sense of control with respect to fatigue complaints. High scores reflected more sense of control.[4]

Disease specific measures for fatigued cancer survivors

Stress response symptoms were measured with the Dutch version of the Impact of Event Scale. This 15 item scale consists of two subscales (intrusion; 7 items and avoidance: 8 items) on a 6-point Likert Scale and measures the extent to which a subject is currently occupied with the coping process after a major event (in this study the diagnose and treatment for cancer). High scores are indicative for intrusively experienced ideas, images, feelings or bad dreams about the event and avoidance of unpleasant feelings or memories of the event.[26-28]

Acceptance of the experience of cancer is measured by the Cancer Acceptance Scale (CAS), a questionnaire of 7 statements on a 4-point Likert Scale (range; not at all applicable to very applicable). High scores indicated low acceptance.[29]

Furthermore two *treatment characteristics* were defined; time since cancer treatment has ended and duration of treatment.

Disease specific measures for patients with neuromuscular disorders

Disease severity / muscle strength: Disease severity was determined using the Medical Research Council (MRC) grading scale (MRC; 0 – 5) investigating the muscle strength of the shoulder abductors, grip force, foot extensors and knee extensors.[30] In order to characterise the patients, these eight values (both left and right) were averaged. High scores indicated muscle strength.

Statistical analysis

Data analysis was performed using SPSS (version 12.1). Because data were not normally distributed non-parametric analyses were used. Spearman rho's correlations were used to assess bivariate correlations with the SIS fatigue / illness. Kruskal Wallis Test, Mann-Whitney U-test and Chi-square were performed testing the differences between the samples. Wilcoxon Signed Ranks Test for matched pairs was used in comparing values of the SIS fatigue and SIS illness within the three samples at T1 and T2. All analysis were tested two-tailed.

RESULTS

Is suffering, as measured with the PRISM, a separate dimension of chronic fatigue?

Table 1 shows negative significant correlations of the SIS fatigue and the severity of fatigue (CIS-fatigue). Patients who experienced less fatigue, positioned the fatigue disk further away of the self disk. For the other eight dimensions overall low and moderate correlations were found with the SIS fatigue. Furthermore, significant correlations were found in investigating the SIS illness and disease specific measures in fatigued cancer survivors and patients with a neuromuscular disorder (Table 2). None of the correlations were to the extent that the PRISM could be seen as a parallel test.

Table 1

Bivariate spearman's rho correlations at T1 between the SIS fatigue and eight dimensions of fatigue.

Dimensions of fatigue	Chronic fatigue syndrome (n=60)		Fatigued cancer survivors (n=82)		Fatigued patients with neuromuscular disorders (n=68)	
	Rho	p-value*	Rho	p-value*	Rho	p-value*
experienced fatigue	- 0.324	0.012	- 0.319	0.003	- 0.422	0.000
functional impairment	0.174	ns	0.149	ns	0.119	ns
physical activity	0.050	ns	- 0.095	ns	- 0.274	0.033
psychological distress	- 0.240	ns	- 0.170	ns	- 0.300	0.016
sleep disturbances	- 0.163	ns	- 0.008	ns	- 0.133	ns
concentration problems	- 0.267	0.039	- 0.166	ns	- 0.337	0.001
impairment of social functioning	- 0.023	ns	- 0.216	ns	- 0.340	0.002
self-efficacy	0.215	ns	0.103	ns	0.171	ns

* *P* > 0.05 are not displayed

Table 2

Bivariate spearman's rho correlations at T1 between the SIS Illness and disease specific measures.

	Rho	p-value*
Fatigued cancer survivors (n=82)		
Cancer Acceptance Scale	- 0.425	0.000
Impact of Event Scale		
• intrusion	- 0.459	0.000
• avoidance	- 0.351	0.001
Time since cancer treatment ended	0.338	0.002
Duration of treatment	- 0.118	ns
Neuromuscular disorder (n=68)		
Muscle strength (MRC)	0.312	0.014

* *P* > 0.05 are not displayed

Is there a difference in suffering between the three patient groups experiencing chronic fatigue?

The three samples significantly differ in the mean level of fatigue severity (Table 3), CFS patients demonstrating the most fatigue, followed by the cancer survivors and the patients with various neuromuscular disorders. In accordance with the fatigue scores, we found that patients with CFS situated the fatigue disk in the closest distance of the self disk, followed by the cancer survivors and the patients with various neuromuscular disorders. These values were statistically significantly different. Investigating the SIS illness, data showed that the patients with various neuromuscular disorders positioned the illness disk significantly closer to the self disk than the cancer survivors. Furthermore, the correlations of the SIS fatigue and the variables of the eight dimensions showed a different profile in the three samples, finding the most significant correlations in the sample of the patients with various neuromuscular disorders (Table 1).

Table 3

Comparison of the mean and sd of fatigue severity, SIS fatigue, SIS illness between three samples (Mann-Whitney U test)

	Chronic fatigue syndrome patients (n=60)	Fatigued cancer survivors (n=82)	Fatigued patients with neuromuscular disorders (n=68)
fatigue severity (CIS-fatigue)	49.8 (5.1)[b,c]	47.3 (6.7)[a,c]	43.3 (5.9)[a,b]
mean SIS fatigue (sd)	4.8 (4.0) [b,c]	7.1 (5.2) [a,c]	9.3 (6.6) [a,b]
mean SIS illness (sd)	-	18.0 (8.4)[c]	9.8 (7.5)[b]

a: significantly different from chronic fatigue syndrome patients ($p < 0.05$)
b: significantly different from fatigued cancer survivors ($p < 0.05$)
c: significantly different from fatigued patients with neuromuscular disorders ($p < 0.05$)

Is it possible to discriminate within a patient between the suffering due to an illness and the suffering due to fatigue?

In investigating this research question the sample of the fatigued cancer survivors was divided into two separate groups. The first group (n=67) positioned the fatigue disk closer to the self disk than the cancer disk. The second group (n=15) positioned the cancer disk closer to the self disk than the fatigue disk. Data showed (Table 4) that the first group revealed higher fatigue severity in contrast with the second group. The second group demonstrated less acceptance and higher intrusion and avoidance scores on the IES compared to the first group. In addition, comments of fatigue cancer survivors when performing the PRISM task at pretreatment were evaluated. Table 5 shows examples of comments of fatigued cancer survivors when performing the PRISM task at pretreatment. These comments revealed that

the suffering of two symptoms can be different. Patients who felt that fatigue was an overruling complaint affecting their total life placed the fatigue disk in closer distance of the self disk, in contrast to patients who had come to terms with the fatigue. Additionally, patients with a short SIS cancer seemed not have dealt enough with the fact that they had cancer. For patients with a large SIS cancer, the disease was no issue more. These kind of comments came up consistently in the other cancer survivors.

Table 4

Position of the two disks with respect to each other (Mann-Whitney U test)

Cancer survivors	SIS fatigue < SIS cancer (n=67)	SIS fatigue > SIS cancer (n=15)	MWU	Z	p-value
CIS fatigue *	48.1 (6.7)	44.3 (5.8)	325.5	-2.127	0.033
Cancer Acceptance Scale**	14.3 (3.5)	16.3 (3.1)	338.5	-.1977	0.044
Impact of Event Scale ***					
• intrusion	4.7 (5.1)	10.8 (6.5)	234.0	-3.246	0.001
• avoidance	4.6 (6.5)	10.5 (6.6)	243.5	-.3173	0.002

* high scores are indicative of a high level of fatigue
** high scores are indicative of low acceptance
*** high scores are indicative of a high stress response

Does suffering diminish following treatment of chronic fatigue?

We investigated the change of the SIS fatigue and SIS illness at T1 and T2 within the three samples (Table 6). The CFS patients and the cancer survivors who were allocated to the CBT condition were divided into two groups: patients who were completely recovered after CBT and had no severe fatigue complaints (CIS-fatigue < 35) and patients who still remained fatigue after CBT (CIS-fatigue ≥ 35). Patients with various neuromuscular disorders did not get any treatment for their fatigue complaints but followed their natural course. CFS patients (n=32) and cancer survivors (n=27) who recovered after CBT showed a significant increase on the SIS fatigue at T1 versus T2. Additionally, the recovered cancer survivors showed a significant increase in SIS illness after CBT. CFS patients (n=28) and cancer survivors (n=14) who still remained severely fatigued after CBT displayed no change of the SIS fatigue at T1 with respect to T2 and the fatigued cancer survivors showed no change on the SIS illness. The patients with various neuromuscular disorders showed stable values of the SIS fatigue and SIS illness at T1 versus T2.

The comments of cancer survivors when performing the PRISM task at pre- and post treatment were examined (Table 7). These comments showed that patients who were recovered after CBT and were less fatigued expressed more positive and in the line of recovery comments at post treatment with respect of pretreatment comments. These kind of comments came up consistently in the other cancer survivors.

Table 5

Examples of comments of four fatigued cancer survivors when performing the PRISM task at T1.

	SIS fatigue < SIS cancer	
SIS-fatigue	Fatigue that's me, that's my life. I always have to take fatigue into consideration when planning my activities. Fatigue has changed my life enormously.	3.6 cm
SIS-cancer	I have no fear for cancer. I don't see it as a threat anymore. If the cancer would recur, I will deal with it than. I'm not worried about that now.	27.0 cm
SIS-fatigue	The fatigue complaints are always present and affect my whole life.	4.9 cm
SIS-cancer	Cancer is not an important part of my life. I'm not afraid of disease recurrence. I have dealt with it.	26.7 cm
	SIS fatigue > SIS cancer	
SIS-fatigue	The fatigue has its influence on my life, but it makes me not desperate. It is just there and I have to deal with it.	17.4 cm
SIS-cancer	14 days ago my sister has been diagnosed with breast cancer. By that a lot of memories of my treatment period returned. Also the thought that my two daughters can be a victim of hereditary haunts me.	5.3 cm
SIS-fatigue	I have learned to accept the fatigue complaints.	12.5 cm
SIS-cancer	The experience with cancer is always present. I do not plan anything in the future. When I feel fine it remains in the background. But at moments I feel sick, have a little pain etc it becomes prominent. It alarms me.	8.5 cm

Table 6

SIS fatigue and SIS illness at T1 and T2 (Wilcoxon signed ranks test for matched pairs).

Group		SIS fatigue	Z	p-value*	SIS illness	Z	p-value*
A	T1	5.3 (4.1)	-.4937	0.000			
	T2	16.5 (6.8)					
B	T1	4.2 (3.9)	-1.430	ns			
	T2	5.5 (5.6)					
C	T1	8.6 (6.8)	-.3592	0.000	17.1 (9.5)	-.2399	0.017
	T2	17.1 (9.5)			23.3 (6.5)		
D	T1	5.9 (4.3)	-.454	ns	16.6 (7.1)	-.847	ns
	T2	6.0 (5.8)			14.7 (8.6)		
E	T1	9.3 (6.6)	-1.321	ns	9.8 (7.5)	- 1.705	ns
	T2	11.4 (7.8)			11.4 (7.8)		

* *P* > 0.05 are not displayed

A: CFS non-fatigued after CBT (n=32); B: CFS still fatigued after CBT (n=28); C: Cancer survivors non-fatigued after CBT (n=27); D: Cancer survivors still fatigued after CBT (n=14); E: Natural course neuromuscular disorders (n=68)

Table 7

Examples of comments of two cancer survivors when performing the PRISM task at pre-treatment and post-treatment

Comment SIS fatigue patient 1	SIS Fatigue	CIS_fat
Pre-treatment: Fatigue has a daily impact and restricts me in functioning the way I want. Fatigue dominates my life	13.8 cm	46
Post-treatment: Fatigue is not anymore an disturbing factor in my life and it does not disable me, in contrast to the period before the cognitive behaviour therapy. I still experience fatigue, but only after physical exertion or stress, and it is gone after a good night rest.	23.1 cm	12
Comment SIS fatigue patient 2	**SIS Fatigue**	**CIS_fat**
Pre-treatment: Fatigue is something that is present every hour of the day and forced me to adjust my life. Because of the fatigue I had to change my goals in life.	2.9 cm	46
Post-treatment: I have much more energy now and build up my activities. I demand less of myself.	17.0 cm	16

DISCUSSION

The present study offers encouraging data for the use of the PRISM as a tool in fatigue research and clinical practice.

Is suffering, as measured with the PRISM, a separate dimension of chronic fatigue?

We did not find extreme high correlations indicative for a parallel test (r >.90 = parallel test) with one of the measurements. Overall moderate correlations were found between the SIS fatigue and the values of the eight dimensions of fatigue and also between the SIS illness and the disease specific measurements. Therefore, it seems that the PRISM contributes uniquely to the dimensions of fatigue and therefore gives us additional information aside from what we already know based on our multidimensional assessment method. Additionally, it seems to measure something different than acceptance, stress symptoms or disease severity (=disease specific measurements). However, is it suffering the PRISM measures? The most important aspects of suffering is the patient's perception of the intrusiveness and controllability of the illness or its symptoms, the 'threat to the self'.[7-9] These aspects are nicely demonstrated investigating the correlations and the qualitative data of the fatigued cancer survivors (Table 2 and 5). Cancer survivors who positioned the cancer disk further away of the self disk were less occupied with the fact that they had cancer and revealed more acceptance. Quite the contrary, if a patient is really occupied with the disease cancer, the influence of this on his life can be enormous. Furthermore, the positive significant correlation of SIS-cancer and the time since cancer treatment can be explained by the fact that intrusion due to illness is fading away with time.[9]

Is there a difference in suffering between the three patient groups experiencing chronic fatigue?

The differences between the samples in the position of the fatigue disk at baseline, were in agreement with the severity of the experienced fatigue measured with the fatigue questionnaire (CIS-fatigue). So fatigue severity seems to be an aspect of suffering in these patient groups. Investigating the positioning of the illness, we found that patients with various neuromuscular disorders positioned the illness disk in closer distance to the self disk than the fatigued cancer survivors. Patients with neuromuscular disorders have a chronic progressive disorder and are confronted with this everyday. The intrusiveness of the disease is present everyday and the controllability low. The significant positive correlation of the SIS illness and the muscle strength supports this explanation. On the other hand, the cancer survivors had an acute disease in the past but were disease-free at the moment of participation in this study. Therefore most of them are not daily confronted with their past disease. Most patients will have accepted their experience with cancer and the treatment for cancer with time and by doing so the suffering will also diminish. This is also represented with the correlation of the SIS illness and the time since treatment.

One would expect that the contributions of different variables to suffering would be different between illnesses, therefore one should expect that the correlations between the PRISM and the other variables would differ from one illness to another. A different pattern of correlations was actually seen within the three samples, with the most significant correlations in the group of patients with a neuromuscular disorder. A neuromuscular disorder is a complex illness with many symptoms besides fatigue. It is possible that for patients with a neuromuscular disorder the fatigue is entangled with all the other symptoms making it difficult for patients to separate. Therefore, fatigue seems to be a symptom of their overall state rather than a predominant focus of their attention, as is likely the case in the other two groups. For that reason the SIS-fatigue is significantly correlated with many dimensions of fatigue. For the fatigued cancer survivors the ‘threat to the self’ is largely in the past, so the suffering in this group appears mainly related to the adjustment to the cancer and previous memories of it.

For patients with CFS, fatigue is the main symptom without the experience of a current or past severe illness. These patients can not attribute their fatigue to a distinct cause and therefore, it’s possible that they are more focussed on their fatigue.

Is it possible to discriminate within a patient between the suffering due to an illness and the suffering due to fatigue?

Fatigue is a symptom which frequently occurs in combination with physical illnesses and it’s difficult to determine when fatigue leads to suffering or when another symptom is more important to a patient. However, this aspect can be of great importance in the clinical practice.

In this study suffering of fatigue and the suffering of a past disease (cancer) was compared in fatigued disease-free cancer patients. We found that fatigued cancer survivors who suffer more due to the fact that they have had cancer compared to the fact that they were severe

fatigued, also revealed less fatigue complaints, more difficulty in coping with their cancer past and were more anxious of disease recurrence (assessed with the IES). Also the qualitative data demonstrated the possibility to separate two kinds of suffering. The comments made by fatigued cancer survivors when performing the PRISM task were in agreement with the aspect that causes the patient the most suffering. By using the PRISM a clinician can observe in a quick and easy way which symptom (of course this not only applies for fatigue) gives the most suffering to the patient and thereby choose the main focus of attention in a treatment. For example, in the fatigued cancer survivors who positioned the cancer disk closer to the self disk than the fatigue disk, the focus of any treatment should be first on handling the experience of cancer before fatigue can be an issue in the treatment.

Does suffering diminish following the treatment of chronic fatigue?
Patients who were recovered and experienced no fatigue after CBT positioned at post-treatment not only the fatigue disk significant further away of the self disk than at pre-treatment, but also the illness disk. Patients who did not recover after CBT or patients with various neuromuscular disorders during natural course did not show a change in the position of the fatigue disk or the illness disk. Comments made when performing the PRISM task at pre- and post treatment were also supporting the change in suffering. Therefore, the PRISM can be a valuable tool in the clinical practice is to assess suffering at pre- and post treatment. In comparing these two assessments the treatment effect can be demonstrated instantly to the clinician as well as the patient.

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Chapter 8

Differences in the experience of fatigue in patients and healthy controls: Patients' descriptions

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ABSTRACT

The primary objective was to develop an adjective checklist, the Fatigue Quality List (FQL), aimed at assessing different perceptions of fatigue.

Nine hundred sixty-one participants filled out the FQL (28 adjectives). A component and confirmatory factor analyses were performed and psychometric properties were evaluated. Differences on factor scores between different patients' groups were investigated and pre- and posttreatment scores were compared in demonstrating change of perceptions after treatment of fatigue.

Four independent factors were found with adequate psychometric properties. Different perceptions were found between the patients' groups. Patients who were recovered after treatment for fatigue showed similar scores on the factors as healthy controls.

The FQL appears to be a promising tool in measuring different perceptions of fatigue, which can be especially interesting for clinical practice.

INTRODUCTION

What is meant by fatigue? Most people are familiar with the experience of fatigue, but the meaning of this sensation can differ between people and even within one person the meaning of fatigue can change. Therefore, fatigue can be defined in different ways and there is no 'gold standard'. Healthy people would characterise fatigue as a pleasant, acute, normal and regulating phenomenon after exercise or a busy day, disappearing after a good night's sleep or a period of rest. However, fatigue can also have a more negative connotation as in fatigue experienced by patients with a health problem. To them fatigue can be a chronic, disabling and life- and activity-limiting experience.[1-6]

There are also differences in the factors underlying fatigue severity between patients with different somatic conditions. Processes involved in the experience of fatigue in patients with chronic fatigue syndrome (CFS) are clearly different from processes related to the experience of fatigue in patients with multiple sclerosis (MS)[2] and there are many differences between severely fatigued breast cancer survivors and females with CFS.[7]

Because fatigue is not clearly defined, poor communication regarding fatigue exist in the clinical practice.[8] Additionally, health care professionals find consultations on fatigue difficult and are often dissatisfied with or uncertain about the care they provide to patients with fatigue complaints.[9,10] Without appropriate assessment, recognition and providing the proper management to patients with chronic fatigue is difficult. The first necessary step towards improving recognition and management is a thorough understanding of the symptom.

Until now fatigue scales are mostly used to measure fatigue severity.[11] However, fatigue severity does not reflect a persons' perception and appraisal of the fatigue. Therefore, the quantitative way of assessing fatigue fails to capture the nuances and differences in the experience of fatigue. In pain research assessment methods already exists in determining the quality of pain in a patient by using adjectives.[12,13]

In this study an adjective checklist, the Fatigue Quality List (FQL), was constructed aimed at assessing different perceptions of fatigue. The development of the FQL was described and additionally three research questions were investigated:

1. Is the FQL a reliable and valid instrument to assess different perceptions of fatigue?
2. Are perceptions of fatigue different between several patient groups with and without chronic fatigue complaints and healthy controls?
3. Do perceptions of fatigue change in patients who recover after treatment for fatigue?

METHODS

Materials

The Fatigue Quality List: Researchers and clinicians working at the Expert Centre Chronic Fatigue of the Radboud University Nijmegen Medical Centre made a large list of all possible adjectives that can be used to characterize the feeling of fatigue. The FQL was developed by asking researchers and health care professionals working with patients with unexplained fatigue complaints to indicate on this large list which of the adjectives best fitted with the experience of the fatigue described by their patients. The final list consisted of 28 adjectives most frequently mentioned by the raters.

In filling out the FQL, subjects are instructed to mark with a cross which of the 28 adjectives fit their experienced fatigue. Multiple answers are possible. In this study the Dutch version of the FQL was used. However, the adjectives were translated into English by a back-translation procedure.

Fatigue severity was measured by a subscale of the Checklist Individual Strength (CIS-fatigue) consisting of 8 items.[14] Each item was scored on a 7-point Likert scale. High scores indicated a high level of fatigue severity. Based on research with CFS patients, a score of 35 or higher on the subscale fatigue severity indicated severe feelings of fatigue. Furthermore, the CIS has excellent psychometric properties.[1,11]

Patients

Nine hundred-sixty-one participants with a mean age of 43.6 years (s.d.=10.2, range 18-79) predominantly female (65%) filled out the FQL. All were either patients or healthy controls participating in scientific studies conducted by the Expert Centre Chronic Fatigue. The total group consisted of:

- 219 cancer survivors. Hundred-twenty-eight (mean age 44.8 (s.d.=8.9); female 72%) experienced severe chronic fatigue and 91 (mean age 46.5 (s.d.=6.3); female 100%) were not fatigued.[3] Forty-one of these cancer survivors were participating in a randomised controlled trial about the effectiveness of cognitive behaviour therapy (CBT) especially designed to reduce chronic fatigue in cancer survivors.[15] These patients filled out the FQL at pre- and post treatment.
- 160 patients who were diagnosed with CFS, according to the CDC criteria (mean age 38.0 (s.d.=10.7); female 69%).[4,16] Eighty-two CFS patients who were included in this study were treated for their chronic fatigue complaints with CBT.[4] These patients filled out the FQL two times, at pre- and post treatment.
- 151 employees on sick leave with unexplained fatigue complaints (mean age 44.0 (s.d.=8.4); female 55%).[17] Sixty-six (44%) of these met research criteria for CFS (mean age 42.9 (s.d.=8.6); female 61%).
- 276 patients with various neuromuscular disorders. Hundred-sixty-five experienced severe fatigue (mean age 42.2 (s.d.=10.6); female 48%) and 120 experienced no fatigue complaints (mean age 42.2 (s.d.=11.3); female 48%).[5,18]
- 77 patients who were diagnosed with pancreatitis. Fifty-three experienced severe fatigue (mean age 49.3 (s.d.=10.0); female 47%) and 24 were not fatigued (mean age

50.2 (s.d.=15.5); female 58%).
- 78 healthy persons who experienced no fatigue complaints (mean age 48.2 (s.d.=6.2); female 100%).[3]

Statistical analysis

Data analysis was performed using SPSS (version 12.0.1). The total participant group was randomly divided into two groups. A principal component factor analysis was performed in the first group to identify independent factors. A varimax rotation was used to facilitate the interpretation. Furthermore, factor loadings had to be above 0.40 with a 0.10 or greater difference in loadings with the other factors. The scree test and the eigenvalues (above 1) were used to identify the number of factors. The factor model was then tested in the second group by using confirmatory factor analyses / AMOS 5.0 (Comparative Fit Index, Goodness of Fit Index, Adjusted Goodness of Fit Index[19,20]).

The internal consistency reliability for each factor was calculated using Cronbach's alpha. Spearman's rho correlations were used to evaluate psychometric properties of the FQL. To investigate the differences between the groups of patients Kruskal-Wallis tests were performed. When the Kruskal-Wallis test was significant, Mann-Whitney-U tests between the groups followed. The sensitivity to change of the FQL was demonstrated by comparing cancer survivors and CFS patients at pre- and post treatment assessment, using the Wilcoxon Signed Ranks Test of matched pairs. To correct for the multiple comparisons, *P*-value was set on < 0.01.

RESULTS

Factor solution

Three of the 28 adjectives were marked with a cross for less than 10% and therefore excluded from further analyses. Final analyses were done with the remaining 25 adjectives. Table 1 presents the final factor solution in the first group (n=476). Seven adjectives were excluded of factor analysis because factor loadings were < 0.40 and/or < 0.10 difference in loadings with the other factors. Both the scree test and eigenvalues indicated a 4-factor solution (Table 2). Factor 1 consisted of 5 adjectives, factor 2 of 4 adjectives, factor 3 of 5 adjectives and factor 4 of 4 adjectives, explaining respectively, 24%, 9%, 6%, 5% of the variance prior to rotation. After rotation the four factors explained respectively, 13%, 12%, 10% and 9% of the variance. Factor 1 was labelled as 'Frustrating', Factor 2 as 'Exhausting', Factor 3 as 'Pleasant' and Factor 4 as 'Frightening'. This four factor model was then tested in the second group (n=485) by using confirmatory factor analysis. The fit indices indicated an adequate fit. Chi-square (129, n=485) = 364.5, $P < 0.001$; Comparative Fit Index = 0.87; Goodness of Fit Index = 0.92; Adjusted Goodness of Fit Index = 0.90.

The four factors were recoded on a 0 to 100 scale, facilitating comparisons between the factors. Higher scores indicate a higher appraisal of the fatigue experience as frustrating, exhausting, pleasant and frightening. The final version of the FQL and the criteria for scoring are presented in appendix A.

Table 1

Final factor solution: principal-components analysis with varimax-rotation in the first group. Cronbach's Alpha of the four factors

	Frustrating	Exhausting	Pleasant	Frightening
discouraging	.735			
incessant	.585			
annoying	.680			
persistent	.559			
frustrating	.704			
exhausting		.690		
wearisome		.537		
extreme		.724		
unbearable		.509		
temporary			.400	
relaxing			.661	
fulfilling			.713	
normal			.522	
pleasant			.792	
upsetting				.727
frightening				.618
inexplicable				.490
insuperable				.444
Cronbach's Alpha	.79	.68	.61	.57

Three adjectives were excluded of factor analysis because they were marked with a cross for less than 10%: Protective, Soothing, Threatening.

Seven adjectives were excluded of factor analysis because factor loadings < 0.40 and/or < 0.10 difference in loadings with the other factors: Demanding, Paralysing, Aggravating, Compelling, Treacherous, Insoluble, Acceptable

Is the FQL a reliable and valid instrument to assess different perceptions of fatigue?

For each factor the internal consistency reliability was calculated in the entire sample of 961 participants, which demonstrated moderate to adequate internal consistencies for all four factors, ranging from 0.57 to 0.79 (Table 1).

Supporting convergent validity we found that all four factors were statistically significant related to fatigue severity (CIS-fatigue) (Table 3). In calculating general psychometric properties statistically significant intercorrelations between the four factors were found (Table 3). Additionally, low correlations were found between the four factors and age and gender, explaining less than 3% of the variance.

Table 2

Principal-components analysis with varimax-rotation, initial eigenvalues

Component	Eigenvalues
1	**4.788**
2	**1.906**
3	**1.285**
4	**1.176**
5	0.984
6	0.875
7	0.813
8	0.742
9	0.714
10	0.664
11	0.623
12	0.593
13	0.568
14	0.514
15	0.503
16	0.445
17	0.428
18	0.380

Table 3

Convergent validity of the 4 factors. Spearman's rho correlation in total group (N=961)

Factor	Frustrating	Exhausting	Pleasant	Frightening
Fatigue severity	0.66*	0.58*	-0.54*	0.43*
Exhausting	0.54*			
Pleasant	-0.48*	-0.35*		
Frightening	0.49*	0.42*	-0.25*	
Age	-0.16*	-0.14*	0.05	-0.03
Gender (1=M, 2=F)	-0.09*	0.03	0.11*	-0.10*

* $p < 0.01$

Tabel 4

Mean score on 4 factors: comparisons between fatigued disease-free cancer patients, CFS patients, employees with unexplained fatigue, fatigued patients with neuromuscular disease, fatigued patients with pancreatitis, non-fatigued disease-free cancer patients, non-fatigued patients with neuromuscular disease, non-fatigued patients with pancreatitis and healthy persons

	Frustrating	Exhausting	Pleasant	Frightening
A. Fatigued disease-free cancer patients	48.6 (30.9)[b,c]	29.3 (28.6)[b,d]	11.7 (17.7)[b,c]	22.7 (24.2)[d,e]
B. Chronic fatigue syndrome patients	58.5 (32.2)[a,d,e]	37.8 (31.5)[a,c,d,e]	6.6 (13.0)[a,c,d]	25.2 (25.9)[d,e]
C. Employees with unexplained fatigue	63.7 (29.2)[a,d,e]	29.5 (28.1)[b,d]	4.3 (11.2)[a,b,d,e]	26.0 (26.6)[d,e]
D. Fatigued patients with neuromuscular disease	41.8 (32.6)[b,c]	17.8 (24.8)[a,b,c]	13.6 (18.5)[b,c]	13.8 (20.1)[a,b,c]
E. Fatigued patients with pancreatitis	41.1 (33.1)[b,c]	25.9 (29.8)[b]	9.1 (13.9)[c]	14.2 (22.7)[a,b,c]
F. Non fatigued disease-free cancer patients	8.1 (16.3)	6.6 (14.4)[g]	38.9 (28.3)[g]	7.7 (17.0)
G. Non fatigued patients with neuromuscular disease	9.0 (16.2)	1.7 (7.1)[f,h]	24.7 (21.3)[f,I]	5.6 (13.9)
H. Non fatigued patients with pancreatitis	13.3 (28.1)	9.4 (17.8)[g]	29.2(23.6)	5.2 (12.7)
I. I. Healthy persons	7.7 (18.3)	3.9 (13.4)	36.2 (23.3)[g]	3.2 (10.2)

a. significantly different from group A, Mann-Whitney test p< 0.01
b. significantly different from group B, Mann-Whitney test p< 0.01
c. significantly different from group C, Mann-Whitney test p< 0.01
d. significantly different from group D, Mann-Whitney test p< 0.01
e. significantly different from group E, Mann-Whitney test p< 0.01
f. significantly different from group F, Mann-Whitney test p< 0.01
g. significantly different from group G, Mann-Whitney test p< 0.01
h. significantly different from group H, Mann-Whitney test p< 0.01
i. significantly different from group I, Mann-Whitney test p< 0.01

Are the perceptions of fatigue different between several patient groups with and without chronic fatigue complaints and healthy controls?

The non-fatigued groups scored significantly lower on Frustrating, Exhausting and Frightening and significantly higher on Pleasant compared with the fatigued groups (Table 4). The following analyses were performed separately in the fatigued groups and the non-fatigued groups.

Frustrating

The non-fatigued groups were similar with respect to the mean scores on Frustrating (P = 0.757). Patients with chronic fatigue syndrome and employees with unexplained fatigue scored significantly higher on Frustrating with respect to the other fatigued groups.

Exhausting

The non-fatigued patients with various neuromuscular disorders scored significantly lower on Exhausting than the non-fatigued cancer survivors and the non-fatigued patients with pancreatitis. Between the fatigued groups, CFS patients scored significantly higher on Exhausting than the other groups. Furthermore, fatigued patients with pancreatitis scored significantly lower with respect to fatigued cancer survivors and employees with unexplained fatigue. Additionally, patients with neuromuscular disorders scored significantly lower than employees with unexplained fatigue.

Pleasant

In the non-fatigued group patients with various neuromuscular disorders scored significantly lower on Pleasant than non-fatigued cancer survivors and healthy persons. In the fatigued group employees with unexplained fatigue scored significantly lower on Pleasant than the other groups. CFS patients scored significantly lower than cancer survivors and patients with neuromuscular disorders.

Frightening

The scores on Frightening in the non-fatigued groups were similar. In the fatigued groups a dichotomy was found between the patients with unexplained fatigue with and without a chronic disease. Fatigued patients without a chronic disease (cancer survivors, CFS patients and employees) scored significantly higher on Frightening than fatigued patients with a chronic disease (patients with a neuromuscular disorder or pancreatitis).

Do perceptions of fatigue change in patients who recover after treatment for fatigue?

Forty-one fatigued cancer survivors and eighty-two CFS patients were treated for their fatigue complaints with CBT at our department and filled out the FQL at pre- and post treatment. Sensitivity to change of the FQL was demonstrated by dividing the CFS patients and the cancer survivors into two groups: patients who were completely recovered after CBT (CIS-fatigue < 35) and patients who remained fatigued after CBT (CIS-fatigue ≥ 35). Baseline scores on the four factors were not significantly different between patient who recovered and patients who remained fatigued. The scores on the four factors at pre- and post treatment were compared. Additionally, we compared the post treatment scores on the four factors with the scores of healthy individuals (Table 5). Cancer survivors who were completely recovered after CBT (n=27) showed a significant decrease on the factors Frustrating, Exhausting and Frightening and a significant increase on the factor Pleasant. The post-treatment scores were not significantly different from those of healthy individuals. In contrast, the cancer survivors who still remained fatigued after CBT (n=14) did not show a change in the scores on the four factors from pre- to post treatment. Furthermore, their scores at post treatment were significantly different from the scores of healthy individuals. In investigating CFS patients who recovered after CBT (n=47) the same pattern was found. They also decreased

significantly on the factors Frustrating, Exhausting and Frightening and increased significantly on the factor Pleasant. The scores at post treatment were not significantly different from those of healthy individuals. CFS patients who were not recovered after CBT (n=35) showed no change between pre- and post treatment scores on the factors Frustrating, Exhausting and Pleasant. Although a significant decrease was seen on the factor Frightening, the posttreatment scores of the four factors were significantly different form those of healthy individuals.

Table 5

Comparison of pre- and post treatment scores on the four factors. Comparison of the post treatment scores with those of healthy individuals

			Frustrating	Exhausting	Pleasant	Frightening
	Cancer survivors					
A	non fatigued after CBT (n=27)	pre-treatment	52.6 (27.8)	27.8 (24.4)	11.1 (14.0)	22.2 (23.3)
		post-treatment	11.9 (23.0)*	5.6 (20.0)*	36.3 (25.4)*	6.5 (11.2)*
B	still fatigued after CBT (n=14)	pre-treatment	67.1 (27.9)	46.4 (30.8)	8.6 (17.0)	19.6 (24.4)
		post-treatment	58.6 (34.6)	33.9 (38.7)	7.1 (12.7)	12.5 (19.0)
	Chronic fatigue syndrome patients					
C	non fatigued after CBT (n=47)	pre-treatment	60.4 (26.5)	42.0 (31.8)	4.7 (8.6)	20.2 (22.5)
		post-treatment	11.1 (18.1)*	3.2 (8.4)*	32.3 (30.5)*	5.9 (11.9)*
D	still fatigued after CBT (n=35)	pre-treatment	57.7 (30.6)	44.3 (35.9)	5.1 (11.2)	24.3 (24.6)
		post-treatment	45.1 (31.2)	30.0 (33.1)	9.1 (17.0)	12.9 (15.3)*
	Healthy individuals		7.7 (18.3)[b,d]	3.9 (13.4)[b,d]	36.2 (23.3)[b,d]	3.2 (10.2)[b,d]

CBT = cognitive behaviour therapy

* significant difference between pre- and post treatment scores, Wilcoxon signed rank test p< 0.01

a. significantly different from post treatment scores of group A, Mann-Whitney-U test p< 0.01

b. significantly different from post treatment scores of group B, Mann-Whitney-U test p< 0.01

c. significantly different from post treatment scores of group C, Mann-Whitney-U test p< 0.01

d. significantly different from post treatment scores of group D, Mann-Whitney-U test p< 0.01

DISCUSSION

The present study shows that the FQL provides a self report instrument that assesses the perceptions of fatigue. The FQL consists of four coherent factors, namely Frustrating, Exhausting, Pleasant and Frightening. The stable pattern of these factors was indicated with a confirmatory factor analyses, revealing an invariant internal structure in a second group of

patients. Furthermore, the data of this study show that the FQL has adequate psychometric properties. Both the intercorrelations and the correlations of the four factors with the subscale CIS-fatigue were not to the extent that the factors could be seen as a parallel test, thus supporting the relative uniqueness of each factor.

The assumption that fatigue is experienced differently by everybody is confirmed with the data of this study. Severely fatigued patients had different perceptions of fatigue compared to healthy individuals. The healthy persons described fatigue as temporary, relaxing, fulfilling, normal and pleasant. None of these adjectives were chosen by 70% of the severely fatigued patients. Even patients with similar fatigue severity, appreciated fatigued differently. Different patterns were seen on the four factors of the FQL between the different populations of patients experiencing fatigue. CFS patients and severely fatigued employees had the highest score on the factors Frustrating, Exhausting and Frightening and also the lowest score on the factor Pleasant in contrast with the other fatigued groups. Until now the underlying aetiology of CFS still remains unclear.[21,22] Because the patients can not attribute their fatigue to a distinct cause, it's possible that they are more focussed on their fatigue and perceive their fatigue in a more negative way, than the other groups. In agreement with this finding, Moss-Morris et al.[23] found that CFS patients had a more negative view about their symptoms than patients with Rheumatoid arthritis (RA). Additionally, Taillefer et al.[24] found higher levels of illness worry in CFS patients than MS patients who were fatigued. Results of the FQL also showed that patients with a current chronic disease experience their fatigue as less frightening than patients with no current or a past disease. It is possible that these patients attribute their fatigue to their illness and therefore perceive it as less frightening. Cancer survivors may experience fatigue as highly anxiety provoking because they can see fatigue as a symptom for disease-recurrence. Therefore fatigue can be labelled as frightening.[25] Future research is necessary to examine if the FQL is applicable for individual assessment and furthermore investigate what the effect of these different perceptions is on the management of fatigue complaints in the clinical practice.

To reach recovery not only a decrease in fatigue severity is important, it is also important that a change in the evaluation of fatigue in the patient occurs. As fatigue is also a part of normal health, being recovered also includes feeling tired sometimes. This makes it difficult to decide where experiencing fatigue as a sign of illness ends and the experience of normal health surfaces. During CBT patients learn that fatigue may occur as part of normal healthy life. When a decrease is seen in the fatigue severity of a patient and the evaluation of the fatigue stays negative, it implicates that a patients still suffers and is disabled due to the fatigue. The patient cannot be seen as fully recovered.[26] The results of this study showed that the FQL can demonstrate change in fatigue perceptions following treatment of fatigue. Patients who were recovered after CBT had the same scores on all four factors compared to healthy persons. So, not only the fatigue severity changed after therapy but also the evaluation of fatigue. The FQL can therefore be a helpful tool to define full recovery in the clinical practice.

Appendix A

Fatigue Quality List (FQL)

Fatigue can be described in different ways. The adjectives below can be seen as descriptions of fatigue.

Please indicate which adjectives accurately describe the fatigue you experienced during the last two weeks by marking them with a cross.

upsetting	persistent
discouraging	frustrating
temporary	relaxing
exhausting	inexplicable
incessant	fulfilling
wearisome	insuperable
frightening	unbearable
annoying	normal
extreme	pleasant

Appendix A continued

Scoring Fatigue Quality List (FQL)

Subsequently the four factors are calculated by summing the respective items (0 – 100):

Factor 1: Frustrating
Score of each item: 20
Adjectives: discouraging, incessant, annoying, persistent, frustrating

Factor 2: Exhausting
Score of each item: 25
Adjectives: exhausting, wearisome, extreme, unbearable

Factor 3: Pleasant
Score of each item: 20
Adjectives: temporary, relaxing, fulfilling, normal, pleasant

Factor 4: Frightening
Score of each item: 25
Adjectives: upsetting, frightening, inexplicable, insuperable

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Chapter 9

General Discussion

What is known about postcancer fatigue?

A literature review

GENERAL DISCUSSION

In this final chapter the results of the studies presented in the preceding chapters will be placed into the perspective of the existing literature of postcancer fatigue. The literature presented is based on two previously written review articles in which postcancer fatigue was discussed.[1,2] These reviews are updated with manuscripts that appeared since 2005 till May 2007. The following topics will be discussed:

1. Fatigue measurements;
2. The prevalence and course of post-cancer fatigue;
3. Predisposing, precipitating and perpetuating factors of postcancer fatigue;
4. Interventions on postcancer fatigue.

1. Fatigue measurements

The assessment of fatigue in cancer survivors is beset by a number of methodological challenges. Whilst the studies on postcancer fatigue are growing, there is still no universally accepted definition of postcancer fatigue. This lack of a commonly agreed on definition of fatigue is perhaps the greatest challenge. In the absence of such a definition, it is not surprising that there is a lack of consensus about the optimal approach to assessing fatigue. As a result, a great variety of self-report techniques are used. To give an indication, in studies on postcancer fatigue alone 15 different fatigue questionnaires are used, all developed in a time period of about 7 years. Furthermore, fatigue can be assessed in different ways. It is possible to use single-item measures, asses fatigue as a general concept in multi-item unidimensional measures (sometimes incorporated in other instruments) and in a more comprehensive approach in multi-item multi-dimensional measures.

The purpose of this paragraph is to report on psychometric characteristics of fatigue instruments used in studies on postcancer fatigue.[3-55] The majority of the information is based on three previously written review articles in which assessment measures of fatigue were discussed.[56-58] Table 1 gives an overview of a single item fatigue measure, unidimensional fatigue measures and multidimensional fatigue measures. Information is provided on the characteristics of each fatigue scale, describing the subscales, number of items, response format, time frame, the reliability and validity. With regard to the validity, questionnaires are mentioned that are associated with the fatigue questionnaire as proof of concurrent validity. Good discriminative and sensitivity to change is indicated with a plus (+). A minus (-) indicates that there is no information available on the validity. In addition, the number of studies on postcancer fatigue in which the instrument is used are mentioned.

1.a. Single item measurement

The Visual Analog Scale-Fatigue (VAS-F) is a single item measurement.[59] Very simple and quick to complete with minimal burden for the patients and therefore especially useful in the clinical setting. Although a commonly agreed on definition of fatigue is lacking, more consensus has been derived at the multidimensional concept of fatigue and a single item measure does not differentiate between different aspects of fatigue. Furthermore, it cannot be evaluated for many forms of statistical reliability.

1.b. Multi-item unidimensional measures

Multi-item unidimensional measures have better psychometric properties than single-item measures and provide information about patients' general level of fatigue severity. In studies on postcancer fatigue 5 unidimensional measures are used of which 4 are incorporated in other questionnaires.

The Fatigue subscale of the EORTC QLQ-C30 is used to measure postcancer fatigue Although, the EORTC QLQ-C30 is translated in 42 languages and therefore quite appropriate for use in multicultural clinical settings,[60] the questionnaire is not developed to measure fatigue, but to measure quality of life.

The Short Form-36 (SF-36) is developed for measuring general health status.[61] Five studies used the subscale Vitality as a measure for postcancer fatigue.[7,8,23,45,50] With the SF-36 Vitality it is possible to identify cases with severe fatigue. In three studies the prevalence of fatigue was measured, two studies used the cutoff point of 50 or less as fatigue caseness[8,45] and one used a score of 40 or less.[23] You could wonder if the concept of Vitality is the same as the concept of fatigue. In our own data we found a correlation between the CIS-fatigue and SF-36 Vitality, however not to the extent that the scales could be seen as a parallel test (r = -.562, unpublished data). Furthermore, the SF-36 has a very long reference period (4 weeks), which makes it less appropriate to measure fatigue fluctuations.

The Profile of Mood State (POMS)[62] is developed to measure change in mood states in psychiatric outpatients. The subscale Fatigue (POMS-F) is used as an additional questionnaire in 3 studies on postcancer fatigue, but not as a primary outcome measure.[51,52,55] Although the POMS-F is short and easy to use, the questionnaire is less adequate because the psychometric properties are untested.[58]

The Functional Assessment of Cancer Therapy-Fatigue (FACT-F)[63] is developed specifically in the cancer population. To asses fatigue alone, the brief subscale Fatigue (13 items) may be used in isolation of the full FACT-F scale (the subscale is validated independently). To assess both fatigue and its consequences the total FACT-F must be used. The Brief Fatigue Inventory (BFI)[64] is also developed in the area of cancer research. The scale is virtually interchangeable with the FACT-F, but the authors claim to use a simpler language and is therefore easier to understand and to translate. Also the BFI measures fatigue severity and the impact of fatigue.

1.c. Multi-item multidimensional measures

In measuring only severity or intensity of the fatigue, unidimensional fatigue measures fail to capture the full spectrum of the fatigue complaint. To assess fatigue in a more comprehensive way, measuring different aspects of fatigue, a multi-item multi-dimensional questionnaires is the most appropriate. Most studies assess postcancer fatigue with a multidimensional measure. In total 9 different questionnaires are used. In Table 1 the dimensions measured by each instrument has been summarized in column two.

Table 1

Characteristics and properties of fatigue questionnaires used in studies on postcancer fatigue

Fatigue questionnaire	Fatigue- scale (no. items)	Response format	Time frame	Reliability	Validity		Used in postcancer fatigue studies
Single item							
VAS-Fatigue [59]	Fatigue severity (1)	10 cm line	Present	0.91	Concurrent validity Discriminative validity Sensitivity to change	: SSS, POMS-F : - : +	One [24]
Multi-item, incorporated in other instruments							
EORTC-QLQ C30 [60]	Fatigue subscale (3)	4-point scale	Past week	Fatigue subscale: 0.80-0.85	Concurrent validity Discriminative validity Sensitivity to change	: + : + : +	Two [10,14]
SF-36 Vitality [61]	Vitality subscale (4)	6-point scale	During the past 4 weeks		Concurrent validity Discriminative validity Sensitivity to change	: FSI, MFSI : + : +	Five [7,8,23,45,50]
POMS-F [62]	Fatigue-inertia subscale (7)	5-point scale	Past week including today		Psychometric properties of POMS-F are untested		Three [52,55]
FACT-F [63]	41 items General (28) Fatigue (13)	5-point scale	Past 7 days	0.95	Concurrent validity Discriminative validity Sensitivity to change	: POMS-F, PFS : - : -	Four [16,22,28,33]
Unidimensional							
BFI [64]	Fatigue Severity (3) Impact of Fatigue (6)	0-10 scale	Now / Past 24 hours	0.96	Concurrent validity Discriminative validity Sensitivity to change	: FACT, POMS : + : -	Four [9,12,17,31]

Table 1 continued

Fatigue questionnaire	Fatigue- scale (no. items)	Response format	Time frame	Reliability	Validity		Used in postcancer fatigue studies
Multidimensional							
CIS [66]	Experienced fatigue (8) Concentration (5) Motivation (4) Activity (3)	7-point scale	Past 2 weeks	0.90	Concurrent validity Discriminative validity Sensitivity to change	: MBI-GS : + : +	Nine [3,5,6,11,37,40-42,44]
MFI [65]	General fatigue (4) Physical fatigue (4) Concentration (4) Motivation (4) Activity (4)	5-point scale	Lately / previous days	average 0.84	Concurrent validity Discriminative validity Sensitivity to change	: VAS-F : + : +	Seven [5,18,30,32, 36,46,53]
PFS [70]	40 items, 7 subscales: Temporal, Intensity, Affective, Sensory, Evaluative, Associated symptoms, Relief components	Visual analogue scale 0 – 100	present / today	0.85	Concurrent validity Discriminative validity Sensitivity to change:	: POMS : - : -	One [50]
R-PFS [72]	Behavioural/severity (6) Affective meaning (5) Sensory (5) Cognitive/mood (6)	10 point Likert Scale	present / today	0. 92	Concurrent validitiy Discriminative validity Sensitivity to change	: FQ : - : -	Four [25,29,38,54]
FQ (FRS, CFS, FS)[73]	Physical fatigue (7) Mental fatigue (4)	yes/no & 4-point scale	Last month	0.85 0.82 total : 0.89	Concurrent validity Discriminative validity Sensitivity to change	: interview :R-CIS : + : +	Nine [13,20,21,34,35, 43,47, 48,49]

Table 1 continued

Fatigue questionnaire	Fatigue- scale (no. items)	Response format	Time frame	Reliability	Validity		Used in postcancer fatigue studies
Multidimensional continued							
FSI [74]	Fatigue (5) Frequency (2) Interference (6)	11-point scale	Past week	> 0.94	Concurrent validity Discriminative validity Sensitivity to change	: POMS-F, SF-36 Vitality : + : +	Five [16,26,51,52,55]
RSCFS [75]	6 items Physical Perceptual	5-point scale	In the past 2 to 3 days	0.88 0.81 total : 0.90	Concurrent validity Discriminative validity Sensitivity to change	: + : - : -	One [4]
MFSI [76]	83 items (SF=30 items) General, Emotional, Physical, Mental, Vigour	5-point scale	In the past 7 days	Subscales: 0.87-0.92	Concurrent validity Discriminative validity Sensitivity to change	: POMS-F, SF-36 Vitality : + : -	Two [19,51]
CaFS [77]	15 items: Physical Affective Cognitive	5-point scale	Right now	0.79-0.89	Concurrent validity Discriminative validity Sensitivity to change	: VAS : - : -	One [39]
Other instruments used in this dissertation							
PRISM [79]	A4 shaped paper (=patients' life) with a yellow fixed disk at the bottom (=patient), 2 detachable disks (=cancer, fatigue)	where would you put fatigue / cancer to reflect its importance in your life at the moment At this moment			Concurrent validity Discriminative validity Sensitivity to change	: Dimensions of fatigue : + : +	Chapter 7 evaluates use of PRISM in fatigue research.

Table 1 continued

Fatigue questionnaire	Fatigue- scale (no. items)	Response format	Time frame	Reliability	Validity		Used in postcancer fatigue studies
Other instruments used in this dissertation							
FQL [80]	18 adjectives characterizing fatigue experience 4 subscales: Frustrating Exhausting Pleasant Frightening	Mark with a cross the adjectives that fit fatigue experience	Last two weeks	0.57-0.79	Concurrent validity Discriminative validity Sensitivity to change	: CIS : + : +	Chapter 8 reports about the development and psychometric testing of the FQL

Fatigue questionnaires: VAS – Visual Analog Scale; EORTC QLQ-C30 - European Organization for Research and Treatment of Cancer Quality of Life Questionnare-C30; SF 36 – Short Form 36; POMS-F – Profile of Mood State Fatigue; FACT-F – Functional Assessment of Cancer Therapy Fatigue; BFI – Brief Fatigue Inventory; CIS – Checklist Individual Strenght; MFI – Multidimensional Fatigue Inventory; PFS – Piper Fatigue Scale; R-PFS – Revised Piper Fatigue Scale; FSI – Fatigue Symptom Inventory; RSCFS – Revised Schwartz Cancer Fatigue Scale; MFSI – Multi dimensional Fatigue Symptom Inventory; CaFS – Cancer Fatigue Scale; FQL – Fatigue Quality Scale; PRISM – Pictorial Representation of Self and Illness Measure; SSS – Stanford Sleepiness Scale; MBI-GS – Maslach Burnout Inventory General Survey; R-CIS – Revised Clinical Interview Schedule

The Checklist Individual Strength (CIS) and the Multi-dimensional Fatigue Inventory (MFI) were developed together. However, the MFI is developed in the research area of cancer treatment[65] and the CIS is developed and well validated amongst patients with chronic fatigue syndrome.[66-69] The CIS and MFI closely resembles each other. Both questionnaires have 20 items and share 18 identical items. Subscales are comparable, however the MFI distinguishes the subscales 'general fatigue' and 'physical fatigue', whereas the CIS combines these into one subscale 'fatigue severity'. The main difference between both instruments is the time frame covered. Compared to the CIS, the MFI assesses momentary fatigue (previous days). The CIS asks about the last two weeks. In the MFI a 5 point Likert scale is used, while the CIS uses a 7 point Likert scale. At this moment more norm data are available for the CIS than for the MFI, in chronic fatigue syndrome (CFS) as well as in postcancer fatigue. Furthermore, based on research of patients with CFS, cancer survivors and healthy controls, a cutoff of the CIS-fatigue is available to measure fatigue caseness (CIS-fatigue >= 35).

The Piper Fatigue Scale (PFS) is developed for the use in research in cancer patients.[70] The wording of the PFS assumes that the patient is already suffering from fatigue and therefore requiring initial screening before use. Besides shortcomings of psychometric qualities, the PFS was criticized for its lack of clarity and length, limiting its application with patients who are very ill or tired.[71] The PFS was therefore revised in 1998.[72] This Revised Piper Fatigue Scale (RPFS) is shorter and the response format was changed to a Likert scale, making it easier to score. Confusingly, this new version is often still referred to as the PFS.

The Fatigue Questionnaire (FQ) is also referred to as the Fatigue Rating Scale (FRS), the Chalder Fatigue Scale (CFS) and the Fatigue Scale (FS). The FQ was developed to establish the prevalence of excessive fatigue in the general population or in primary care patients.[73] The FQ is easily and quickly to complete. Another advantage is the presence of a cutoff point to assess fatigue caseness (>= 4).

The Fatigue Symptom Inventory (FSI) is developed by Hann et al[52,74] in cancer research. Besides fatigue severity, the FSI also provides information about the fatigue intensity, duration and the interference with various aspects of quality of life.

The Revised Schwartz Cancer Fatigue Scale (RSCFS)[75] is the shortest (6 items) multidimensional measure specifically developed for fatigue in cancer patients. However, the psychometric properties need further examination.

The Multidimensional Fatigue Questionnaire (MFSI)[76] is based on literature of cancer related fatigue, discussions with cancer treatment providers and a survey of available measures of fatigue. Although, good psychometric properties, the questionnaire is limited by its length (83 items) and therefore difficult to complete for already fatigued patients. In response to this limitation a short version is developed, the MFSI-Short Form (30 items).

The Cancer Fatigue Scale (CaFs) is developed based on interviews with cancer patients.[77] The questionnaire can be easily completed in 2 minutes. A score of 18 or higher was found to be an optimal cutoff point for fatigue casesness.[78] However, the psychometric properties need further examination.

1.d. Other measures used in this dissertation

Fatigue research is mostly done by measuring fatigue severity in a quantitative way. In *Chapter 7* and *Chapter 8* two different assessment methods for assessing fatigue were introduced.

The Pictorial Representation of Self and Illness Measure (PRISM) is an instrument which assesses suffering caused by an illness.[79] In *Chapter 7* the use of the PRISM in fatigue research was investigated. The PRISM can also be used to investigate the difference between suffering of fatigue and suffering of the cancer experience. It may be helpful to differentiate between these two underlying causes when managing fatigue.

Both healthy persons and patients experience fatigue. However, fatigue shows differences in the characteristics of the experience of fatigue between healthy persons and patients. In addition, the meaning of the fatigue experience may differ between persons. This makes it difficult to define fatigue. The Fatigue Quality List (FQL) is developed to investigate these different experiences of fatigue between healthy persons and patients, but also between different patients groups by use of adjectives[80] (*Chapter 8*). Additionally, the FQL is a helpful tool to define recovery in the clinical practice after treatment for fatigue[81].

Conclusion

Given the number and variety of instruments to measure fatigue currently used in studies on postcancer fatigue, selecting which tool to use can be a challenge. Clearly, researchers have made great efforts to develop fatigue instruments to diagnose or evaluate fatigue severity, however at this moment no gold standard is available. In the future fatigue researchers must try to reach such a gold standard and should agree about the use of common instruments. This would make it easier to compare results of different studies.

In choosing a questionnaire, it is important to select one that is psychometrically sound and validated for the language and cultural setting of the study population. Furthermore, all efforts should be taken to ensure that the questionnaire is measuring the concept that the study intends to measure. For example, some fatigue measures state they asses fatigue severity, but in reality proves to assess the limitations caused by the fatigue. So, read carefully the items before selecting a questionnaire (for example “Because of my fatigue complaints, I am not able to keep my thoughts on it” compared to “When I am doing something, I can not keep my thoughts on it”). Furthermore, the choice of a questionnaire should be closely aligned with the goal of measurement, for example research versus clinical assessment. In clinical practice, it is important to unravel fatigue systematically rather than waiting until patients report the symptoms spontaneously. A cutoff point to differentiate between normal variations or a pathological level of fatigue is helping the clinician in his decisions. Also important to consider is the respondent burden and possible limitations in processing information. Therefore, a brief and simple measurement would be most appropriate to use in a clinical setting. In research other standards can apply. The fatigue questionnaire should match the research questions being asked. For example, a study focusing on possible cognitive manifestations of fatigue should consider use of a measure that includes a mental or cognitive scale. The amount of research on the management of postcancer fatigue is

growing in the last years. Instruments used in intervention studies must be sensitive enough to detect change over time and stable enough to be used repeatedly.
The CIS, MFI, FQ and the FSI are most used in studies on postcancer fatigue. All these questionnaires have good psychometric qualities. The additional value of the CIS and the FQ is that these questionnaires have cutoff points to capture the presence of severe and clinically important cases of fatigue. These instruments can be used in the individual patient to identify severely fatigued patients and also for prevalence estimates in populations.

2. What is known about prevalence and the course of postcancer fatigue?
In this paragraph the following topics will be discussed:
2.a. What is the prevalence of postcancer fatigue? (cross-sectional studies)
2.b. What is the relationship between time since treatment and postcancer fatigue?
2.c. What is the course of postcancer fatigue? (longitudinal studies)
At this moment 7 cross-sectional studies reported about the percentages of cancer survivors suffering postcancer fatigue.[5,27,34,40,44,45,49] Five longitudinal studies investigated the course of postcancer fatigue.[6,8,20,23,37] In Table 2 these studies are summarized, describing the mean time since treatment, study design, diagnosis and treatment characteristics, patients characteristics, prevalence of fatigue, fatigue instrument used and the cutoff point of the instrument representing fatigue caseness. The studies are classified in sequence of time since end of curative treatment.

2.a. What is the prevalence of postcancer fatigue?
The cross-sectional study of Servaes et al.[40] investigated a sample of breast cancer survivors, in which 38% experienced severe fatigue 2.5 years after cancer treatment. This percentage was significantly higher than the incidence of severe fatigue in matched healthy volunteers without a history of cancer (11%). Within a large sample of breast cancer survivors, 35% reported severe fatigue 2.9 years after treatment.[45] In another study of Servaes et al. investigating a sample of patients who were treated a mean of 3 years earlier for various kind of cancers, 19% experienced persistent severe fatigue.[44] Sugawara et al. investigated fatigue in breast cancer survivors without major depression.[27] Thirty-seven percent of the patients exhibited fatigue 4 years after treatment. Thirty-five percent of cancer survivors experienced severe fatigue 9.3 years after finishing stem cell transplantation (SCT) for leukemia or malignant lymphoma.[5] In a sample of Hodgkin's survivors, with a mean of 12 years after curative treatment, 26% had substantial fatigue. This percentage was significantly higher than the percentage among the general Norwegian population (11%).[49] Sixteen percent of disease-free testicular cancer patients were identified as having chronic fatigue 12 years after treatment. Fatigue was more prevalent than in males of the general population (10%).[34]
In conclusion: The percentages of fatigued cancer survivors found in cross-sectional studies ranged from 16%-38%. Three studies demonstrated that the percentage of fatigued cancer survivors was significantly higher than the percentage in a control group of persons without cancer, which was about 10-11%.

Table 2

Cross-sectional (CS) and longitudinal studies (LS[1,2,3,4,5]) investigating prevalence of post-cancer fatigue: arranged on time since curative treatment

Study	Study design	Time since treatment	Diagnosis and treatment	Patient characteristics	prevalence of fatigue	Measurement / Fatigue Casesness (FC)
Nieboer et al, 2005 [23]	LS[1]	1 year	Breast cancer survivors treated with standard-dose chemotherapy or high-dose chemotherapy	N=430, mean age around 45	19%	SF 36 – Vitality FC ≤ 46
Nieboer et al, 2005	LS[1]	2 years			22%	
Servaes et al., [6] *Chapter 2*	LS[2]	2.4 years	Breast cancer survivors treated with surgery and/or radiotherapy and/or chemotherapy	N=121, mean age 47 (sd 6) *subgroup Servaes et al., 2002* [40]	39%	CIS-Fatigue FC ≥ 35
Servaes et al., 2002 [40]	CS	2.5 years	Breast cancer survivors treated with surgery and/or radiotherapy and/or chemotherapy	N=150, mean age 46 (sd 6) *Reference group:* 78 women without history of cancer, mean age 48 (sd 6)	38%	CIS-Fatigue FC ≥ 35
Bower et al., 2000 [45]	CS	2.9 years	Breast cancer survivors treated with chemotherapy and/or radiotherapy	N=1953, mean age 55	35%	SF 36 – Vitality FC ≤ 50
Servaes et al., 2001 [44]	CS	3 years	Cancer survivors with different cancer diagnosis treated with chemotherapy and/or radiotherapy	N=85, mean age 48 (sd 14), 60% male	19%	CIS FC ≥ 35
Bower et al., 2006 [8]	LS[3]	3.5 years	Breast cancer survivors treated with chemotherapy and/or radiotherapy.	N=761, mean age around 59 years *Subgroup Bower et al., 2000* [45]	34%	SF 36 – Vitality FC ≤ 50

Table 2 continued

Study	Study design	Time since treatment	Diagnosis and treatment	Patient characteristics	prevalence of fatigue	Measurement / Fatigue Casesness (FC)
Sugawara et al., 2005 [27]	CS	4 years	Breast cancer survivors treated with surgery and/or radiotherapy and/or chemotherapy	N=79, mean age 48 (sd 6)	37%	CFS FC ≥ 18
Servaes et al. *Chapter 2*	LS[2]	4 .5 years			23%	
Servaes et al., 2003 [37]	LS[4]	6 years	Cancer survivors with bone and soft tissue tumours, (malignant and benign tumours) treated with surgery and/or radiotherapy and/or chemotherapy	N= 71 malignant tumour, mean age 43 (sd15), 54% male N= 99 benign tumour, mean age 34 (sd13), 53% male	28%	CIS-Fatigue FC ≥ 35
Bower et al., 2006	LS[3]	6.3 years			21%	
Servaes et al., 2003	LS[4]	8 years			26%	
Hjermstad et al., 2005 [20]	LS[5]	8 years	Hogkin's disease survivors treated with radiotherapy and/or chemotherapy. 15 patients underwent a SCT	N=476, median age 46, 56% male	28%	FQ FC ≥ 4 on dichotomized scale
Hjermstad et al., 2005 [20]	LS[5]	8 years	Hogkin's disease survivors treated with radiotherapy and/or chemotherapy. 15 patients underwent a SCT	N=476, median age 46, 56% male	28%	FQ FC ≥ 4 on dichotomized scale

Table 2 continued

Study	Study design	Time since treatment	Diagnosis and treatment	Patient characteristics	prevalence of fatigue	Measurement / Fatigue Casesness (FC)
Gielissen et al., 2007 [5] *Chapter 6*	CS	9.3 years	Cancer survivors diagnosed with acute/chronic leukaemia, lymphoma treated with a SCT	N=98, mean age 45 (sd 11), 58% male	35%	CIS-Fatigue FC ≥ 35
Loge et al., 1999 [49]	CS	12 years	Hodgkin's disease survivors treated with radiotherapy and/or chemotherapy	N=459, mean age 44 (sd 12), 56% male *Reference group: N*=2214 general population, mean age 45 (sd 17), 49% male	26%	FQ FC ≥ 4 on dichotomized scale
Fosså et al., 2003 [34]	CS	12 years	Testicular cancer survivors, 41% had postorchiectomy radiotherapy 39% had postorchiectomy chemotherapy	N=791, median age 44 *Reference group:* 1112 males of general population	16%	FQ FC ≥ 4 on dichotomized scale
Hjermstad et al., 2005	LS[5]	16 years			25%	

Fatigue questionnaires: CIS-Fatigue - Checklist Individual Strength subscale Fatigue; SF 36 Vitality –Short Form 36 Health Survey,subscale Vitality; CFS - Cancer Fatigue Scale; FQ- Fatigue Questionnaire.
SCT : stem cell transplantation

2.b. What is the relationship between time since treatment and postcancer fatigue?

Seven studies found no association with postcancer fatigue and time since diagnosis.[16,32,45,47,49,51,52] One study did report an association between the time since diagnosis of haematological malignancy and fatigue, with those more recently diagnosed experiencing more fatigue.[38] Thirteen studies found no association with time since end of treatment.[5,6,19,20,27,28,34,36,43,44,46,47,50] Hann et al. found that the longer the time elapsed since bone marrow transplantation in breast cancer survivors, the more severe fatigue occurred.[55]

In conclusion: Most studies did not find an association between postcancer fatigue and time since end of treatment or time since diagnosis.

2.c. What is the course of postcancer fatigue?

A longitudinal study of Nieboer et al. demonstrated that fatigue levels before cancer treatment were similar with those observed 1, 2 and 3 years after this baseline assessment.[23] All patients had completed chemotherapy at the 1 year time point. Approximately 20% of women were classified as fatigued at each assessment point. In a study of Servaes et al. 39% of the breast cancer survivors experienced severe fatigue at 2.4 years post treatment.[6] After a follow-up period of 2 years 23% of the original group of patients were persistent severely fatigued, demonstrating a decrease of 16%. Bower et al. showed that within a large sample of breast cancer patients 34% experienced fatigue at 3.5 years after cancer treatment, this percentage decreased to 21% six-and-a-half years after cancer treatment.[8] In a sample survivors of bone and soft tissue tumors Servaes et al found that the percentage of severe fatigue remained about equal, 28% (6 years after treatment) to 26% (8 years after treatment).[37] Hjermstad et al. found in a large study that 28% of Hodgkin's survivors experienced fatigue 8 years after treatment. This percentage remained about equal after a 8 year follow-up (16 years after treatment), namely 25%.[20]

In conclusion: The percentages of fatigued cancer survivors found in longitudinal studies ranged from 19%-39%. A longitudinal design is the most methodologically sound approach to determine the temporal variability of postcancer fatigue; the same group of cancer survivors are measured with the same fatigue questionnaire at two different time points. Because costly in terms of both time and resources, most researchers use a cross-sectional design to determine the prevalence and/or course of postcancer fatigue. At this moment there are only 5 longitudinal studies.

Conclusion

Postcancer fatigue is an important problem for a considerable subgroup of cancer survivors. The percentages of fatigued cancer survivors found in all studies ranged from 16%-39%. Setting these studies against time since end of curative treatment, demonstrates that there is a recovery of fatigue during the first 3 – 4 years after curative treatment after which it remains a persistent problem for about a quarter of the cancer survivors.

There are three exceptions in this pattern. The first exception is found in the results of the study of Nieboer et al.[23] Bower wrote an editorial as reaction on this paper.[82] Besides the merits of the study, like the study design (before and yearly after randomisation), Bower also made some critical comments. The percentage of patients who were categorized as fatigued

was quite low, and the mean levels of fatigue were comparable with Dutch population norms. These results might lead one to conclude that fatigue is not a significant problem among cancer survivors. However, in other studies considerable higher percentages of cancer survivors with persistent fatigue were found (see Table 2). In addition, there are also studies that have shown that fatigue is more prevalent in cancer survivors than in persons without a history of cancer.[34,40,49] Bower indicates that women in the study of Nieboer et al. were participants in a clinical trial and may not be representative of the broader population of cancer patients. In addition, the cutoff point used to classify fatigued patients in this study was more stringent than used in previous research (SF-36 Subscale Vitality < = 46, instead of < = 50), which may have restricted the size of the fatigued group. Servaes et al. found 3 years after cancer treatment a lower percentage than expected, 19% of the cancer survivors experienced severe fatigue.[44] Because this study has been conducted in our research centre we know the shortcomings of this study. The sample probably does not represent a well balanced cancer survivors population. It might be that patients without fatigue were more inclined to participate. In contrast, the results of *Chapter 6* demonstrated that the percentage of patients with fatigue is higher than expected, 35% of the cancer survivors experience severe fatigue even 9 years after treatment.[5] However, this result is in agreement with the assumption that patients with more aggressive treatments are more at risk for persistent fatigue.[6,8,37,54] For more definitive conclusions, a longitudinal design in this particular group is necessary.

In conducting research on postcancer fatigue the importance of a comparison group should be kept in mind. Since fatigue is a common symptom in the general population, some frame of reference is necessary in order to evaluate data on postcancer fatigue. Additionally, more longitudinal studies that assess patients before, during and after cancer treatment are necessary to determine more accurately the prevalence of fatigue in cancer patients and to identify the exact course of fatigue. This kind of research will enable us to calculate how many patients begin treatment with significant fatigue, how many develop fatigue during treatment and how many experience persistent fatigue long after cancer treatment completion. This kind of research will also enable us to identify those cancer patients most at risk for postcancer fatigue.

3. Predisposing, Precipitating and Perpetuating factors of postcancer fatigue

For a better understanding of postcancer fatigue we used the model of predisposing, precipitating and perpetuating factors. In this model particular factors in a patient's life can lay the groundwork for, initiate or maintain the process of persistent fatigue. The predisposing factors are the characteristics of a patient that enhance the chance to develop fatigue as soon as a precipitating factor is present. Precipitating factors trigger the onset of fatigue in cancer patients. The perpetuating factors are factors that maintain the fatigue over time. In this paragraph the existing literature on the three factors of the model will be discussed. Because the focus of this dissertation is on postcancer fatigue, the emphasis in this paragraph will also be on the perpetuating factors of postcancer fatigue and therefore will be discussed more elaborately than the other two factors.

3.a. Predisposing factors

Studies investigating predisposing factors of postcancer fatigue are difficult to conduct. In order to examine predisposing factors of postcancer fatigue, large prospective studies are needed investigating people in the general population, subsequently look into those patients who develop cancer. These patients need to be followed during and long after cancer treatment to explore which patients develop postcancer fatigue. These kind of studies are nearly impossible. Until now the well known large cohort studies never focused on fatigue.

To our knowledge, there are only two prospective studies trying to examine predisposing factors of postcancer fatigue by investigating patients just before cancer treatment, just after cancer treatment and long after cancer treatment ended. Smets et al. investigated possible predictors of persistent fatigue by assessing patients before, within two weeks of completion of radiotherapy and 9 months after radiotherapy.[53] The degree of fatigue, functional disability and pain before radiotherapy started were the best predictors of fatigue at 9 months follow-up, explaining 30%, 3% and 4% of the variance respectively. Geinitz et al. evaluated fatigue 8 days before radiotherapy, after radiotherapy, 2.5 years after treatment and found that patients who had elevated levels of fatigue, anxiety or depression at pre-treatment, were at risk for fatigue 2.5 years after radiotherapy, explaining 60% of its variance.[83]

A cross-sectional study of Loge et al. found that retrospective self-reported psychiatric symptoms before and during cancer treatment were no predictors of postcancer fatigue.[48]

Furthermore, two studies found that women were more prone to experience postcancer fatigue than men.[47,53] However, in nine studies this relationship was not found.[5,16,20,25,36,37,43,44,48]

In conclusion: There is some evidence that fatigue, functional disability, pain, anxiety and depression before cancer treatment are predictors of postcancer fatigue. However, we could wonder if the variables discussed (except for gender), are really predisposing factors of postcancer fatigue. The moment of assessment was just before treatment and the patients were already diagnosed with cancer. Therefore, it is impossible to differentiate if the studies are measuring predisposing factors or already disease related variables.

3.b Precipitating factors

Fatigue is one of the most common complaints of people with cancer. It affects the majority of patients actively undergoing cancer treatment, with proportions of as high as 99% having been reported.[1,2] It is generally accepted in clinical practice that fatigue complaints during cancer treatment are a result of the cancer and/or its treatment. However, the studies on this topic do not easily identify fatigue-related factors and contradictory results exists on each factor.[1,2] Factors thought to be involved among others are: the anti-cancer treatment, anaemia, cancer treatment side effects like nausea and vomiting, metabolic and endocrine alterations, emotional distress, sleep disturbances, prolonged inactivity, pain and infections.

In conclusion: It is clear that fatigue originates in the time period of diagnosis and anti-cancer treatment. Though the exact determinants of the onset of the fatigue is still poorly understood, its multifactorial nature seems to be generally acknowledged. There is the primary influence of the tumour on the organs involved. Second, secondary effects of the

tumour, like anemia, can play a role. Third, the anti-cancer treatment can be an important cause of fatigue, and finally, psychological factors like anxiety, emotional distress, depression can lead to complaints of fatigue.[1,2,84-86]

3.c Perpetuating factors

Are disease and/or treatment characteristics related to postcancer fatigue?

Once fatigue has developed, several maintaining factors can impede recovery. Starting from the hypothesis that postcancer fatigue is initially caused by the cancer itself and/or cancer treatment, many studies investigated the association between postcancer fatigue and initial disease and treatment characteristics. The majority of the studies found no association between postcancer fatigue and cancer type (head and neck, gastrointestinal, gynaecological, lung, breast, prostate, testis, Hodgkin's disease, Non-Hodgkin's lymphoma, acute leukaemia, bone and soft tissue tumours),[5,28,32,37,44,46,53] disease stage at time of diagnosis,[20,39,47-53] size of original tumour,[39,52,55] nodal involvement,[27,39,55] the cancer treatment received (e.g. type of treatment, regime, dose, cycles, length of treatment, treatment burden).[5,6,8,16,20,22,27,32,34,39,40,44, 46,47,49,50-53,55,86,87] However, five studies found a positive association between postcancer fatigue and intensity of cancer treatments.[5,6,8,37,54] Servaes et al. found a relation between persistent fatigue and duration of cancer treatment.[6] Patients who finished treatment within 1 month were less fatigued than patients of whom the treatment proved to be longer than 1 month. This is in agreement with the results of another study of Servaes et al. in which a relation was found between post-treatment fatigue and number of former operations.[37] Patients whose surgery had been without complications and who had not received any adjuvant therapy were less at risk of developing severe fatigue than other patients. Bower et al. showed in a longitudinal study that women treated with either radiation or chemotherapy alone showed a small improvement in fatigue compared with patients who received a combination treatment of both radiation and chemotherapy.[8] This finding is in agreement with the results of Woo et al. who found that patients who received combination therapy had the highest fatigue scores.[54] In a cross-sectional study of Gielissen et al. no natural recovery of fatigue was found, even up to 15 years after finishing SCT.[5] The percentage of survivors experiencing postcancer fatigue remained high.

Two studies found an association between postcancer fatigue and the presence of B-symptoms during cancer treatment[20,36] (B-symptoms: fever; drenching sweats, especially at night; unintentional weight loss of >10% of normal body weight over a period of 6 month or less).

In conclusion: Previous disease and treatment characteristics are unrelated to postcancer fatigue. However, there is some evidence that patients who are treated with only a surgery are less at risk for postcancer fatigue and survivors who are treated with more aggressive treatments are more at risk.

Are demographic variables related to postcancer fatigue?

Nine studies found an association between postcancer fatigue and age.[19,25,34,36,38,45,48,54,87] On the contrary, ten studies did not find such relationship.[5,8,16,27,32,37,43,51-53,55] The relation between age and fatigue is complicated by an inconsistency in the direction of the association. Five studies found that older survivors experience more fatigue,[25,34,36,38,48] whereas four studies reported that younger survivors experience more fatigue.[19,45,54,87]

Only a few studies found that education,[48,50] income[25,38,50] and marital status[25] were related to fatigue, most studies did not find such relationship.

In conclusion: There is no clear relationship between demographic characteristics and postcancer fatigue.

Is current somatic co-morbidity related to postcancer fatigue?

As a consequence of cancer treatment, survivors can be at risk for a number of long term side effects, some of which may contribute to the persistence of fatigue. Servaes et al. found that fatigue severity was predicted by the number of oncological complications after cancer treatment.[37] Hodgkin's disease survivors with pulmonary dysfunction were more fatigued than those with normal pulmonary function.[43,47] In addition, two studies found an association with fatigue and cardiac problems.[8,16] However, Knobel et al. did not find such relationship.[43]

Three studies did not detect an association between well treated hypothyroidism and postcancer fatigue.[16,43,47] This finding is not surprising, because a well treated hypothyroidism is even not an exclusion criterion for the diagnosis of chronic fatigue syndrome.[89]

Women often become menopausal as a result of chemotherapy. Menopausal symptoms seem to be both more prevalent and more severe in cancer survivors than in healthy women[90,91] and is associated with postcancer fatigue.[6,22,30,45,51] Current tamoxifen use was unrelated to fatigue severity.[6,819,22,27,45,51,52,55,87]

Patients with current co-morbidity (related or unrelated to the cancer treatment) were significantly more fatigued than patients without co-morbidity.[5] Gielissen et al. found no difference in fatigue between survivors without medication, with antibiotics or with beta blockers.[5] In contrary, Ng et al. found that medications for a mood disorder was an independent factor for Hodgkin's disease survivors in explaining fatigue.[16]

In conclusion: Current co-morbidity, related as well as unrelated to the previous cancer treatment, might be a factor in the persistence of the fatigue.

Is depression related to postcancer fatigue?

All studies examining the association of depression to fatigue concluded that a relationship exists[1,2,8,19] This suggest that fatigue is closely linked to depression in cancer survivors. Does this also mean that depression is the explanation of postcancer fatigue?

First, it is important to realize that all studies that found an association between postcancer fatigue and depression used a depression questionnaires and did not diagnose a clinical depression with the DSM IV criteria assessed by a psychologist or psychiatrist. This means that there is a positive association between depressive mood and postcancer fatigue. But if there may be a relation between clinical depression and postcancer fatigue has not been

answered by the existing literature. Second, the association between fatigue and depression is complex. Fatigue can occur as a symptom of depression or may precipitate feelings of depression because of its interference with mood, work and leisure activities. In agreement with this last viewpoint, some studies show that fatigue in cancer survivors could not be explained by depression alone. Servaes et al. reported that 12% of a group fatigued breast cancer survivors could be considered clinically depressed.[40] This was measured with the Beck Depression Inventory for primary care (BDI-pc). The BDI-pc is composed of cognitive and affective items only to prevent an overlap between the physical aspects of fatigue with the somatic symptoms of depression.[92] Still in 88% of the severe fatigued patients no diagnosis of depression could be made. In another study the breast cancer group and benign breast problems group did not differ with regard to depressive symptoms, while they did differ with respect to fatigue scores.[50] Also Sugawara et al. found that a significant portion of cancer survivors without clinical depression experienced fatigue.[27] In this last study, the diagnosis of past and current clinical depression was based on a semi structured clinical interview conducted by a psychiatrist (SCID).

In conclusion: There is an association between depressive mood and postcancer fatigue. However, the majority of severely fatigued cancer survivors is not clinically depressed. Therefore, clinical depression is not a frequent perpetuating factor of postcancer fatigue.

Other possible perpetuating factors

All studies that examined the association of anxiety to fatigue concluded that a relationship exists.[1,2,6,8,19,27] Like depression, it is important to realize that all studies that found an association also used an anxiety questionnaires and did not diagnose anxiety disorders with the DSM IV criteria. Typically, feelings of anxiety in cancer survivors are higher than before the diagnosis, especially when a follow-up visit draws near.[93] In some patients anxiety levels may be continually and excessively elevated. There is evidence that a subgroup of fatigued cancer survivors experience excessive fear of disease recurrence.[5,19,37]

Some fatigued survivors coped poorly with the experience of having had cancer and cancer treatment. They continue to be (pre)occupied with what has happened to them (long) after the anti-cancer treatment has finished, exhibiting posttraumatic stress symptoms[5,94]

Furthermore, severely fatigued cancer survivors tend to attribute their complaints to their having had cancer or to the subsequent treatment they have undergone. These somatic attributions can perpetuate the fatigue.[3,5,37,40] Literature shows us that fatigued cancer survivors more frequently revert to ‘catastrophising’ as their coping strategy. Fatigue-related catastrophising cognitions sustain or even magnify the complaints.[5,51] Self-efficacy, reflecting the extent to which a patient feels or thinks to be able to control his symptoms, may also be implicated and appears pivotal in cancer survivors, in whom a low or negative self-efficacy has been related to increases in fatigue levels.[5,6,40] This relationship was also found in patients with chronic fatigue syndrome and in fatigued patients with multiple sclerosis.[95] Results of a study of Sugawara et al. demonstrated that fatigue in breast cancer survivors without depression was mainly predicted by neuroticism, explaining 25% of the variance.[27] On the contrary, two studies did not find an association between neuroticism and fatigue.[19,53]

Persisting sleep problems, irregular sleep patterns, poor quality of sleep is significantly related to postcancer fatigue in many studies.[5,6,40,45,50,51,53,55,87]
Pain was reported in 4 studies.[30,44,45,52] In these studies fatigue was significantly associated with pain. Servaes et al. demonstrated that patients with chronic fatigue syndrome reported more intense pain compared to fatigued cancer survivors.[44]
Significant associations between severe fatigue and self-reported physical functioning and physical activity was found in several studies.[5,6,16,25,28,32,40,44,52,53] Worse physical functioning and lack of activity was associated with more fatigue. Here, a fear that activity will aggravate the fatigue may be implicated. However, some survivors can be physically overactive, an overly active patient tends to overtax himself continuously, with all the consequential physical and emotional adverse effects. Both over and inactivity may perpetuate the symptoms of fatigue.[42,96] In addition, Young et al. found that negative beliefs about activity was significantly associated with fatigue.[19]
Severely fatigued cancer survivors experienced an insufficiency of supporting interactions compared to non-fatigued cancer survivors.[40] They have less social support than they would like. Lack of social support is a strong predictor for worse quality of life in cancer survivors.[97]
In conclusion: Anxiety, poor coping with cancer/cancer treatment, somatic attributions, catastrophizing, self-efficacy, sleep problems, pain and physical (in)activity, insufficiency of social support can perpetuate postcancer fatigue.

Conclusion

The reviewed studies in this paragraph support the model of predisposing, precipitating and perpetuating factors of postcancer fatigue. Disease and treatment characteristics have been demonstrated to be unrelated to the severity of the postcancer fatigue. The proposed precipitating factors for fatigue occurring during cancer treatment, i.e. the disease itself and its treatment, do no longer explain the persistent post-treatment fatigue (except there is some evidence for a positive relation between postcancer fatigue and intensity of the cancer treatment). Other factors seem to be much more important in perpetuating fatigue. Therefore, these factors should be the main target in the management of somatically unexplained postcancer fatigue.

4. Interventions to reduce post-cancer fatigue

Given the adverse effect of fatigue on the life's of cancer survivors development of interventions is critical. Especially because the population of cancer survivors is growing. Fortunately, the amount of research on the management of post-cancer fatigue increased considerably in the last years. Including papers on interventions in which survivors were a mean of 6 months after cancer treatment, 15 papers were found. All papers were published between 2003 and 2007. Two papers were published in 2003, two in 2004, three in 2005, seven in 2006 and at the time of writing one in 2007. Nine studies were pilot studies on management of postcancer fatigue. In this paragraph these published interventions for post cancer fatigue will be discussed.

4.a. Randomised controlled trials

Randomized controlled trials (RCT's) are widely considered the most reliable form of scientific evidence in assessing the effectiveness of interventions. Seven RCT's investigated the effect of an intervention on postcancer fatigue, measured as a primary or secondary outcome. In Table 3 the seven RCT's are elaborately described. Information is given on the content and duration of the intervention, patient's characteristics, number of assessments, fatigue questionnaire used and the effect of the intervention on fatigue.

Two RCT's found positive effects in reducing fatigue. Pinto et al. investigated the effects of a home-based physical activity program[24] and showed a beneficial effect on fatigue, with an effect size of 0.64. Cognitive behaviour therapy (CBT) especially designed for postcancer fatigue was found to be an effective treatment for cancer survivors with somatically unexplained fatigue (effect size 1.05; *Chapter 4*).[11] This latter study is the only RCT that analyzed the data by intention to treat. The uncontrolled follow-up results described in *Chapter 5* indicate that the positive results of CBT were maintained in patients who completed CBT after a mean follow-up period of about 2 years (effect size 1.7).

Five RCT's did not find positive effects in reducing fatigue. Courneya et al. reported on the efficacy of individualized aerobic training.[33] Fatigue was measured as a secondary outcome. Although cardiopulmonary function increased, no significant change on fatigue was found.

Basen-Engquist et al. investigated in a pilot study the effect of a lifestyle physical activity group program. The lifestyle group had significantly better physical endurance, however no increase was seen in physical activities. Also no effect was found on fatigue.[7]

Bennet et al. evaluated the effect of a motivational interviewing (MI) on increasing physical activity and improving fatigue, measured at three time points (baseline, 3- and 6 months follow-up).[4] The results of the MI intervention showed a significant increase in regular physical activities, but no improvement on fatigue could be found.

Molassiotis et al. conducted a RCT and found that a two-week acupuncture program (and to a lesser extent acupressure) showed beneficial effects on fatigue compared with sham acupressure.[15] However, after a two-week follow-up period this effect disappeared. In this study no data were collected about the exact time since end of cancer treatment (personal communication) and it was not possible to calculate the effect sizes. A second pilot study found no on effect on fatigue of a 7-week yoga programme.[10]

Table 3

Interventions on postcancer fatigue: content and duration of the intervention, patients characteristics, number of assessments, fatigue questionnaire used and the effect of the intervention on fatigue (Effect sizes / ES)

Intervention			Patients characteristics				Assessment		
content	duration	group (n); individual	Specific characteristics	patients (n)	mean age in years	time after diagnosis or treatment in months	number of assessments	fatigue instrument	Effect on fatigue
(1) Intervention: Exercise training on cycle ergo meters. 15 minutes exercise for week 1 through 3 and then systematically increased by 5 minutes every 3 weeks thereafter to 35 minutes for weeks 13 through 15. Control: Waiting list condition	3 times a week for 15 weeks	individual	breast cancer survivors	I : 24 C: 28	59 (sd 5) 58 (sd 6)	Treatment: 14 (sd 6) 14 (sd 7)	Two : T1: baseline T2: 15 weeks after baseline	secondary outcome : FACT- FS	no effect on fatigue
(2) Intervention: Home-based physical activity program. Survivors were encouraged to exercise 10 minutes on 2 days a week, then increased over the 12 weeks to 30 minutes per day on 5 days per week.	12 phone calls in 12 weeks	individual	within 5 years of breast cancer diagnosis sedentary survivors: exercised < one time per week for 20 minutes at vigorous intensity or	I : 42 C: 40	53 (sd 9) 53(sd10)	Diagnosis: 20 (sd 18) 23 (sd 17)	Two: T1: baseline T2: 12 weeks after baseline	Visual Analog Scale - 10 cm	effect on fatigue ES: 0.64

Table 3 continued

Intervention content	duration	group (n); individual	Patients characteristics Specific characteristics	patients (n)	mean age in years	time after diagnosis or treatment in months	Assessment number of assessments	fatigue instrument	Effect on fatigue
Study 2 continued									
Control: Were asked not to change their current level of activity. Phone calls to monitor problems that can affect normal activity of daily life	12 phone calls in 12 weeks		< two times per week for 30 minutes at moderate intensity for the past 6 months						
(3) Intervention: Cognitive behaviour therapy focused on perpetuating factors of postcancer fatigue; poor coping with cancer/treatment, fear of disease recurrence, dysfunctional cognitions regarding fatigue, dysregulation of sleep and activity and low social support. Control: Waiting list condition	13 sessions of 60 min in 6 months	individual	Survivors who experienced somatically unexplained severe fatigue : CIS >=35 completed curative treatment for cancer at least 1 year 49% female cancer types: 31% breast, 26% testicular, 17% hematologic, 26% other solid tumors	I : 50 C: 48	45(sd10) 45(sd10)	treatment: 66 (sd 52) 55 (sd 41)	Three: T1: baseline T2: 6 months after baseline T3: 1.9 years after T2	CIS-fatigue	effect on fatigue T2 : ES: 1.1 T3: ES: 1.7

Table 3 continued

Intervention content	duration	group (n); individual	Patients characteristics Specific characteristics	patients (n)	mean age in years	time after diagnosis or treatment in months	Assessment number of assessments	fatigue instrument	Effect on fatigue
(4) Life-style physical activity intervention: teaching cognitive behavioural skills related to exercise Guided discussion cancer-related topics Written informational material was provided Control: Standard care plus two mailings of the same written material.	21 sessions of 90 min. in 6 months	group; 7 – 15	within 7 years of breast cancer diagnosis not engaged in moderate physical activity for 30 minutes or more a day most days of the week	I : 35 C: 25	56(sd11) 54(sd12)	diagnosis: 39 (sd17) 37 (sd. 14)	Two: T1: baseline T2: 6 months after baseline	SF-36 Vitality	no effect on fatigue
(5) Intervention: Yoga according to a strict yoga protocol Control: Waiting-list condition	? sessions of 75 min. in 7 weeks	group; max. 10	minimum of 3 months post treatment 95% female 85% breast cancer survivors	I : 20 C: 18 total 38	+/- 50	diagnosis: +/- 56	Two: T1: baseline T2: 7 weeks after baseline	Subscale fatigue of EORTC QlQ-C30	no effect on fatigue

Table 3 continued

Intervention content	duration	group (n); individual	Patients characteristics Specific characteristics	patients (n)	mean age in years	time after diagnosis or treatment in months	Assessment number of assessments	fatigue instrument	Effect on fatigue
(6) Intervention: Motivational interviewing, to help to explore solutions to behavioural change to engage in moderate-intensity planned physical activity for 30 minutes on most days of the week Control: Were asked to maintain their current levels of physical activity. The calls were used to set times for measurement appointments and for brief social conversation.	one session inperson 2 phone calls of 20 min in 4.5 months 2 phone calls in 4.5 months	individual	survivors who experienced fatigued were under active: engaged in planned exercise < 3 days a week for 20 minutes 89% breast cancer survivors	I : 28 C: 28	56 (sd 9) 60(sd11)	treatment: 34 (sd 31) 50 (sd54)	Three: T1: baseline T2: 3 months after baseline T3: 6 months after baseline	Schwartz Cancer Fatigue Scale	no effect on fatigue
(7) Intervention: Acupuncture: Based on the Traditional Chinese Medicine, points for 'energy' were punctured	6 sessions of 20 min. in 2 weeks	individual	survivors who experienced moderate to severe fatigue: ≥ 5 on a 0 – 10 scale 68% female	I : 15	53(sd13)	post chemo and up to 5 years after diagnosis	Three: T1: baseline T2: 2 weeks after baseline	MFI (20 items)	effect of both interventions on fatigue at T2

Table 3

Intervention content	duration	group (n); individual	Patients characteristics Specific characteristics	patients (n)	mean age in years	time after diagnosis or treatment in months	Assessment number of assessments	fatigue instrument	Effect on fatigue
Intervention 7 continued									
Acupressure: Survivors were taught to massage/press the points that are associated with 'energy'	one session, daily 1min at home		cancer types: 36% lymphoma, 32% breast, 15% gastrointestinal, 11% lung, 4% gynaecological, 2% brain.	I : 16			T3: 4 weeks after baseline		effect lost at T3 ES: ??
Control: Sham acupressure: were taught to apply pressure in three points that are not associated with 'energy'	one session, daily 1min at home			C: 16 total 47					

Studies:

1. Courneya et al. Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. J Clin Oncol 2003; 21(9): 1660-1668
2. Pinto et al. Home-based physical activity intervention for breast cancer patients. J Clin Oncol 2005; 23(15): 3577-3587.
3. Gielissen et al: *Chapter 4* and *Chapter 5*.
4. Basen-Engquist et al. Randomized pilot test of lifestyle physical activity intervention for breast cancer survivors. Patient Educ Couns 2006; 64: 225-234.
5. Culos-Reed et al. A pilot study of yoga for breast cancer survivors: physical and psychological benefits. Psycho-Oncol 2006; 15: 891-897.
6. Bennett et al. Motivational interviewing to increase physical activity in long-term cancer survivors. Nursing Research 2007; 56(1): 18-27.
7. Molassiotis et al. The management of cancer-related fatigue after chemotherapy with acupuncture and acupressure : a randomised controlled trial. Complement Ther Med, in press

Number:
I : intervention condition
C: control condition
Fatigue questionnaires: SF 36 – Short Form 36, EORTC QLQ C30 – European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; FACT-FS - Functional Assessment of Cancer Therapy – Fatigue Scale ; MFI – Multidimensional Fatigue Inventory ; CIS- Checklist Individual Strength.
Effectsize (ES):
Post-treatment assessment of both conditions were used in the calculation Cohen's d. In study 3 the follow-up ES is calculated using the pre-treatment and follow-up assessment.

4.b. Non-randomised/non-controlled studies

Nine non-randomised/non-controlled studies reported about the efficacy of an intervention on postcancer fatigue.[9,12,14,18,21,26,29,31,35]

Fatigue affects the majority of patients actively undergoing cancer treatment, with proportions of as high as 99% having been reported.[1,2] As indicated earlier in this review, the proportion of fatigued cancer survivors range from 16%-39% on the long term. This demonstrates that a majority of the patients recover from fatigue in the first years after treatment. Therefore, if an intervention is given just after cancer treatment, it is particularly essential to compare patients in the intervention group with patients in a control group. Otherwise the results can well be based on natural recovery. All nine non-randomized/non-controlled also included patients who were less than 1 year after curative treatment

Lindemalm et al. reported on the effect of a group intervention on fatigue severity and was focused on multidisciplinary education and support groups.[21] An effect was found on fatigue, however this effect was no longer present at a 3 months follow-up. This study is the only non-randomized/non-controlled that included a follow-up assessment. Four pilot studies reported on the efficacy of exercise training on fatigue. Two of them were pilot studies and investigated the effect of individualized aerobic exercise.[9,35] Both studies found a significant improvement of fatigue severity. The two other pilot studies described the effect of a home based physical activity programmes.[26,29] Wilson et al. showed a beneficial effect on postcancer fatigue,[26] Christopher et al. did not.[29] Two studies demonstrated the positive effect of a rehabilitation group program, combining physical exercise and psycho-education.[14,18] One pilot study reported on the effect of acupuncture and showed an improvement on postcancer fatigue.[31] A study on the effect of methylphenidate, a psycho stimulant that blocks the presynaptic dopamine uptake, showed a decrease in fatigue severity.[12]

Conclusion

Although research on management of postcancer fatigue has increased, there are still just seven RCT's with their own shortcomings and only two RCT show positive effects in reducing fatigue. When conducting intervention studies follow-up assessments are essential. It is important to know if the benefits remain over time after the intervention has finished. Only one of the two effective RCT's included a follow-up assessment[3]. In *Chapter 5* it is demonstrated that the positive effects of CBT were maintained at about 2 years after finishing the therapy. However, this long term effect was investigated in an uncontrolled design.[3] Two other RCT's also included a follow-up assessment. Bennett et al.[4] and Molassiotis et al.[15] reported no positive effects at follow-up.

The existing evidence suggest that until now CBT especially designed for postcancer fatigue[3,11] and a home-based physical activity intervention [24] are effective in treating postcancer fatigue. A common element in those two interventions lies within the area of physical activity. However, two different kinds of activity enhancement were investigated, graded exercise and graded activity. Graded exercise is a program of usually 12 weeks aimed at increasing fitness. Patient engage in intensive to strenuous exercise and the

intensity is often monitored with a hart-rate recorder. Graded activity is a program with gradual increase in physical activity, without striving for increase of fitness. In the two positive trials different goals of physical activity were used. Pinto et al.[24] investigated a home-based graded exercise program and recommendations were done for moderate-intensity physical activities with the aim of increasing physical fitness (brisk walking, biking, swimming, or use of home exercise equipment). Graded activity is one of the treatment modules of the CBT for postcancer fatigue.[11] Forty-nine percent of the CBT time was spent on issues around graded activity (*Chapter 3*). These studies seem to suggest that some increase in physical activity is necessary to relieve fatigue, although the exact mechanism by which activity enhancement decreases fatigue remains to be determined. On the contrary, three RCT's show an increase in physical activities or physical fitness but no decrease in fatigue complaints.[4,7,33] CBT for postcancer fatigue addresses also other factors besides physical activity. Therefore we think that other factors are also important in relieving fatigue, supported by the larger effect size of the CBT-study compared to the graded exercise study. Future studies should be aimed at investigating how important the role of physical activity is in decreasing fatigue.

Within the context of prevention, more longitudinal studies (design: pre-cancer treatment, post-cancer treatment and follow-up) are required to determine more accurately the developing of postcancer fatigue. This kind of research will enable us to identify early determinants and risk factors of postcancer fatigue and may facilitate the development of new and the improvement of existing interventions. Ultimately, this hopefully leads to preventing persistent fatigue in cancer survivors by delivering early interventions to those most in need.

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Summary

Earlier and more accurate diagnosis and improved observation and treatment have resulted in an increased number of people that has been successfully treated for cancer. Despite the fact that these persons have been cured from cancer, a substantial minority of the cancer survivors experience severe fatigue long after the cancer treatment has ended. From 1996, the Expert Centre Chronic Fatigue studied causes, natural course, consequences and factors relating to postcancer fatigue. Based on these studies the model of precipitating and perpetuating factors is believed to be useful in understanding postcancer fatigue. The assumption is that cancer itself and/or cancer treatment may have triggered fatigue (precipitating factors), but other factors are responsible for persistence of fatigue complaints (perpetuating factors). These perpetuating factors should be the target in the management of postcancer fatigue.

This dissertation consists of two studies on the subject of postcancer fatigue complaints, three on the management of postcancer fatigue and two on the assessment of fatigue.

The goal of *Chapter 2* was to investigated in a longitudinal study the prevalence of persistent fatigue in 121 breast cancer survivors, whether fatigue was related to former treatment modalities and to investigate possible predictors of persistent fatigue. Patients were assessed at 2.4 years and 4.5 years after curative treatment on psychological, physical, social, cognitive and behavioral aspects. Furthermore, patients filled out a monthly fatigue questionnaire during a two-year period. Based on the monthly fatigue questionnaires, 24% of the cancer survivors experienced persistent fatigue. Persistent fatigue seemed to be related to the duration of former treatment but unrelated to type of surgery, type of adjuvant therapy and time since treatment finished. We found that patients who did not receive any kind of adjuvant therapy and who did not experience any kind of complications during treatment, i.e. those patients that completed treatment for cancer within one month, were at lower risk for persistent fatigue. High anxiety, high impairment in role functioning and low sense of control over fatigue symptoms at the first assessment were predictors of persistent fatigue. These predictors of persistent fatigue were used, among others, in the development of a cognitive behavioral intervention for postcancer fatigue. The treatment protocol of this intervention is presented in *Chapter 3*. The treatment protocol encompasses six modules that coincide with the six factors assumed to perpetuate the symptoms of fatigue, such as poor or inappropriate coping skills, a heightened fear of a recurrence of the cancer, dysfunctional fatigue-related cognitions, dysregulatory sleep-wake cycles, dysregulatory activity patterns, and insufficient social support and negative interactions. The perpetuating factors are not the same for each patient. To determine the key factors for each patient, the patient completes several assessment instruments. Based on the tools' norm scores it is determined whether the patient has a deviant or problem score. Subsequently, founded on the outcomes of the assessment instruments and the patient-therapist interview an individually tailored treatment plan is drawn up comprising only the patient-relevant modules. In this chapter the rationale of each module is discussed, followed by the relevant assessment instrument and the proposed

course of action. Explanation of the model of perpetuating factors, challenging fatigue-related cognitions, attaining and maintaining a base level of physical activity, gradual increase of physical activity were modules that became part of the tailored treatment plan of all patients. The regulation of sleep-wake rhythm, by encouraging to adhere to fixed bedtimes and wake-up times and instilling more realistic expectations toward the patient's social support group were part of the treatment protocol for the majority of the patients. Acquiring better coping with the experience of cancer and challenging the thoughts of fear of disease recurrence were necessary for a subgroup of the patients.

The next step was studying the effectiveness of cognitive behaviour therapy (CBT) for postcancer fatigue. This study is presented in *Chapter 4*. In a randomised controlled trial we compared CBT with a waiting list condition. At the time of participation in the trial cancer survivors completed curative treatment at least 1 year previously and had no evidence of disease recurrence. Data of 112 cancer survivors with somatically unexplained fatigue were analyzed on an intention-to-treat basis and the last observation was carried forward if data were missing. Both conditions were assessed two times, at baseline and 6 months later. Results showed that CBT was significantly more effective than the waiting list condition for the two primary outcome variables, fatigue severity and functional impairment and for the secondary outcome variable, psychological distress. Furthermore, the proportion of patients in the intervention condition with clinically significant improvement on fatigue severity (54%), functional impairment (50%), and self-rated improvement (66%) was significantly higher than in the waiting list condition (respectively, 4%, 18%, 21%).

Patients in the waiting list condition were informed beforehand that, if desired, they could start therapy directly after the waiting period of 6 months. In *Chapter 5* the long term effects of CBT were investigated in patients that were involved in the RCT described in Chapter 4 and completed CBT, including patients in the intervention condition and patients who had been treated after the 6 months waiting list. Therefore, this chapter describes the results of an uncontrolled follow-up study. Furthermore, predictors of fatigue severity at follow-up were exploratory investigated. In total 68 fatigued cancer survivors completed CBT and were assessed at pre-treatment, post-treatment and at follow-up. The mean length of time between completion of therapy and the follow-up assessment was 1.9 years (sd=1.0) with a range of 6 months to 4 years. Improvements on fatigue severity, functional impairment and psychological distress after CBT appeared to remain stable during the follow-up period. Patients who were not fatigued anymore at follow-up had the same level of fatigue, functional impairment and a lower level of psychological distress compared to a reference group of non-fatigued cancer survivors. The explorative regression analysis showed a trend that more fatigue, higher psychological distress and stronger somatic attributions at pre-treatment contributed to persistent fatigue severity at follow-up. These results suggest that if a patients continues to think that the cancer itself and/or cancer treatment is responsible for the experienced fatigue, the chance on recovery is lowered. Somatic attributions should receive more attention during the CBT. Because somatic attributions in fatigued cancer survivors can be reinforced by inaccurate information delivery about the cause of postcancer fatigue, the chance of improvement with CBT can be increased by (further) education on postcancer

fatigue for professionals working in cancer care. In addition, fatigued cancer survivors with high scores on psychological distress (probably indicative of psychiatric comorbidity) proved to have hardly any chance to improve with CBT for postcancer fatigue.

Literature suggests that cancer survivors with more aggressive treatments are more at risk for postcancer fatigue. Therefore, we investigated in *Chapter 6* ninety-eight cancer survivors after completion of a highly aggressive and demanding medical intervention, a stem cell transplantation (SCT). Diagnoses included were acute myeloid or lymphatic leukaemia in first complete remission, chronic myeloid leukaemia in first chronic phase, Non-Hodgkin lymphoma in first complete remission. The conditioning regime included total body irradiation. All patients had to be in persistent complete remission for at least one year after SCT. Furthermore, patients with Graft versus Host Disease (GVHD) grade III and IV, acute GVHD or extensive chronic GVHD were excluded. Also patients with a hemoglobin (Hb) concentration of 10 g/dl and lower were not eligible for this study. We studied the prevalence of fatigue, the association between medical variables and fatigue and if the model of perpetuating factors of postcancer fatigue derived from previous studies in cancer survivors, without SCT, is applicable in SCT survivors. Thirty-five percent of the patients experienced severe fatigue, while an additional 12 patients (12%) had heightened fatigue scores. The percentage cancer survivors with severe fatigue remained stable during the years after transplantation, even after more than 15 years. Previous literature suggest that fatigue complaints continue to decrease during the first 3 – 4 years after curative treatment and remains a persistent problem for about a quarter of the cancer survivors. In patients after a SCT the percentage of fatigue remains high. This finding is in agreement with the assumption that patients with more aggressive treatments are more at risk for persistent fatigue. We found no associations with fatigue severity and characteristics of the medical history (e.g. diagnose, transplantation type, time since transplantation, grade of GVHD, hospitalization and complications) and current medical characteristics (e.g. medication use, Hb-concentration, body mass index). There was one exception, patients with a current medical comorbidity scored higher on fatigue severity compared to patients without a current medical comorbidity. The model of perpetuating factors derived from previous studies in cancer survivors, not undergoing transplantation, appeared to be applicable in SCT cancer survivors as well. Persistent fatigue was well predicted by the supposed perpetuating factors: poor coping with the experience of cancer, fear of disease recurrence, dysfunctional cognitions concerning fatigue, dysregulation of sleep, dysregulation of activity and insufficiency in social support. In total 68% of the variance of fatigue severity was explained by the six factors. These results suggests that in the absence of clear medical causes, the CBT especially designed for fatigued cancer survivors after conservative treatment, could also be used in the management of fatigue after SCT.

Chapter 7 offers encouraging data for the use of the Pictorial Representation of Illness Measure (PRISM) as a tool in fatigue research and clinical practice. Patients were shown a A4 shaped paper with a yellow fixed disk at the bottom-right hand corner and were asked to imagine that the paper represents his/her life as it is at the moment. The disk represents the subjects' self. Detachable disks was used to represent the fatigue and illness. Subjects were

asked: ‘where would you put fatigue/illness to reflect its importance in your life at this moment? We tried to get a better understanding of suffering associated with fatigue using this simple, graphic instrument in three different samples of fatigued patients; 60 chronic fatigue syndrome patients, 82 fatigued cancer survivors and 68 fatigued patients with various neuromuscular disorders. The objective was to investigate if suffering was a separate dimension of chronic fatigue, if there was a difference in suffering between different fatigued patient groups, if it was possible to discriminate within a patient between suffering due to an illness and suffering due to fatigue and if suffering diminished following treatment for chronic fatigue. We did not find high correlations, indicative for a parallel test, with other dimensions of fatigue (fatigue severity, functional impairment, physical activity, psychological distress, sleep disturbances, concentration problems, social functioning, self-efficacy, causal attributions). Therefore, the PRISM contributes uniquely to the dimensions of fatigue. We found differences between the samples in the position of the fatigue disk and the illness disk. Fatigue is a symptom which frequently occurs in combination with physical illnesses and it’s difficult to determine when fatigue leads to suffering or when another symptom is more important to a patient. The PRISM was able to discriminate between different kinds of suffering. Furthermore, the PRISM showed sensitivity to change in patients who recovered of severe fatigue after CBT.

Chapter 8 reports about the development and psychometric testing the Fatigue Quality List (FQL). Fatigue measurements are mostly used to assess fatigue severity. However, fatigue severity does not reflect a persons’ perception and appraisal of the fatigue. Therefore, the quantitative way of assessing fatigue fails to capture the nuances and differences in the experience of fatigue. The primary objective of Chapter 8 was to develop an adjective checklist aimed at assessing different perceptions of fatigue. The FQL consisted of 28 adjectives describing the experience of the fatigue. Subjects were instructed to mark with a cross which of the 28 adjectives fit their experienced fatigue. Multiple answers were possible Nine-hundred-sixty-one fatigued and non-fatigued participants filled out the FQL (cancer survivors, CFS-patients, employees on sick leave, various neuromuscular disorders, pancreatitis, healthy persons). A component and confirmatory factor analyses were performed and demonstrated four coherent factors (18 adjectives), which were named: Frustrating, Exhausting, Pleasant and Frightening. Furthermore, the data of this study showed that the FQL had adequate psychometric properties and sensitivity to change. The FQL can therefore be a helpful tool in clinical practice, for example to define recovery. When a decrease is seen in fatigue severity and the perception of the fatigue stays negative, which implicates that a patients still suffers and is disabled due to the fatigue, a patient can not be seen as fully recovered. To reach recovery not only the fatigue severity has to change but also the perception of fatigue.

Finally, in *Chapter 9* the results of the studies presented in this dissertation were placed into the perspective of the existing international literature of postcancer fatigue. Different topics were discussed; measurements, prevalence and course of postcancer fatigue, the predisposing, precipitating and perpetuating factors of postcancer fatigue and existing interventions on postcancer fatigue.

Samenvatting

Het eerder en nauwkeuriger diagnostiseren van de ziekte kanker en een verbeterde behandeling heeft ertoe geleid dat steeds meer mensen met succes behandeld worden voor kanker. Maar ondanks het feit dat deze mensen genezen zijn van kanker, blijkt lang na het einde van de behandeling van kanker (minimaal 1 jaar) een substantieel deel van deze ziekte-vrije oncologie patiënten ernstige vermoeidheidsklachten te ervaren. Vanaf 1996 heeft het Nijmeegs Kenniscentrum Chronische Vermoeidheid (NKCV) de oorzaken, natuurlijk beloop, consequenties en factoren die samen gaan met deze vermoeidheid onderzocht. Gebaseerd op deze studies is gebleken dat voor het begrijpen van vermoeidheid lang na curatieve behandeling van kanker er onderscheid gemaakt dient te worden tussen uitlokkende factoren en huidige, instandhoudende factoren. Ziekte- en behandelingskenmerken blijken namelijk geen relatie te vertonen met de ernst van de vermoeidheid lang na het afsluiten van de behandeling. M.a.w. de veronderstelde uitlokkende factoren voor vermoeidheid tijdens de behandeling van kanker, nl. de kanker zelf of de behandeling ervoor, vormen lang na de behandeling geen verklaring meer voor de vermoeidheid. Het is aannemelijk dat de vermoeidheid wel geïnitieerd is door de behandeling, maar dat na verloop van tijd andere factoren ervoor zijn gaan zorgen dat de klachten blijven bestaan. Een behandeling voor vermoeidheid na kanker zou gericht moeten zijn op deze instandhoudende factoren.

In dit proefschrift zijn twee hoofdstukken opgenomen die gericht zijn op het in kaart brengen van de aard van vermoeidheid na kanker (hoofdstuk 2 en 6), drie hoofdstukken over de cognitieve gedragstherapie speciaal ontwikkeld voor vermoeidheid na behandeling van kanker (hoofdstuk 3, 4 en 5) en twee hoofdstukken over het meten van vermoeidheid (hoofdstuk 7 en 8).

Het doel van *Hoofdstuk 2* was om in een longitudinaal studie de prevalentie van aanhoudende vermoeidheid te onderzoeken in een cohort van 121 ziekte-vrije borstkanker patiënten. Bovendien wilden we weten of de aanhoudende vermoeidheid gerelateerd was aan de eerdere oncologische behandeling en wilden we onderzoeken welke factoren bijdroegen aan de instandhouding van de vermoeidheid. Patiënten werden onderzocht 2.4 jaar en 4.5 jaar na het einde van de curatieve behandeling van kanker op psychologische, fysieke, sociale, cognitieve en gedragsmatige aspecten. Verder hebben alle deelnemers aan de studie gedurende twee jaar maandelijks een vermoeidheidsvragenlijst ingevuld. Gebaseerd op deze maandelijkse vermoeidheidsvragenlijsten vonden we dat 24% van de ziekte-vrije borstkankerpatiënten aanhoudende klachten van vermoeidheid ervoer. De aanhoudende vermoeidheid bleek gerelateerd aan de duur van de oncologische behandeling, maar niet aan het type operatie, type adjuvante behandeling en tijd sinds het einde van de behandeling. We vonden dat persisterende vermoeidheidsklachten minder vaak voor komt bij patiënten bij wie de behandeling relatief kort heeft geduurd, waarbij de behandeling binnen één maand afgerond is. Hierbij moet men dus denken aan patiënten die een chirurgische behandeling (borstbesparende operatie of amputatie) hebben ondergaan

zonder complicaties en zonder nabehandeling (radiotherapie en/of chemotherapie). Deze patiënten lijken dus minder kans te hebben op persisterende vermoeidheidsklachten. Angst, beperkingen met betrekking tot het uitvoeren van dagelijkse activiteiten thuis of op het werk en het idee weinig controle te hebben over de vermoeidheidsklachten bleken voorspellers van aanhoudende vermoeidheid te zijn. O.a. deze voorspellers werden gebruikt in de ontwikkeling van een cognitief gedragsmatige behandeling. Het protocol van deze cognitief gedragsmatige behandeling staat beschreven in *Hoodfstuk 3*. Het behandelprotocol bestaat uit zes modulen die gebaseerd zijn op de zes factoren waarvan verondersteld wordt dat ze de vermoeidheid in stand houden; verwerking van het feit dat men kanker heeft gehad, angst voor het terugkeren van de ziekte, opvattingen rondom vermoeidheid, het slaap waak ritme, (lichamelijke) activiteitenpatroon en ervaren sociale steun en interacties. De instandhoudende factoren zijn niet voor iedere vermoeide patiënt dezelfde. Om te bepalen welke factoren bij welke patiënt van belang zijn, worden meetinstrumenten gebruikt. Op basis van normgegevens voor deze meetinstrumenten kan vastgesteld worden of er sprake is van een problematische score van de betreffende patiënt. Op grond van de vragenlijsten en het gesprek tussen therapeut en patiënt wordt er voor elke patiënt een individueel behandelplan gemaakt bestaande uit de modulen die voor de betreffende patiënt relevant zijn. In dit hoofdstuk 3 wordt per module eerst de verantwoording van de module besproken, vervolgens welk meetinstrument hierbij gebruikt wordt en tenslotte de werkwijze in de behandeling. De modulen, uitleg over het model van uitlokkende en instandhoudende factoren, opvattingen rondom vermoeidheid, activiteitenregulatie en opbouw van fysieke activiteit bleken bij iedere patiënten onderdeel van het behandelprotocol (65 patiënten). Bij een meerderheid van de patiënten was regulatie van slaap-waak ritme en het bevorderen van realistische verwachtingen ten aanzien van de omgeving van de patiënt onderdeel van het protocol. Verwerking van het feit dat de patiënt kanker heeft gehad en hiervoor behandeld is en verhoogde angst voor het terugkeren van de ziekte was slechts voor een minderheid van de patiënten nodig om te behandelen.

Na de ontwikkeling van het protocol ‘cognitieve gedragstherapie (CGT) voor vermoeidheid na behandeling van kanker’ zijn we gaan onderzoeken of deze behandeling effectief is in het verminderen van de vermoeidheidsklachten en beperkingen in ziekte-vrije oncologiepatiënten. Deze studie wordt in *Hoofdstuk 4* gepresenteerd. In een gerandomiseerd gecontroleerd onderzoek wordt naar het effect gekeken van CGT door patiënten die therapie hebben gehad te vergeleken met patiënten die wachten op deze behandeling. Op het moment van deelname aan de studie hadden de ziekte-vrije oncologie patiënten de behandeling van kanker minimaal 1 jaar geleden afgerond en waren er geen aanwijzingen voor een recidief. Metingen voor beide groepen vond op twee momenten plaats: bij de start van het onderzoek en na 6 maanden. Data van 112 patiënten met lichamelijk onverklaarde vermoeidheidsklachten zijn geanalyseerd. De resultaten lieten zien dat CGT effectiever is dan op een wachtlijst staan van 6 maanden, zowel op de twee primaire uitkomstmaten vermoeidheid en beperkingen als op de secundaire uitkomstmaat psychisch welbevinden. Het aantal patiënten met een klinisch relevante verbetering op de drie uitkomstmaten was groter voor de patiënten die de CGT hadden gevolgd dan voor de patiënten die op de

behandeling wachten, namelijk voor vermoeidheid 54% versus 4%, beperkingen 66% versus 18% en psychisch welbevinden 66% versus 21%. CGT speciaal gericht op de instandhoudende factoren van vermoeidheid na kanker blijkt dus een effectieve behandeling. Aan de patiënten in de wachtlijst groep werd aan het begin van het onderzoek vermeld dat zij, als zij dat wilden, meteen na de wachtlijst, ook de CGT konden volgen. In *Hoofdstuk 5* wordt verslag gedaan van het lange termijn effect van CGT voor vermoeidheid na kanker. Dit effect is onderzocht bij patiënten die deelnamen aan het onderzoek beschreven in Hoofdstuk 4 en die volledig de behandeling hebben gevolgd. Het gaat hier om zowel patiënten die in de CGT groep zaten als patiënten die na een periode van 6 maanden zijn behandeld. Verder werd er ook nog exploratief gekeken naar voorspellers van vermoeidheid op lange termijn. In totaal hadden 68 patiënten volledig de CGT voor vermoeidheid na kanker afgerond. De vermoeidheid van deze patiënten werd op drie momenten in kaart gebracht, voor de CGT (voormeting), na afloop van de behandeling (nameting) en op lange termijn (follow-up meting). De gemiddelde tijd van het einde van de CGT tot aan de follow-up meting bedroeg 1.9 jaar (sd=1.0) met een spreiding van 6 maanden tot 4 jaar. De verbeteringen op vermoeidheid, beperkingen en psychisch welbevinden gemeten net na de CGT bleven gehandhaafd tot aan 1.9 jaar na de therapie. Patiënten die helemaal geen vermoeidheidsklachten meer ervoeren ten tijde van de follow-up meting waren even vermoeid, hadden evenveel beperkingen en een hoger psychisch welbevinden vergeleken met een referentie groep van niet vermoeide ziekte-vrije oncologiepatiënten. Verder was er een trend te zien dat meer vermoeidheidsklachten, minder psychisch welbevinden en een sterke somatische attributie bij de voormeting voorspellers waren van meer vermoeidheid tijdens de follow-up meting. Deze resultaten lijken erop te wijzen dat als een patiënt blijft denken dat de kanker en/of de behandeling van kanker nu nog steeds verantwoordelijk is voor de vermoeidheid, de kans op herstel lager is. Tijdens de CGT zou daarom meer aandacht besteed moeten worden aan somatische attributies. Daarnaast kunnen somatische attributies bekrachtigd worden door verstrekking van onjuiste informatie aan de patiënt over de oorzaak van vermoeidheid na kanker. De kans op herstel door middel van CGT zou dus ook kunnen worden vergroot door kennis over vermoeidheid na kanker over te dragen aan professionals die werken in de zorg voor oncologie patiënten. Verder blijkt dat vermoeide patiënten met een lage score op psychisch welbevinden (mogelijk een signaal voor psychiatrische co-morbiditeit) weinig kans hebben om te herstellen met CGT.

Er zijn aanwijzingen in de internationale literatuur dat ziekte-vrije oncologie patiënten die een agressieve behandeling hebben ondergaan voor kanker meer kans op hebben op ernstige vermoeidheid lang na het einde van deze behandeling. In *Hoofdstuk 6* hebben we 98 ziekte-vrije oncologie patiënten onderzocht die een extreem agressieve en veeleisende behandeling hebben ondergaan, namelijk een stamceltransplantatie (SCT). Dit waren patiënten gediagnosticeerd met acute myeloide of lymfatische leukemie in eerste complete remissie, chronische myeloide leukemie in eerste chronische fase, Non-Hodgkin lymfomen in eerste complete remissie. Alle patiënten hadden een totale lichaamsbestraling ondergaan. Patiënten met een Graft versus Host Disease (GVHD) graad van III en IV, acute GVHD of een uitgebreide chronische GVDH werden ge-excludeerd van de studie. Ook patiënten met

een hemoglobine (Hb) concentratie van 10 g/dl en lager werden niet toegelaten in de studie. De prevalentie van vermoeidheid en de relatie tussen medische factoren en vermoeidheid werden onderzocht. Daarnaast werd gekeken of het model van instandhoudende factoren van vermoeidheid na kanker voortgekomen uit de vorige studies vanuit het NKCV ook toepasbaar was bij patiënten na een SCT. Vijf-en-dertig procent van de deelnemers aan de studie ervoeren ernstige vermoeidheidsklachten en nog eens 12% had een verhoogde vermoeidheidsscore. Literatuur over vermoeidheid na kanker laat zien dat in de eerste 3-4 jaar na de behandeling van kanker het percentage patiënten met ernstige vermoeidheidsklachten afneemt en dat het een aanhoudend probleem blijft voor ongeveer een kwart van de ziekte-vrije oncologie patiënten. Maar het percentage ernstig vermoeide patiënten na een SCT bleef hoog, zelfs bij patiënten die meer dan 15 jaar geleden een SCT hadden ondergaan. Dit is in overeenstemming met de assumptie dat patiënten die een agressievere behandeling voor kanker hebben ondergaan, meer kans hebben op ernstige vermoeidheid. We vonden geen relatie met vermoeidheid en het medisch verleden van de patient (zoals diagnose, transplantatie type, tijd sinds transplantatie, GVHD graad, opname duur en complicaties). Ook werd er geen relatie gevonden met vermoeidheid en huidige medische factoren (zoals medicatie gebruik, Hb concentratie en Body Mass Index). De enige relatie die gevonden werd, was dat patiënten met een huidige lichamelijk co-morbiditeit een hogere vermoeidheidsscore hadden ten opzichte van patiënten zonder huidige lichamelijke co-morbiditeit. Verder bleek het model van instandhoudende factoren goed toepasbaar te zijn op ziekte-vrije patiënten na een SCT. Vermoeidheid werd namelijk goed voorspeld door de veronderstellede instandhoudende factoren: verwerking van het feit dat men kanker heeft gehad, angst voor het terugkeren van de ziekte, opvattingen rondom vermoeidheid, het slaap waak ritme, (lichamelijke) activiteitenregulatie en ervaren sociale steun. In totaal werd 68% van de variantie voorklaard door de zes instandhoudende factoren. De resultaten van deze studie laten zien dat in de afwezigheid van een lichamelijke oorzaak, CGT speciaal ontwikkeld voor vermoeidheid na kanker ook gebruikt kan worden in de behandeling van vermoeide patiënten na een SCT.

Hoofdstuk 7 laat bemoedigende resultaten zien in het gebruik van de Pictorial Representation of Illness Measure (PRISM) als meetinstrument in vermoeidheidsonderzoek en in de klinische praktijk. Bij drie verschillende groepen van vermoeide patiënten werd de PRISM afgenomen; 60 patiënten met het chronisch vermoeidheidssyndroom (CVS), 82 vermoeide ziekte-vrije oncologie patiënten, en 68 patiënten met een neuromusculaire aandoening. Deze patiënten kregen een A4 papier te zien met een gele cirkel in de rechter onderhoek en werden gevraagd zich voor te stellen dat het papier hun leven was op dit moment. De gele cirkel staat voor de persoon zelf, de “ik-cirkel”. Er zijn ook nog twee losse cirkels, die voor “vermoeidheid” en “ziekte” staan. Aan de patiënt werd gevraagd: “Waar zou u op dit moment uw vermoeidheid/ziekte plaatsen in uw leven?” Met de PRISM, een simpel, grafisch instrument wilde we meer inzicht krijgen in het lijden van de patiënt gerelateerd aan vermoeidheid. We onderzochten of lijden een aparte dimensie was van chronische vermoeidheid, of er verschillen waren in lijden tussen de drie verschillende groepen patiënten, en of het mogelijk was om onderscheid te maken tussen het lijden veroorzaakt

door de ziekte en lijden veroorzaakt door vermoeidheid. Als laatste werd er gekeken of lijden verminderd na behandeling voor chronische vermoeidheid. Voor alle vraagstellingen werden positieve resultaten gevonden.

In *Hoofdstuk 8* wordt de ontwikkeling en psychometrische toetsting van de Fatigue Quality List (FQL) beschreven. De meeste vermoeidheidsvragenlijsten worden gebruikt om de ernst van vermoeidheid in kaart te brengen. Echter, de ernst van vermoeidheid geeft niet de perceptie weer die een patiënt heeft van vermoeidheid. Hierdoor faalt de kwantitatieve manier van het meten van vermoeidheid met het in kaart brengen van nuances and verschillen in de ervaring van vermoeidheid. Het belangrijkste doel van Hoofdstuk 8 was om een checklist met bijvoeglijke naamwoorden te ontwikkelen die verschillende percepties van vermoeidheid omschrijft. De orginele FQL bestond uit 28 bijvoeglijke naamwoorden. De proefpersoon moest aangeven met een kruisje welke van de bijvoeglijke naamwoorden het beste past bij zijn/haar beleving van vermoeidheid. Meerdere antwoorden mochten gegeven worden. 961 vermoeide en niet-vermoeide deelnemers aan het onderzoek hebben de FQL ingevuld (ziekte-vrije oncologie patiënten, CVS patiënten, werknemers in de ziekte-wet, patiënten met neuromusculaire aandoeningen, patiënten met pancreatitis, en gezonden personen). Een componenten en een confirmatorische factor analyse werden uitgevoerd en toonde aan dat de checklist uit vier samenhangende factoren bestond (18 bijvoeglijke naamwoorden), welke de naam kregen: Frustrerend, Uitputtend, Aangenaam en Beangstigend. Verder liet deze studie zien dat de FQL adequate psychometrische eigenschappen heeft. The FQL kan daarom als een waardevol instrument gezien worden voor de klinische praktijk, bijvoorbeeld om herstel aan te tonen. Als er een afname gezien wordt in de ernst van de vermoeidheid, maar de perceptie van de patiënt van de vermoeidheid blijft negatief, dan kan deze patiënt niet als volledig hersteld gezien worden. Om herstel te bereiken moet niet alleen de ernst van de vermoeidheid afnemen maar ook de perceptie van vermoeidheid moet veranderen.

In *Hoofdstuk 9* worden de resultaten die in dit proefschrift zijn beschreven in perspectief gezet met de bestaande internationale literatuur over vermoeidheid na kanker. Verschillende onderwerpen komen aanbod: meetinstrumenten, prevalentie en beloop, de predisponerende, precipiterende en perpetuerende factoren van vermoeidheid na kanker en interventies gericht op vermoeidheid na kanker.

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Curriculum Vitae

Marieke Gielissen werd op 26 oktober 1977 geboren in Deurne. In 1996 behaalde zij het VWO diploma aan het College Asten Someren te Asten. Zij studeerde psychologie aan de Katholieke Universiteit Nijmegen en ronde in 2000 de studie af in de neuro- en revalidatiepsychologie. Vervolgens was zij onderzoeksassistent van een longitudinaal onderzoek naar vroege kenmerken van dyslexie bij de interfacultaire werkgroep voor Taal- en Spraakgedrag van de Radboud Universiteit Nijmegen. Vanaf 2001 was zij werkzaam als junior onderzoeker bij het Nijmeegs Kenniscentrum Chronische Vermoeidheid (NKCV) van het Universitair Medisch Centrum St. Radboud. Dit onderzoek, getiteld “Cognitieve gedragstherapie om ernstige vermoeidheid en beperkingen in het dagelijks leven te verminderen na curatieve behandeling van kanker” werd mogelijk gemaakt met een subsidie van KWF Kankerbestrijding en staat beschreven in dit proefschrift. In maart 2006 heeft ze van KWF Kankerbestrijding een fellowship gehoneerd gekregen voor sociaal-oncologisch onderzoek, met het NKCV als werkplek. Hierdoor krijgt ze de mogelijkheid om zich verder te ontwikkelen op het gebied van vermoeidheid in de psychosociale oncologische zorg en in het wetenschappelijk onderzoek.

Marieke Gielissen woont in Nijmegen en is getrouwd met Geert Corstens. Samen verwachten ze in maart 2008 een zoon.