Cognitive Behaviour Therapy for Chronic Fatigue Syndrome

Long-term Follow-up and Internet-based Treatment

Anthonie Janse

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About the cover

Hans Lie, Uchi-Mata 1984

To me, the pictured judo match represents cognitive behaviour therapy for chronic fatigue syndrome. Is it a fight against (prejudice of) others or against internal symptoms? The answer lies somewhere in the middle. Regardless the answer, it requires skill to overcome.

Cognitive Behaviour Therapy for Chronic Fatigue Syndrome: Long-term Follow-up and Internet-based Treatment

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Faculteit der Geneeskunde

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Chapter 1

General introduction

Chronic fatigue Syndrome

Chronic fatigue syndrome (CFS), also known under the name Myalgic Encephalomyelitis (ME) is characterised by persistent fatigue. Several case definitions exist, stating that the fatigue should persists for at least 6 months. Chronic fatigue is a common symptom, with prevalence rates even up to 30% of the general population [1]. Only a small proportion of people with chronic fatigue have *severe* and *disabling* fatigue, two characteristics of CFS/ME. The Health Council of the Netherlands estimated the number of CFS/ME patients at 30.000-40.0000 patients resulting in a 0.17-0.23% of the general population in 2018 [2]. Compared to recent international prevalence rates ranging from 0.2 to 1.2% , the Dutch estimate seems conservative [3-5].

Case definitions are used to diagnose CFS/ME, as there are no known somatic markers. A case definition often used is the US Centers for Disease, Control and prevention (CDC) criteria [6] revised in 2003 [7]. According to this case definition CFS/ME patients are severely fatigued for at least 6 months with substantial impairment in daily living. In addition, patients need to report four out of the following eight symptoms: unrefreshing sleep, muscle pain, multi-joint pain, post-exertional malaise, sore throat, headaches, tender cervical or axillary lymph nodes, impaired short-term memory and/or concentration problems [6,7].

However, not all patients with chronic fatigue have substantial levels of impairment or meet the additional symptom criterion. The CDC does refer to this chronically fatigued group with idiopathic chronic fatigue (ICF). Even though prevalence rates of ICF are much higher than of CFS/ME [8], research is primarily focused at patients with CFS/ME. As a result, there is a lack of knowledge how to treat ICF.

In 2015, the US Institute of Medicine proposed yet another case definition [5]. The case definition of Systemic Exertion Intolerance Disease (SEID) is fulfilled when patients report severe and persistent fatigue, disabilities and unrefreshing sleep, cognitive problems and/or orthostatic intolerance, and post-exertional malaise. Main aims to propose another set of criteria was to provide a definition based on a recent review of the literature and to introduce a new destigmatizing name [5]. In this thesis, al studies still used the CDC criteria revised in 2003 for patient inclusion. In chapter 3 and 7 we compared treatment outcome of the subgroup also fulfilling SEID with those fulfilling the CDC criteria only.

Somatic or psychological factors can act as triggers for the development of CFS/ME. Many patients reported stressful events in the preceding year before onset of complaints [9]. Multiple risk factors for CFS/ME were identified [10] but only a few were replicated like being female [11], past psychopathology [12] and childhood maltreatment [13,14].

The role of behaviour and beliefs in the perpetuation of CFS/ME

Based upon clinical experience and cross-sectional studies, some assumed that behaviour and beliefs can perpetuate the syndrome. According to Wessely et al. (1989) somatic attributions, physical inactivity and depressive symptoms together resulted in physical deconditioning [15].

Deconditioning was assumed to be a maintaining factor of the syndrome. Later models highlighted the importance of beliefs that would stimulate inactivity when being fatigued like 'activity should be avoided', or 'I need rest when I am fatigued' [16]. A substantial subgroup of patients however has beliefs that would actually stimulate activity to meet responsibilities. These patients are characterised by bursts of activity with increased symptoms and inactivity afterwards. Later, it was assumed that negative patient evaluations of their own output (for example 'my output is low') would stimulate bursts of activity [17].

Vercoulen et al. (1998) statistically tested a cognitive behavioural model that placed fatigue severity, functional impairment and the physical activity level as central elements together with low self-efficacy and focusing on bodily symptoms as cognitive elements [18]. This model formed the basis for a cognitive behavioural intervention for CFS/ME [19-21].

Cognitive behavioural therapy

Without treatment, chances to recover from CFS/ME are low [22]. Different CBT for CFS/ME protocols were developed) [23-25].

We will limit ourselves to a description of the Dutch protocol, as this is the protocol used in all our studies [23]. In a recent comparison study between the Dutch and the UK CBT for CFS/ME protocol, it was found that treatment gains were higher when the Dutch protocol was used [26]. According to latter protocol, patients start by setting targets for the end of therapy to resume activities like work, study, sport or social activities. Patients learn to hold on a fixed sleep-wake pattern, are being taught how to formulate helpful beliefs in response to symptoms and shift their attention away from fatigue. Furthermore, patients learn how to communicate about CFS/ME with others. Therapy is continued with the graded activity program and resumption of work/study and other personal goals.

Protocol adaptations

An important protocol adaptation was made after it was found that patients with a very low activity pattern treatment did not profit from CBT [19,27]. Since then, treatment was tailored to the activity level. Two physical activity pattern can be discerned, a low active and relative active pattern [28]. Low active patients are generally less active than the mean activity level of CFS/ME patients and start early with gradually increasing physical activity. Relative active patients have periods of (over)activity alternated with periods of rest, and first learn to divide activities more evenly before they start to increase physical activity.

Based upon mediation (: 'How-does-it-work') studies, the protocol was adapted throughout the years. It was found that a change in perceived activity and self-efficacy towards fatigue mediated treatment outcome instead of increased objective physical functioning [29-31]. The results suggest that how a patient perceives their level of activity is more important than the objectively assessed activity level. As a result of this finding, the aim of therapy shifted more towards change of beliefs

instead of increasing activity. Hence, since then the graded exercise program was mainly intended to enhance beliefs about sense of control and the ability to be(come) active [32]. Lastly, also more emphasis was given to how to reduce focus on fatigue as less focus on fatigue was related to better outcome [33].

The effect of CBT for CFS/ME

The first RCT testing the efficacy of CBT for CFS/ME dates back to 1996 [34]. Until now, the efficacy of CBT is still subject of debate (for example [35,36]. In 2001, data on the efficacy of the Dutch CBT for CFS/ME tested in a multicentre RCT was published. The therapy resulted in lower fatigue severity, less overall impairments, and improved physical functioning [19]. Since then, the beneficial role of CBT for adults and adolescents was repeatedly shown [21,37-39] with a subgroup who recovers [20, 40,41].

Follow up

Treatment benefits of CBT for CFS/ME can be maintained up to eight months post end of treatment [19,42,43]. A longer follow-up study found sustained treatment effects up to a median of 1.5 year after end of treatment [44]. Only one small study (*n* = 25) did a follow up assessment five years after end of treatment [45]. Significantly more patients were severely fatigued and fewer patients reported healthy physical functioning when compared to results at end of therapy. This suggests that when follow-up time is longer than what is commonly reported in most RCT's, less favourable outcomes might be found. However, studies with large samples with longer term follow-up outcomes (>5 years after end of treatment) are not reported yet.

Different ways to deliver CBT

Throughout the years, the manualized individual face-to-face therapy protocol was adapted into different treatment formats. Treatment [23] was provided and tested in groups [21,46] or via guided-self instruction, a minimal intervention [47]. This minimal intervention consisted of a workbook and email contact with a trained CBT for CFS/ME therapist. Later, the minimal intervention was used as a first step in stepped care for CFS/ME (with face-to-face therapy as second step) [48]. For adolescents, the CBT for CFS/ME protocol [20] was shown to be effective and eventually developed into an e-health intervention (called FITnet [39]).

Implementation of CBT for CFS/ME

CBT for CFS/ME was developed and tested in a tertiary care treatment centre. There are concerns whether outcomes of RCT's performed in highly specialized treatment centres (like those which tested the efficacy of CBT for CFS/ME), can also be reached in clinical routine [49]. In the past, implementation projects in several community based mental health care centres made CBT also available outside the specialized treatment centre [50,51]. For implementation, CBT therapists

were trained to deliver face-to-face CBT for CFS/ME. Most clinical routine settings met the statistical benchmark with respect to the effect on fatigue and physical functioning based on the results of RCT's testing the efficacy of CBT [50]. From this, one can conclude that CBT can be successfully implemented in routine clinical care. One implementation study showed that guided self-instruction could also be successfully implemented [52]. Interestingly, in this study psychiatric nurses were being taught to deliver the first step of stepped care i.e. the minimal intervention. In a tertiary care setting, this minimal intervention was part of a stepped care model with face-to-face CBT as a second step. Stepped care is characterised by increasing intensity of treatment at each step [53]. There are no studies known that tested implemented stepped care for CFS/ME in routine clinical care.

OUTLINE OF THE THESIS

This thesis has three main subjects: 1) Long-term outcome of CBT for CFS/ME. 2) The efficacy of CBT for patients with less severe symptoms. 3) Further development of CBT for CFS/ME using e-health.

Long-term outcome after CBT for CFS/ME

Little is known about the long-term outcome of CBT for CFS/ME. **Chapter 2** presents long-term outcome data up to 10 years after CBT. The cohort being studied is composed of patients from four published CBT for CFS/ME studies. The main research question is to what extent treatment benefits are maintained over time after therapy had ended. In **Chapter 3**, we try to predict who is able to maintain treatment benefits at long term follow up. The predictive value of demographic variables, cognitive-behavioural perpetuating factors, and CFS/ME characteristics is explored for both fatigue severity and physical functioning at long term follow-up.

Implementation of stepped care and long term follow-up of implemented care

The implementation of stepped care for CBT for CFS/ME, consisting of guided self-instruction with email contact with a therapist and as a second step face-to-face CBT, was not evaluated before. In **Chapter 4**, we present the effectiveness of stepped care directly following treatment and at long term follow up. Furthermore, we compare treatment outcomes of this implemented care with treatment outcome of a CFS/ME tertiary care treatment centre.

CBT for idiopathic chronic fatigue

There is a general lack of knowledge how to treat less severe CFS/ME patients. In **Chapter 5**, we study whether a CBT for CFS/ME can also be beneficial to patients that *do not* fulfil full diagnostic criteria for CFS/ME. Specifically, we determine the efficacy of the minimal intervention for chronically fatigued patients with less than four additional symptoms and/ or less overall impairment than

CFS/ME patients, i.e. patients with ICF according to the CDC guidelines on CFS/ME.

E-health and CBT for CFS/ME

In Chapter 6 the protocol of a study testing the efficacy of a web-based cognitive behavioural therapy for adult CFS/ME patients is presented. **Chapter 7** describes the outcomes of this RCT. With this CBT via Internet study (further referred to with iCBT), the initiative to contact is varied over two conditions. In the protocol driven condition, the therapist supports the patient at regular intervals via email contact. In the feedback on demand condition, support via Internet is only provided, when the patient initiates this. Efficacy and efficiency of both web-based conditions are compared to a waiting list control group. Also, safety of the intervention is investigated.

Chapter 8 discusses future research directions and implications for clinical care.
The appendices contain the summary and the contribution of each author for the studies in this thesis.

Expert Centre for Chronic Fatigue

All studies described in this thesis were conducted at the Expert Centre for Chronic Fatigue (ECCF) a tertiary treatment and research centre located at Amsterdam UMC. The ECCF is part of the department of Medical Psychology.

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Chapter 2

Long-Term Follow-up After Cognitive Behaviour Therapy for Chronic Fatigue Syndrome

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ABSTRACT

Objective: Cognitive behaviour therapy (CBT) is an effective treatment for chronic fatigue syndrome (CFS). Main aim was to determine whether treatment effects were maintained up to 10 years after treatment.

Methods: Participants (*n* = 583) of previously published studies on the effects of CBT for CFS were contacted fora long-term follow-up assessment. They completed questionnaires on main outcomes fatigue severity (CIS) and physical functioning (SF-36). The course of these outcomes since post-treatment assessment was examined using mixed model analyses.

Results: Between 21 and 125 months after finishing CBT, 511 persons (response rate 88%) completed a follow-up assessment. At follow-up, mean fatigue severity was significantly increased to 37.60 (SD = 12.76) and mean physical functioning significantly decreased to 73.16 (SD = 23.56) compared to post-treatment assessment. At follow-up still 37% of the participants had fatigue scores in the normal range and 70% were not impaired in physical functioning.

Conclusion: Positive effects of CBT for CFS on fatigue and physical functioning were partly sustained at long-term follow-up. However, a subgroup of patients once again reported severe fatigue, and compromised physical functioning. Further research should elucidate the reasons for this deterioration to facilitate the development of treatment strategies for relapse prevention.

INTRODUCTION

Patients with chronic fatigue syndrome (CFS/ME) suffer from medically unexplained, severe fatigue leading to substantial disability [5]. According to the US Centers for Disease Control and Prevention (CDC), persons with CFS/ME have experienced fatigue for at least six months, and their fatigue must be accompanied by other symptoms [5,6]. Cognitive behaviour therapy (CBT) is an effective treatment for CFS/ME and has been developed based on a model of perpetuating factors [7]. This model assumes that behaviour- and fatigue-related beliefs maintain fatigue and disability. CBT aimed at these cognitive-behavioural factors significantly reduces fatigue and disability [8,9] and a minority of patients are fully recovered post-treatment [3,10]. However, little is known about the long-term effects of CBT for CFS/ME [8].Research into the long-term efficacy of CBT for other disorders has shown that sustainment of treatment effects is not self-evident [11,12].

For CFS/ME, several studies that investigated short-term treatment effects found sustained effects up to eight months after the end of treatment [13–15]. Two studies had a longer follow-up period [16,17]. In the smaller study of Deale et al. [16], most patients reported sustained improvement at five-year follow-up. However, significantly more patients were severely fatigued and fewer patients reported good physical functioning at long-term follow-up compared to short-term follow-up. More recently, Sharpe et al. [17] found sustained positive effects of CBT on fatigue and physical functioning at a median follow-up period of 19 months.

Previous research showed that CFS/ME patients with somatic co-morbidity [3] and more pain [18] have less favourable outcomes following CBT. Mental health problems are more prevalent in CFS/ME patients and are known to be associated with fatigue [19]. All of these factors might not only influence treatment outcome but especially when they occur after end of treatment also influence long-term effects of CBT.

Aims of the study

In this study, we examined whether the positive effects of CBT on fatigue severity and physical functioning were maintained up to 10 years after the end of treatment. We also included participants' short-term follow-up data in the analyses. In order to determine what factors might be influencing treatment outcomes, we also examined whether somatic co-morbidity that occurred since the end of treatment and was still present, participants' pain and mental health at the time of the long-term follow-up, and several other patient and treatment characteristics were associated with the course of fatigue and physical functioning over time.

METHODS

Study design and participants

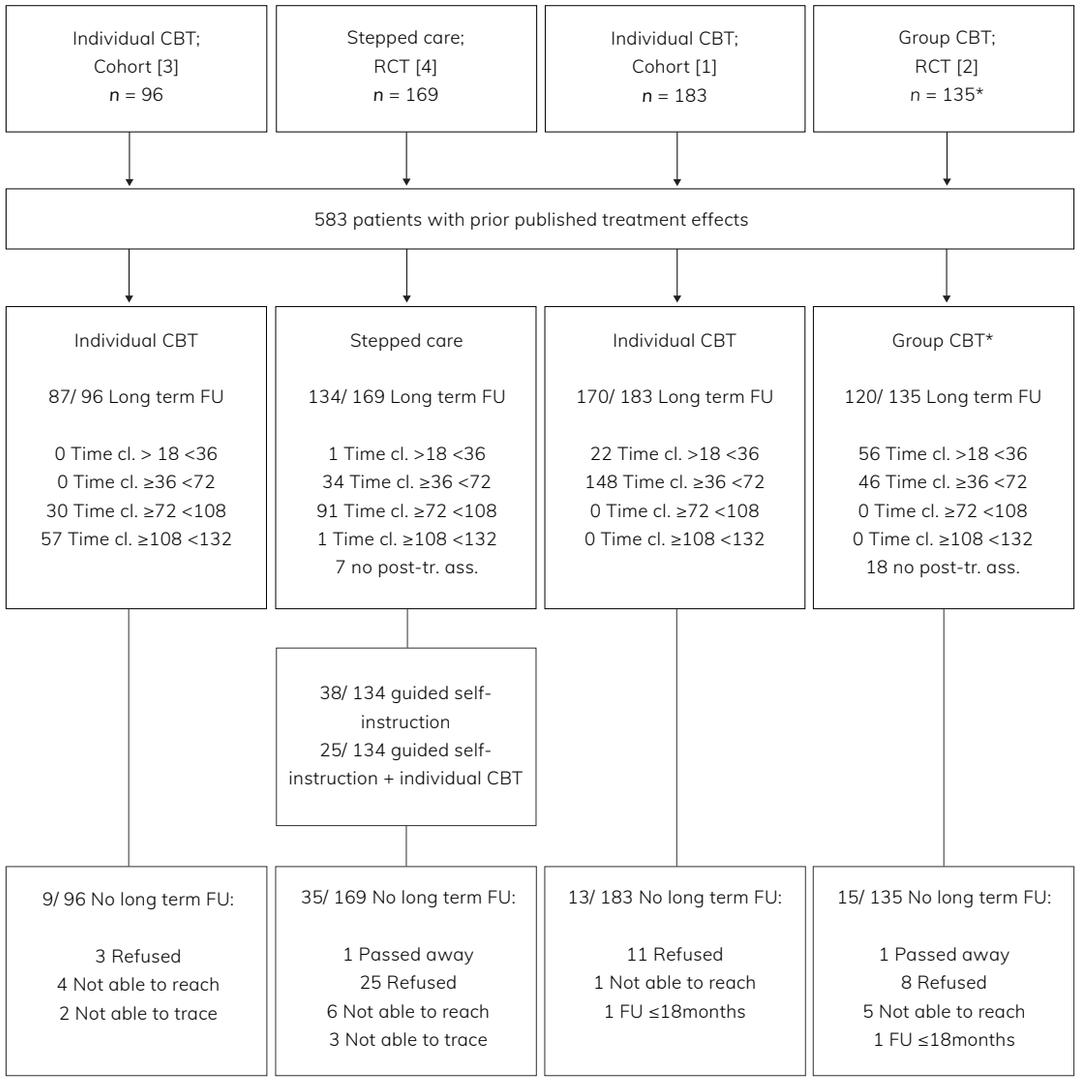
Participants from four published studies that had tested the effects of CBT were contacted for a long-term follow-up assessment. These studies had been conducted at the Radboud university medical center in The Netherlands (see [1–4]). All patients were consecutively referred and met CDC criteria for CFS/ME when included in the original study [5,6]. Patients were both severely fatigued and severely impaired, operationalized as scoring ≥35 on the Fatigue Severity subscale of the Checklist Individual Strength (CIS) [20] and a weighted score of ≥700 on the Sickness Impact Profile (SIP) [21], respectively. All patients had signed a written informed consent. Participants had received CBT in different formats: individual therapy, group therapy or stepped care [1–4,22–24]. The wait-list group of the group CBT study was not assessed at long-term follow-up because the effect of CBT following the waiting list was not published [2]. We only included patients who had received CBT in the published studies.

The stepped care consisted of a minimal intervention based on the CBT protocol (booklet with instruction combined with email contact with a therapist), followed by individual CBT if the patient had not profited enough from the minimal intervention [4] (see Figure 1). Two studies were RCT's [2,4] and in both the principle of intention-to-treat was applied. The two other studies were cohort studies [1,3], which enrolled consecutively referred patients who started treatment.

All CBT formats are aimed at changing fatigue perpetuating beliefs and behaviour [23]. CBT starts with informing patients about the cognitive behavioural model of CFS/ME. The patient formulates treatment goals aimed at recovery, defined as no longer being severely fatigued and disabled. Patients learn to regulate their sleep-wake pattern, to shift attention away from fatigue and to formulate helpful beliefs with respect to fatigue and the ability to become more active. All patients follow a graded activity program. Patients who are relatively active, characterised by a variable level of physical activity, first learn to divide their activities more evenly before they start increasing their level of activity, usually by walking or cycling. Low active patients, who are characterised by a very low level of physical activity, immediately start increasing their physical activity. If patients believe that they are able to increase activity, they start realising their goals, including resumption of work. Therapy ends with an evaluation.

Patients were assessed at baseline, post-treatment and at short-term follow-up about six months after finishing their treatment. The effects of CBT at post-treatment have been published. Previous studies have shown that at short-term follow-up the effects of CBT were sustained.

The present study focused on the results of the long-term follow-up, but we also examined data on short-term follow-up in order to compare the data with previous short-term follow-up studies. Short-term follow-up assessments were previously collected as part of the routine clinical care. Most short-term follow-up studies on CBT for CFS/ME conducted a follow-up assessment between six and eight months after treatment [13–15] and a large follow-up study after a median of 19 months after the final outcome assessment [17]. We defined short-term follow-up as an assessment between three and eighteen months after post-treatment assessment. Long-term follow-up was defined as an assessment that took place more than eighteen months after post-treatment assessment.



Notes: *Original N was 204; 1 person received wrong intervention and all (**n** = 68) persons of the wait list were not included. FU = follow up; time cl. = time cluster in months; post-tr. ass. = post-treatment assessment

Figure 1 - Flow chart for follow up of the primary outcome fatigue severity.

Procedures

A research assistant contacted potential participants by telephone, and once they agreed to fill in a long-term follow-up assessment, they received an invitation letter and questionnaires by mail or e-mail (with a link to the complete questionnaires online). The questionnaire was sent again if the participant did not return it by post or complete it online within two weeks. If only a postal or e-mail address was known, the invitation letter was sent without an initial phone call. If no address was known, the municipal registration was consulted. When participants refused to fill in questionnaires, they were asked to complete the subscale fatigue severity of the CIS by phone. Before participating in one of the previous studies, all the participants had already provided written informed consent. These studies and the follow-up study were approved by the local medical ethical committee [1–4].

Measures

The long-term follow-up assessment consisted of three parts and took a maximum of 15 min to complete. A general questionnaire contained items on the participant's work situation, somatic co-morbidity, life events, CFS/ME and treatment for fatigue.

Fatigue was assessed with the Fatigue Severity subscale of the CIS [20] consisting of eight items scored from one to seven. The subscale score varies between eight and 56. A score below 35 indicates fatigue in the normal range, a score of 35 or higher indicates severe fatigue [25]. The CIS is a reliable and valid instrument for CFS/ME [26].

Physical functioning, mental health and bodily pain were assessed with the respective subscales of the SF-36 [27]. Weighted subscale scores range from 0 to 100, higher scores indicate a better health status. A score of ≥ 65 was used as a criterion for physical functioning in the normal range [2]. The SF-36 is a reliable and valid instrument for different patient populations [28].

Statistical analyses

All analyses were performed with IBM SPSS Statistics 20. The threshold for significance was $p < 0.05$ (two-tailed). Sample characteristics were described using numbers, percentages and mean scores. With the use of independent *t*-tests, non-participants and participants were compared with regard to age and scores on the subscale fatigue severity and physical functioning at post-treatment and short-term follow-up.

Each participant had fatigue and physical functioning data of maximal four measurement points: baseline, post-treatment, short-term follow-up and long-term follow-up. Mean scores on all points were displayed in a figure. The long-term follow-up was subdivided into different time clusters of the number of months between post-treatment and follow-up. Mean fatigue and physical functioning was displayed for the time clusters in a separate figure.

To examine the course of fatigue and physical functioning scores over time, linear mixed model analyses were applied, where the repeated measures at post-treatment, short and long-term follow-up were clustered within the subject. Mixed models are by default able to handle missing data when at least one assessment is available [29]. For both outcome variables, a linear and a quadratic development over time were modelled. Additional analyses were performed in which the influence of covariates was investigated, as follows: somatic co-morbidity that occurred since the end of treatment and is still present, pain and mental health at long-term follow-up, gender, age at long-term follow-up, significant life events within the last year before long-term follow-up, type of CBT other than face-to-face CBT and design of the original study as either a randomised control trial [2,4] or a cohort study [1,3]. For dichotomous outcomes (0 = within and 1 = outside normal ranges) the same models were used using logistic GEE analyses with an exchangeable correlation structure.

In additional analyses, the development of fatigue and physical functioning since post-assessment was assessed by comparing mean scores at post-assessment with those at short and at long-term follow-up by including time as a categorical variable in the models.

Finally, the percentage of participants scoring above the cut-off criterion for severe fatigue, the percentage of participants with paid work, serving as an indicator of healthy functioning, and the mean fatigue score at long-term follow-up were compared with a sample from the Dutch general population matched for age and gender using Chi-square tests and a *t*-test for independent samples. The controls were gathered from a cohort ($n = 2294$) of panel members of CentERdata, a Dutch research institute at Tilburg University consisting of Dutch households representative of the Dutch population.

RESULTS

Sample characteristics

Two of the 583 possible participants [1–4] had died. Of the remaining 581 subjects, 511 participated (response rate 88%). In 20 cases (4%), only fatigue severity assessed by phone could be obtained. Of the 70 persons who did not participate in this follow-up study, 47 (67%) refused participation, 16 (23%) did not respond to letters and/ or telephone calls, 2 (3%) completed the assessment too early (≤ eighteen months since post-assessment) and for 5 persons there were no contact data (7%) (see Figure 1 for details). Of the long-term follow-up participants, 379/ 511 (74%) participated also with the short-term follow-up.

Mean age at long-term follow-up was 44.5 years (SD = 11.0), 388/ 511 (76%) of the sample was female, 264/ 490 (54%) had paid work, 114/ 430 (27%) received a disability pension, 88/ 511 (17%) had self-reported somatic co-morbidity with the onset after treatment, 171/ 427 (40%) reported life events during last year with impact on health, 209/ 427 (49%) did not regard themselves as a CFS/ME patient, and 52/ 428 (12%) did receive treatment for fatigue complaints.

The mean time between post-assessment and short-term follow-up was 5.96 months (SD = 1.86). The mean time between post-assessment and long-term follow-up was 64.97 months (SD = 28.56). Mean scores at long-term follow-up on the SF-36 mental health and bodily pain were

67.39 (SD = 17.83) and 62.35 (SD = 27.21), respectively. At time of diagnosis of CFS/ME, none of the participants had any somatic or psychiatric co-morbidity that could explain the fatigue.

Comparison of participants with non-participants

At pre-treatment assessment, the follow-up participants did not significantly differ from non-participants regarding mean age, fatigue severity and physical functioning. At post-treatment assessment, the non-participants (n = 72) scored significantly higher on fatigue severity (M = 36.05, SD = 14.13 compared to M = 29.74, SD = 13.80, $p < 0.01$) and lower on physical functioning (M = 67.93, SD = 23.86 compared to M = 79.53, SD = 20.63, $p < 0.01$) than the follow-up participants. At short-term follow-up assessment, the difference between both groups was still significant for physical functioning (M = 75.69, SD = 20.12 compared to M = 83.40, SD = 19.06, $p = 0.04$) but not for fatigue.

Fatigue and physical functioning assessed at the different measurement points

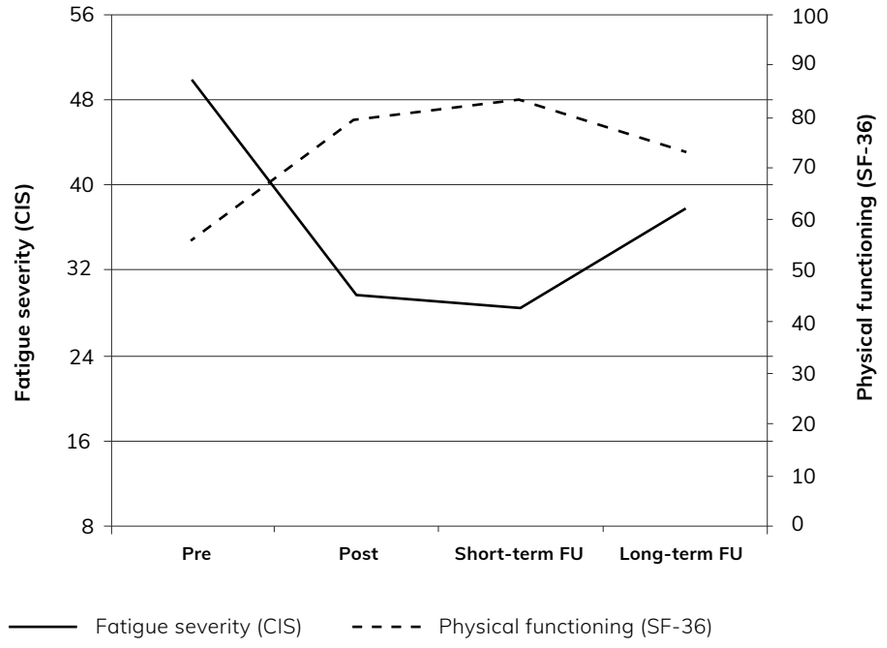
The mean fatigue and physical functioning scores on the four measurement points are displayed in Figure 2.

The percentage of patients with fatigue scores in the normal range, and without impairment are displayed in Figure 3. Deterioration of treatment effect seem to occur after short-term follow-up (up to 18 months). In additional Figure A, the time span of the long-term follow-up period was divided into smaller units of time with their respective mean fatigue and physical functioning scores. The figure indicated that scores are relatively stable over time periods.

The effect of time since post-assessment on fatigue and physical functioning

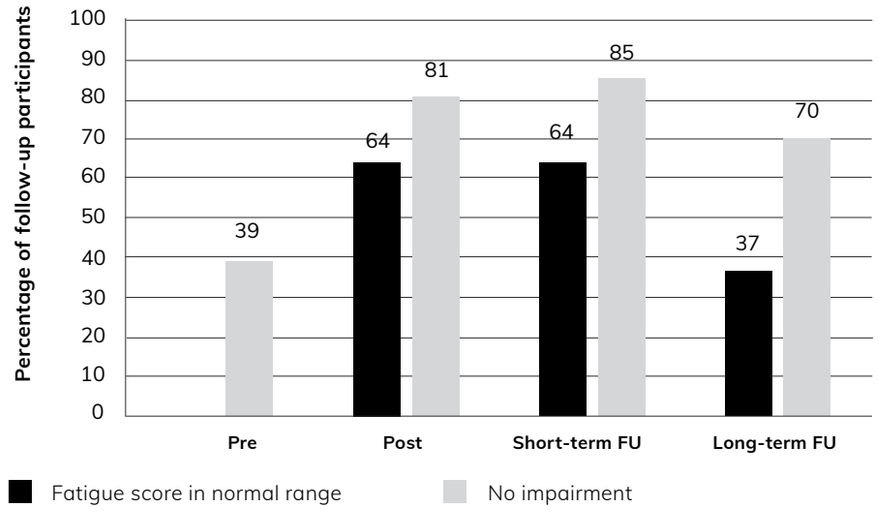
Linear mixed model analyses showed a quadratic increase over time of fatigue severity and a quadratic decrease of physical functioning (Table 1). This quadratic effect of time remained stable when covariates were added. Being older, reporting more pain and worse mental health at long-term follow-up was significantly associated with increased levels of fatigue and reduced levels of physical functioning from post-treatment to long-term follow-up. Somatic co-morbidity at long-term follow-up was also significantly associated with worse physical functioning.

By including time as a categorical variable, comparison of post-treatment assessment with short-term follow-up showed no significant difference in fatigue or physical functioning. At long-term follow-up fatigue severity significantly increased (mean change 7.30, $p < 0.01$) and physical functioning significantly decreased (mean change –6.21, $p < 0.01$) compared to post-treatment assessment.



Notes: left Y-axis: CIS: Checklist Individual Strength, fatigue severity subscale, range 8-56 from no to severe fatigue; right Y-axis: SF-36: Short Form-36, subscale physical functioning, range 0-100 from worse to good physical functioning

Figure 2 - Mean fatigue and physical functioning scores at the four assessments.



Notes: 'Fatigue in normal range' = Checklist Individual Strength, fatigue severity subscale <35; 'No impairment' = Short Form-36, subscale physical functioning in the normal range ≥65

Figure 3 - Percentage of patients with fatigue in the normal range, and without impairment.

	Linear mixed models				Logistic generalized estimating equations			
	Fatigue		**Physical functioning**		**Severe fatigue**		**Impaired physical functioning**	
	B (SE)	*p*	B (SE)	*p*	B (SE)	*p*	B (SE)	*p*
Crude model								
Time linear	0·23 (0·02)	<0·01*	-0·17 (0·04)	<0·01*				
Time quadratic	-0·00 (0·00)	<0·01*	0·00 (0·00)	0·01*				
Model with covariates								
Time								
Time linear	0·21 (0·03)	<0·01*	-0·19 (0·04)	<0·01*	0·05 (0·01)	<0·01*	0·03 (0·01)	<0·01*
Time quadratic	-0·00 (0·00)	<0·01*	0·00 (0·00)	<0·01*	0·00 (0·00)	<0·01*	0·00 (0·00)	<0·01*
Patient characteristics								
Gender (being male)	1·68 (1·10)	0·13	2·01 (1·70)	0·24	0·38 (0·22)	0·08	0·05 (0·24)	0·82
Age at long-term follow-up	0·11 (0·04)	0·02*	-0·45 (0·07)	<0·01*	0·01 (0·01)	0·15	0·05 (0·01)	<0·01*
Significant life events	-1·22 (0·96)	0·21	2·56 (1·50)	0·09	-0·22 (0·18)	0·22	-0·26 (0·20)	0·20
CBT and study characteristics								
Group CBT versus individual CBT	0·65 (1·58)	0·68	-0·22 (2·45)	0·93	0·10 (0·26)	0·72	-0·39 (0·36)	0·27
Guided self-instruction vs· ind· CBT	0·94 (2·07)	0·65	1·18 (3·21)	0·71	0·46 (0·41)	0·26	-0·07 (0·42)	0·87
Stepped care versus individual CBT	2·10 (2·41)	0·39	-4·63 (3·73)	0·22	0·51 (0·45)	0·26	0·29 (0·56)	0·61
Original study design RCT vs cohort	1·12 (1·40)	0·43	-0·56 (2·18)	0·80	0·11 (0·24)	0·64	0·25 (0·28)	0·38
Health status at long-term follow-up								
Self-reported somatic co-morbidity	-0·71 (1·20)	0·55	3·81 (1·85)	0·04*	-0·15 (0·21)	0·49	-0·35 (0·21)	0·10
Bodily pain (SF-36)	-0·20 (0·02)	<0·01*	0·41 (0·03)	<0·01*	-0·04 (0·00)	<0·01*	-0·05 (0·00)	<0·01*
Mental health (SF-36)	-0·16 (0·03)	<0·01*	0·10 (0·04)	0·03*	-0·03 (0·01)	<0·01*	-0·00 (0·01)	0·51

Notes: Higher scores on the CIS subscale fatigue indicate more severe fatigue, higher scores on the SF-36 subscale physical functioning indicate better functioning *significant at $p < 0.05$

Table 1 - Development of fatigue and physical functioning between post-assessment and long-term follow-up.

Scoring outside normal ranges of fatigue and physical functioning: course since post-treatment assessment

The likelihood of scoring outside the normal range of fatigue and physical functioning showed a quadratic increase over time from post-assessment (Table 1). Of the covariates, reporting more pain was significantly associated with a higher probability of scoring outside the normal range of fatigue and physical functioning. Worse mental health at long-term follow-up was significantly associated with scoring higher on fatigue, and being older was associated with scoring lower on physical functioning.

Time was included as a categorical variable. Comparison of the percentages of patients scoring outside the normal range of fatigue and physical functioning between post-assessment and short-term follow-up showed a small but significant increase for fatigue [beta 0.40, $p < 0.01$, Odds Ratio (OR) 1.49] but not for physical functioning. At long-term follow-up the percentages of patients scoring outside normal ranges were significantly higher for fatigue (beta 1.43, $p < 0.01$, OR 4.18) and physical functioning (beta 0.84, $p < 0.01$, OR 2.31) compared to post-treatment assessment.

Comparison of long-term follow-up outcomes with general population scores

Participants' fatigue scores at long-term follow-up were significantly higher than the general population scores ($M = 37.60$, SD = 12.76 compared to $M = 26.69$, SD = 11.83, $p < 0.01$). A significantly higher percentage of the population controls scored within the normal range of fatigue (72% compared to 36.8%, $p < 0.01$) and had paid work (69.7% compared to 53.9%, $p < 0.01$).

DISCUSSION

This study is the largest thus far to investigate the long-term effects of CBT for CFS/ME and the first to assess these effects over a time period of more than five years after treatment. The study showed that the positive effects of CBT on fatigue severity and physical functioning were stable up to 18 months following treatment. More than half of patients were no longer severely fatigued and more than three-quarter no longer disabled. At long-term follow-up, more than a third of the participants were not severely fatigued, 70% were not impaired in physical functioning, >50% had paid work, and about 50% did not consider themselves suffering from CFS/ME. This is a remarkable result as some consider CFS/ME to be a chronic condition in which behavioural interventions only help patients to adapt to persistent fatigue and disability. However, at long-term follow-up, fatigue severity had significantly increased and physical functioning decreased compared to the end of treatment. The deterioration in fatigue was more marked. This is in accordance with the 5-year follow-up study of Deale et al. [16] and might indicate that it is more difficult to sustain the positive effects on fatigue than on physical functioning.

When comparing our findings to other studies, our results seem to be in contrast with those of Sharpe et al. [17] who found that the positive effects of CBT did not decrease until 12 to 41 months after final outcome assessment. However, similar to Sharpe et al. [17], we also found no clear decrease in effects up to 18-months post-treatment. Since this time period is only a subset of the long-term time period we studied, perhaps it partly explains why Sharpe et al. [17] did not find long-term significant deterioration as half of their sample had a follow-up period of 18 months or less. In addition, our study also included a substantial number of patients who completed treatment four or more years ago, which is above the maximum follow-up period in the study of Sharpe and colleagues. When compared to the PACE study [10], our findings further showed that more patients reported a level of fatigue within the normal range post-treatment in our studies (64% versus 41% in the PACE). However, at long-term follow-up, our percentage (37%) was more comparable to the 41% found in the PACE study. Our results of relatively stable treatment effects on fatigue and physical functioning at short-term follow-up corroborate previous findings [13–15]. An exception was the small but significant increase in the probability of scoring outside the normal range of fatigue between post-assessment and short-term follow-up. This finding is not in line with our other results. An explanation might be the relatively high amount of missing data at short-term follow-up and that the comparison was conducted within a GEE model with several covariates [30].

The deterioration of treatment effects seems to occur relatively long after treatment. According to the cognitive behavioural model of CFS/ME, fatigue arises as a reaction to a trigger (e.g. disease or another stressful life event) and persists due to cognitive-behavioural factors [31]. The more time elapses after treatment, the higher the chance that people face a new trigger. When such a trigger occurs, some patients may have difficulties to apply the techniques learned during CBT to their new situation. This hypothesis, however, would suggest a linear effect of time instead of a quadratic one as we found.

In line with our hypotheses, more pain, worse mental health and self-reports of somatic co-morbidity at long-term follow-up were significantly associated with worse outcomes. Also being older was a significant covariate. Those variables might explain part of the outcomes but not the deterioration of the treatment effect in itself. The type of the prior followed CBT was not significantly associated with outcomes.

Depression research has shown that persons who had a depressive episode remain sensitive to the development of depressive symptoms, even after successful treatment [32]. The same seems true for CFS/ME. Even if fatigue, the central symptom of CFS/ME, can return to normal levels after CBT, the presence of episodes of severe fatigue and physical impairment might be a recurrent condition for a substantial subgroup of patients. For depression and chronic pain, interventions have been developed in order to maintain effects of behavioural therapy [11,12,33]. For CFS/ME, such interventions are not yet available, but it is advisable that they will be developed and tested for their efficacy.

Limitations and future directions

The strengths of this study are its large sample size, long follow-up period and high response rate. A limitation is that the outcome variables were restricted to fatigue severity and physical functioning. Although these are central features of CFS/ME and the two main outcome measures in most follow-up studies in the field, other characteristic symptoms exist, like post-exertional malaise. We did not collect data on the course of these other symptoms. Furthermore, the results of this study are dependent on the applied definition of normal ranges of fatigue and physical functioning. Since the outcome variables were measured only once per measurement point, it remains unclear whether severe fatigue at long-term follow-up was present longer than two weeks (time frame questionnaire). This is different from the CDC criterion of six months for CFS/ME. The natural course of severe fatigue, when it is present shorter than six months, is known to be favourable [5]. This could mean that the prevalence of severe fatigue at long-term follow-up, although substantial higher than in the general population, does not have to be as persistent as fatigue in CFS/ME. It is not easy to clearly distinguish CFS/ME symptoms from normal fluctuations in fatigue, which healthy persons also can experience. However, half of participants still regarded themselves suffering from CFS/ME, so it seems unlikely that severe fatigue for all patients at long-term follow-up was always a brief, singular episode.

Another limitation is that the non-participants had on average worse post-treatment outcomes when compared to the post-treatment scores of participants. This could have introduced a selection bias. Furthermore, the short-term follow-up assessment had the highest number of missing values. The mixed-model approach is able to handle missing values [29], but it is conceivable that those patients who were dissatisfied with CBT would choose not to complete the short-term follow-up measurement, leading to only positive mean values at short-term follow-up. As such, this possibility indicates that our sample was perhaps not completely representative for the population of CFS/ME patients who received CBT, and, therefore, our results might be too positive with regard to the course of CBT effects. Besides the possibility of selection bias, our study group received CBT in different forms of delivery. One could argue that these different delivery formats could have led to different changes over time in fatigue and functioning. However, this line of thought was not confirmed as the different CBT delivery forms were part of the covariates in our mixed model analysis and did not result in significant different changes over time. This finding might be explained by the fact that all treatment delivery forms were based on the same cognitive behavioural model addressing to the perpetuating factors of CFS/ME and all studies were performed within the same CFS/ME treatment centre. However, the power to detect the effect of the format on long-term outcome was limited due to the small number of patients who received other formats than individual CBT.

In an ideal world, it would have been interesting to have a controlled follow-up with a randomised usual care condition without receiving CBT for CFS/ME. However, due to the long follow-up period this seems unethical as CBT became more and more the first treatment of choice

[6,34] and is also practically impossible to withhold treatment for such a long period. Future long-term follow-up studies with equal time periods between the assessment points for each patient could allow for more precise conclusions regarding the moment when deterioration of treatment effects occurs. It would also be interesting to collect more information about the work situation of participants at the different measurement points. At long-term follow-up, it was unclear how many hours people worked and whether the presence of severe fatigue was the reason for not having paid work. A further limitation of the study is that somatic co-morbidity was assessed by means of one open-ended question, as part of the general questionnaire. A strength, however, is that psychiatric co-morbidity was assessed by using the subscale mental health of the SF-36, a well-established questionnaire. Nevertheless, future research could more comprehensively assess somatic and psychiatric co-morbidity.

CONCLUSION

A substantial number of patients reported experiencing sustained effects of CBT, even more than five years after end of treatment. About half did not consider themselves suffering from CFS/ME. For a substantial subgroup however, it seems difficult maintaining their gains in physical functioning and feeling less fatigued. This implies that CBT for CFS/ME could be optimized. Longitudinal, qualitative studies and a planned prediction study could help gain insight into the timeline and causes of the deterioration of treatment effects, which would, in turn, enable the development of CBT interventions that help more patients to maintain their treatment gains.

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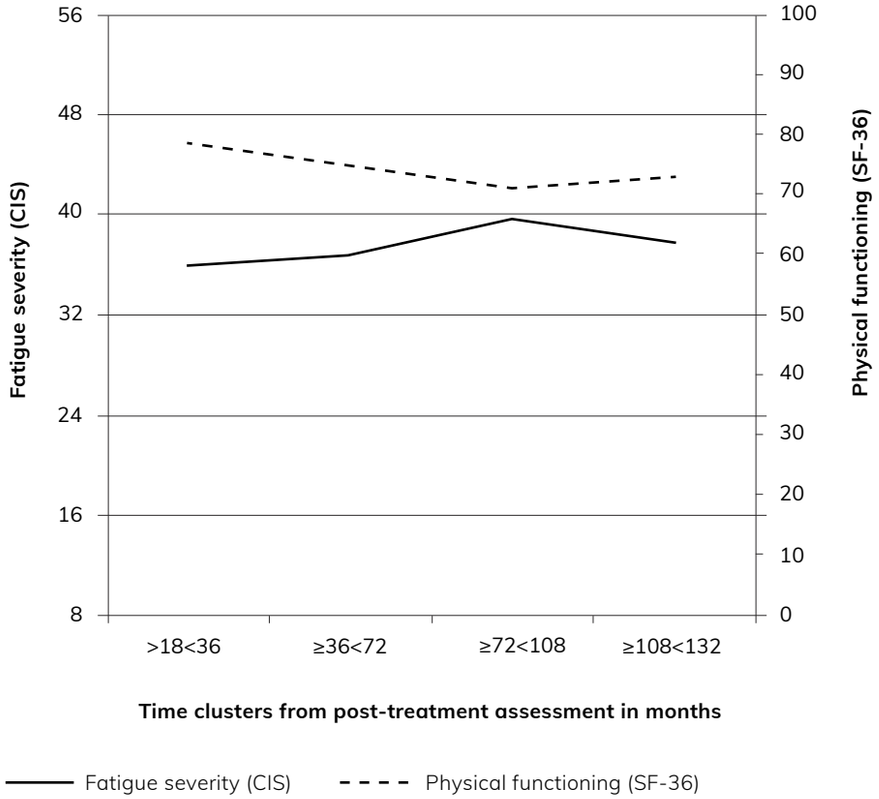
APPENDIX



Notes: left Y-axis: CIS: Checklist Individual Strength, fatigue severity subscale, range 8-56 from no to severe fatigue; right Y-axis SF-36: Short Form-36, subscale physical functioning, range 0-100 from worse to good physical functioning

Additional figure A - Fatigue severity and physical functioning since post- treatment assessment.

Chapter 3

Prediction of Long-Term Outcome After Cognitive Behavioural Therapy for Chronic Fatigue Syndrome

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ABSTRACT

Objective: To determine which variables predicted long-term outcome after cognitive behavioural therapy (CBT) for chronic fatigue syndrome (CFS/ME).

Methods: A cohort of 511 CFS/ME patients from four different CBT for CFS/ME studies, i.e. two cohort studies and two RCT's. Before treatment, all patients fulfilled the 2003 US CDC criteria for CFS/ME and treated with CBT, were assessed at long-term follow-up, up to 10 years after end of treatment. We tried to predict fatigue severity and physical functioning at follow-up with demographics, cognitive-behavioural perpetuating factors, and CFS/ME characteristics as predictors in linear regression analyses. Logistic regression analysis was used to explore significant predictors of fatigue scores within normal limits at long-term follow-up.

Results: Lower fatigue severity at long-term follow-up was predicted by a shorter duration of CFS/ME symptoms and lower fatigue levels at baseline, and lower frustration in response to fatigue and lower fatigue levels directly post-treatment. Fatigue scores within normal limits at follow-up was predicted by lower fatigue severity and lower levels of frustration in response to fatigue, both assessed directly post-treatment. Better physical functioning at follow-up was predicted by higher sense of control over fatigue, better physical functioning at post-treatment, and being younger at baseline. In some of the additional analysis pain at baseline also predicted physical functioning at follow-up.

Conclusion: The finding that lower fatigue severity and higher physical functioning at long-term follow-up were positively associated with its outcomes at post-treatment underline the importance of fully maximizing the positive effects of CBT for the sustainment of outcomes. Furthermore, augmenting sense of control and starting treatment sooner after diagnosing CFS/ME could positively influence long-term outcome. Interventions aimed at pain management deserve more attention in research.

INTRODUCTION

Following the 2003 US Centers for Disease Control (CDC) criteria, chronic fatigue syndrome (CFS/ME) is diagnosed when medically unexplained, severe, and persisting fatigue leads to substantial functional impairment [1,2]. Additionally, patients must report four out of the following eight symptoms: memory and/ or concentration problems, post-exertional malaise, unrefreshing sleep, headaches, sore throat, multi-joint pain, tender lymph nodes, and muscle pain [1,2]. Recently, a new case definition was presented by the Institute of Medicine (IOM) with unrefreshing sleep, post-exertional malaise, cognitive problems and/ or orthostatic intolerance as conditional symptoms [3]. The cognitive-behavioural model of CFS/ME assumes fatigue is perpetuated by fatigue-related behaviour and beliefs [4]. Cognitive behavioural therapy (CBT) for CFS/ME aimed at changing these perpetuating factors leads to a reduction of fatigue severity and functional impairment directly following treatment [5]. Several studies investigated outcomes at short-term follow-up, up to eighteen months after end of treatment [6]. During this period, treatment gains were generally maintained [6–9] or patients reported even further improvements [10].

However, studies investigating long-term follow-up after CBT revealed a more varied picture. Some studies found significant relapse [6,10], others sustained treatment gains [11]. In the largest study thus far, Janse and colleagues studied the long-term outcome up to 10 years after end of treatment. Higher levels of fatigue severity and lower levels of physical functioning were found at long-term follow-up (LTFU) compared to directly post-treatment. About half of the CFS/ME patients who reported fatigue scores within normal limits at post-treatment, maintained treatment gains up to ten years after CBT [6]. The other half of the patients again reported severe fatigue at LTFU. The relapse rate with respect to physical functioning was lower. No study thus far investigated the predictors of long-term CBT outcomes [11]. Knowledge about what predicts relapse or sustainment of treatment effects could help to identify patients at risk or improve treatment.

The current study aimed to investigate what predicts fatigue severity, fatigue scores within normal limits, and physical functioning at LTFU following CBT. Predictors were classified into three categories: demographics, cognitive-behavioural perpetuating factors thought to maintain CFS/ME symptoms, and CFS/ME characteristics.

We searched the literature for prediction studies that used outcome at follow-up, i.e. an assessment on a time point following assessment directly post-treatment. Until now, no demographical variables were found to predict short term FU [12–16]. We therefore expected that demographics did not predict long-term outcomes. Lower sense of control over fatigue at baseline and greater perceived negative consequences of CFS/ME, both fatigue-perpetuating factors according to the cognitive behavioural model of CFS/ME, negatively predicted fatigue and physical functioning at short term FU [12,13]. We hypothesized that more deviant scores at post-treatment on cognitive-behavioural perpetuating factors (thought to maintain CFS/ME symptoms) predicted more severe fatigue or lower physical functioning at LTFU. CFS/ME characteristics

predicting negatively outcome at short-term FU were higher fatigue severity at baseline, receiving disability insurance benefits, membership of a Myalgic Encephalomyelitis/ Encephalopathy (M.E.)-support group, lower physical functioning levels and higher functional impairment [12,13]. We expected CFS/ME characteristics such as more severe fatigue and low physical functioning levels were negatively related to outcome at LTFU.

METHODS

Patients

Patients from four treatment studies, all conducted at the same tertiary CFS/ME treatment centre of a university hospital in The Netherlands were asked to participate in the follow-up study [6]. All patients met the 2003 CDC criteria for CFS/ME at the start of original studies, scored above the cut-off for severe fatigue of ≥35 on the fatigue severity subscale of the Checklist Individual Strength [17] and had a total score of ≥700 on the Sickness Impact Profile-8 indicative of the presence of substantial impairment in daily life [18,19]. Two studies were RCT's and two were cohort studies. The two RCT's [20,21] applied the principle of intention to treat, and did not exclude patients with protocol deviations from the primary analyses, the two cohort studies [22,23] enrolled consecutively referred patients who started treatment.

Of the 583 patients, 511 (88%) filled in the follow-up assessment. The FU-duration from post-treatment to LTFU varied from 21 months to 125 months (*M* = 65, SD = 29; Table 1). Mean FU-duration for each of the four original studies can be found in additional Table B in the appendix. More details on time since end of treatment were given the previous publication on the LTFU outcome [6].

Interventions

All interventions were delivered by cognitive-behavioural therapists trained in CBT for CFS/ME and supervised by experienced therapists (GB and HK). The therapists used manuals specifically developed for the treatment formats, i.e. individual face-to-face CBT [22,23], a minimal cognitive-behavioural intervention followed by individual face-to-face CBT if needed [20] and group CBT [21]. All CBT formats were aimed at changing fatigue perpetuating beliefs and behaviour [4]. No differences were found in the changes of fatigue over time between the different treatment formats. CBT starts with informing patients about the cognitive-behavioural model of CFS/ME. The patient formulates treatment goals aimed at recovery, defined as no longer being severely fatigued and disabled. Patients learn to regulate their sleep-wake pattern, to shift attention away from fatigue and to formulate helpful beliefs with respect to fatigue and the ability to become more active. All patients follow a graded activity program. Low active patients, who are characterized by a very low level of physical activity, start immediately to increase physical activity gradually. Patients characterized by a variable level of physical activity, first learn to spread their activities more evenly before they start to increase their level of activity, usually by walking or cycling [24]. If patients experience their increased ability to become more active, they start to attain their goals, including resumption of work. Therapy ends with an evaluation.

	n fulfills variable (%)	M	SD	*n*
Baseline				
Age (years)		38·05	10·95	505
Years of education		15·02	2·31	511
Number of CDC symptoms		7·06	1·66	511
Duration of complaints (years)		7·00	6·08	474
Sex (1=man)	123 (24%)			511
Paid job (1=yes)	315 (62%)			511
Prior anx. and/ or depr. tr. (1=yes)[A]	115 (23%)			486
Fulfills SEID (1=yes)[B]	400 (78%)			511
Clinical level of depression (BDI-PC ≥4; 1=yes)[C]	184 (36%)			510
Disablement insurance benefits (1=yes)[D]	125 (24%)			511
Post-treatment				
Sense of control over fatigue[E]		22·30	3·76	456
Perceived activity[F]		8·67	4·89	484
Pleasant appraisal of fatigue (%; 0-100)[G]		26·29	26·13	445
Frustrating appraisal of fatigue (%; 0-100)[H]		27·60	31·95	445
Functional impairment[I]		648·72	598·94	486
Self-observed pain level[J]		3·67	2·96	431
Low activity pattern (actigraphy; 1=yes)[K]	46 (9%)			428
Follow-up				
FU duration from post-treatment (months)		64·97	28·56	486

Notes. A) 1 = followed pre-existent anxiety and/ or depression treatment; B) SEID: systemic exertion intolerance disease = un-refreshing sleep, post exertional malaise and cognitive problems for at least a couple of times per week; C) 1 = a score ≥ 4 on the BDI-PC; Becks Depression Inventory-Primary Care; D) 1 = having a paid job, absence due to CFS/ME and receiving financial compensation under the Sickness Benefit Act; E) SES Self-Efficacy Scale with respect to fatigue; F) CIS Checklist Individual Strength, activity subscale; G) FQL Fatigue Quality List, number of positive adjectives *20%; H) FQL, number of frustrating adjectives *20%; I) SIP Sickness Impact Profile; J) DOP daily observed pain, mean; K) 1 = 11 of 12 assessed days under score of reference score of 66.

Table 1 - Means, standard deviations, n and those fulfilling binary variables for the predictors.

Measures

Outcomes at long-term follow-up

Fatigue severity

Fatigue was assessed with the fatigue severity subscale from the 20-item Checklist Individual Strength (CIS) [17]. Patients rate the severity of fatigue experienced in the previous two weeks. The subscale fatigue severity consists of eight items scored on a seven-point Likert-scale (score range from 8 to 56). It is a reliable and valid questionnaire (Cronbach's α = 0.83–0.92) [17].

Physical functioning

Physical functioning was measured with the subscale 'physical functioning' from the Short Form Health Survey (SF-36) [25] with a Cronbach's α of the Dutch version of 0.92 [19]. The scores on this scale range from 0 to 100, from maximal to no limitations at all.

Fatigue scores within normal limits

Scoring lower than the validated and conservative cut-off score of severe fatigue of 35 on the CIS fatigue severe, fatigue was interpreted as having a level of fatigue scores within normal limits [17].

Putative predictors

Demographics

Data were gathered on *age* in years, *sex* (1 = man), *years of education* (counted from primary school), *having a paid job* (1 = yes), and *prior treatment* for anxiety and/ or mood disorder (1 = yes) using questionnaires. The same questionnaires were used to gather demographic variables in the four studies.

Cognitive-behavioural perpetuating factors of CFS/ME

Sense of control over fatigue The Self-Efficacy Scale (SES) at post-treatment was used to assess the patients' sense of control over fatigue (Cronbach's α = 0.68–0.77) [23,26]. Seven items were scored on a 4- point Likert-scale, with higher scores indicating a higher sense of control (score range 7–28).

Perceived activity Perceived activity at post-treatment was assessed with the activity subscale of the CIS. Patients can rate their perceived problems with activity on three items with a 7-point Likert scale (e.g. "I do quite a lot within a day", "I don't do much during the day", "I have a low output"). The sum score on this scale varies between 3 and 21 with higher scores indicative for lower perceived activity (Cronbach's α = 0.90) [17].

Objective activity – low activity pattern The physical activity pattern was assessed at post-treatment using actigraphy. Patients wore a (matchbox sized) motion-sensing device around the ankle for 12 days that registers physical activity (sampled every 5 s) [24]. The mean activity level per day was calculated. Two activity patterns can be discerned: a low active and a relative active pattern. The low activity pattern was affirmed when 11 of the 12 assessment days do have an average daily actigraphy score below the reference score of 66 [24]. The actometer is a reliable and valid device to assess objective physical activity [24].

CFS/ME characteristics

Fatigue severity and *physical functioning* were assessed at post-treatment. (See above for a detailed description.)

Additional CDC symptoms The eight additional CDC symptoms at baseline were reported on a 4-point scale ranging from 'not at all', 'a few times per month', 'a few times per week' to 'every day'. Symptoms had to be present for at least six months.

Meeting the CFS/ME case definition of systemic exertion intolerance disease (SEID) The CDC symptoms, CIS and SIP scores were used to determine if patients met the criteria of SEID. Following the IOM, SEID is fulfilled when severely fatigued and disabled patients report unrefreshing sleep, cognitive problems and/ or orthostatic intolerance, and post-exertional malaise. Symptoms had to be present for at least several times a week (following [27]). We had no information on the prevalence of orthostatic intolerance. Previous research of our group has shown that the prevalence of postural orthostatic tachycardia in adult CFS/ME patient was similar to a fatigued non-CFS/ME group [27].

Perception of fatigue The perception of fatigue was evaluated with the Fatigue Quality List (FQL) [28]. Several adjectives can be selected when it fits patients' experience and are being transposed into a percentage. CFS/ME patients scored significantly higher on the subscale 'Frustrating', 'Exhausting' and 'Frightening' and lower on 'Pleasant' when compared to other fatigued and non-fatigued patient groups [28]. Following successful CBT, the perception of fatigue normalizes. The subscales 'Pleasant' and 'Frustrating' were used.

Initial symptom duration Initial symptom duration was measured in years.

Depression Depression at baseline was assessed with the Beck Depression Inventory-Primary Care questionnaire (BDI-PC, Cronbach's α = 0.86) [29], with a score ≥4 used as an indicator for the presence of clinically relevant level of depressive symptoms.

Paid job with disablement insurance benefits Paid job with a disablement insurance benefit at baseline was affirmed when patients that had a paid job were absent from work due to CFS/ME and received financial compensation under the Sickness Benefit Act.

Functional impairment Functional impairment at post-assessment was measured with Sickness Impact Profile-8 that consists of a weighted score computed from the subscales sleep-rest, household, mobility, social interactions, walking, alertness and intellectual functioning, work, and recreation [18,30,31].

Pain Pain at post-assessment was assessed (4 times a day over 12 days) with a self-observation list (range per assessment 0 = no pain to 4 = very severe pain). Twelve daily total scores were calculated (range 0–16) and averaged into one daily-observed pain (DOP) score (range 0–16). This measure was used before [32–34] and has a good split half reliability between measures of the first week versus the second week of *r* = 0.87.

Statistical analysis

For all predictors and dependent measures, the mean and standard deviation (SD) were calculated. Patients with complete data at post-treatment and follow-up (on all variables) were compared to patients with missing data of one or both time-points. This was done with respect to fatigue severity and physical functioning at baseline, using an independent *t*-test.

Based on the assumption that data were missing at random, multiple imputation (MI) was used with predictive mean matching for all missing values. Eighty datasets were computed, based on the rule of thumb using the number of datasets in accord with the number of missing data points (of the variable activity pattern and pain).

A hierarchical regression analysis (method enter) was conducted to identify predictors of fatigue severity (CIS-fatigue) and physical functioning (SF-36) at long-term follow-up. Variables were entered in two blocks. The first block contained the baseline and post-treatment assessment of the dependent variable. All other putative predictors were added in block two. The predictive value of meeting SEID criteria was tested in a separate regression, the variable 'number of additional CDC symptoms' was not included in these analyses.

In a post-hoc analysis, the relationship between initial symptom duration and long-term outcome was further investigated. Symptom duration was split into quartiles (0.5–2.99; 3–4.99; 5–9.99; >10 years). Following this, each quartile-variable was coded with 1 against the other quartiles coded with 0 and its predictive value was separately tested in the full model. After the analysis, the regression coefficient was visually inspected. Furthermore, we explored whether the addition of fatigue severity at post-treatment would change the significance of the predictor sense of control over fatigue at post-treatment.

Variance inflation factors (VIF) were evaluated within the linear regression analyses to determine multicollinearity. A cut-off of >10 [35] was seen as indicative of multicollinearity and high correlating predictors were then visually inspected to decide which predictors should be deleted. Hierarchical logistic regression was used for the binary dependent fatigue scores within normal limits at LTFU, using only significant predictors of the linear regression [36]. The regression analyses were repeated using the non-imputed dataset as a sensitivity analysis.

All analyses were performed with SPSS for Windows, v. 22, with $p < 0.05$ used as significance level.

	Baseline			Post-treatment			Follow-up		
	M (SD)	*n*	*n* count 1 (%)	*M* (SD)	*n*	*n* count 1 (%)	*M* (SD)	*n*	*n* count 1 (%)
Fatigue severity[A]	49·62 (5·53)	511		29·73 (13·82)	484		37·60 (12·76)	511	
Physical functioning[B]	55·87 (20·02)	510		79·53 (20·63)	485		73·16 (23·56)	489	
Fatigue scores within normal ranges[C]			0 (0)			311 (61)			188 (37)

Notes: A) CIS 'fatigue severity' subscale; B) SF-36 Short Form Health Survey, 36 items, 'physical functioning' subscale; C) Fatigue severity on CIS fatigue severity subscale <35.

Table 2 - Dependent variables at baseline, post-treatment and at follow-up.

RESULTS

Table 1 displays the descriptive statistics for the predictor variables. Means and standard deviations for the dependent variables at baseline, post-treatment and follow-up can be viewed in Table 2. Correlations between the dependent variables and the predictor variables can be found in additional Table A in the appendix. An overview of all used variables, stratified for each original study are displayed in additional Table B in the appendix.

Patients with complete data (n = 411/ 511; 80%) scored significantly better on physical functioning at baseline (completers: M = 56.85, SD = 19.48, non-completers: M = 51.85, SD = 21.74, t (508) = −2.25, p = 0.03) but had similar fatigue severity scores at baseline (completers: M = 49.7, SD = 5.49, non-completers: M = 49.27, SD = 5.73, t (509) = −0.70, p = 0.49.

Predicting fatigue severity at long-term follow-up

With 19 predictors and an n of 511, at least 26 cases per predictor resulted in sufficient power for the regressions [37]. The baseline and post-treatment assessment of fatigue severity, entered in the first block explained 25–28%
of the variance in fatigue severity at LTFU (meaning that the R^2 of all individual imputed datasets were found in the range between 25 and 28%).

When the other putative predictors were entered in the second block, the explained variance (R^2) increased to 29–32% (depending on the MI dataset). Lower fatigue severity at baseline and at post-treatment, shorter initial symptom duration and lower frustration in response to fatigue at post-treatment significantly predicted lower fatigue severity at LTFU (Table 3).

Post-hoc analysis revealed an initial symptom duration shorter than three years to be associated with lower fatigue severity at LTFU (B = −3.70, 95% CI -6.16 to −1.24, p = 0.003). A symptom duration of 3–4.99 and 5–9.99 years was not significantly associated with fatigue severity at LTFU (B = −1.00, 95% CI -3.33 to 1.33, p = 0.40 respectively B = 0.68, 95% CI -1.61 to 2.98, p = 0.56). A symptom duration of 10 years or more predicted more severe fatigue at LTFU (B = 3.45, 95% CI 1.13 to 5.78, p = 0.004).

Fulfilling criteria of SEID at baseline did not predict fatigue severity at LTFU (B = −0.17, 95% CI -2.61 to 2.27, p = 0.89). The VIF scores of all analyses performed were below the cut-off of 10.

The sensitivity analysis gave similar results except that more frustration in response to fatigue at post-treatment no longer significantly predicted more severe fatigue at LTFU (B = 0.05, 95% CI -0.00 to 0.10, p = 0.07).

Model				B	p	95% CI for B
1			(Constant)	13·63	0·002	4·97 to 22·29
	BL	Fatigue severity		0·21	0·019	0·04 to 0·38
	PT	Fatigue severity		0·46	<0·001	0·39 to 0·53
2			(Constant)	15·01	0·09	-2·53 to 32·56
	BL	Fatigue severity		0·24	0·010	0·06 to 0·42
	PT	Fatigue severity		0·26	0·002	0·10 to 0·41
	BL	Age (years)		0·04	0·40	-0·06 to 0·14
	BL	Sex (1=man)		-2·22	0·07	-4·63 to 0·19
	BL	Years of education		0·06	0·80	-0·39 to 0·50
	BL	Paid job (1=yes)		-0·97	0·41	-3·25 to 1·32
	BL	Prior anx. and/ or depr. tr. (1=yes)[A]		2·02	0·10	-0·39 to 4·42
	BL	Depression (BDI-PC ≥4; 1=yes)[B]		0·06	0·96	-2·03 to 2·14
	BL	Disablement insurance benefits (1=yes)[C]		0·05	0·97	-2·54 to 2·63
	BL	Number of CDC symptoms		0·20	0·54	-0·43 to 0·82
	BL	Duration of complaints (years)		0·22	0·011	0·05 to 0·40
	PT	Low activity pattern (actigraphy; 1=yes)[D]		1·09	0·53	-2·28 to 4·46
	PT	Functional impairment[E]		0·05	0·97	-0·003 to 0·003
	PT	Self-observed pain level[F]		-0·15	0·50	-0·59 to 0·29
	PT	Pleasant appraisal of fatigue (%; 0-100)[G]		-0·03	0·27	-0·07 to 0·02
	PT	Frustrating appraisal of fatigue (%; 0-100)[H]		0·05	0·036	0·003 to 0·09
	PT	Sense of control over fatigue[I]		-0·21	0·29	-0·60 to 0·18
	PT	Perceived activity[J]		0·17	0·27	-0·13 to 0·48
	FU	FU duration from post-treatment (months)		0·02	0·36	-0·02 to 0·05

	Model 1	Model 2
F range	84·94 to 96·28	10·63 to 12·28
p of F	<0·001	<0·001
Df (regr) (res)	(2) (508)	(19) (491)
R^2 range	0·25 to 0·28	0·29 to 0·32

Notes: BL baseline, PT post-treatment, FU long-term follow-up. Ranges are provided for F and R^2 whereas pooled data was not provided by SPSS. B-values are unstandardized weights.

A) 1= followed pre-existent anxiety and/ or depression treatment; B) 1= a score ≥4 on the BDI-PC; Becks Depression Inventory-Primary Care; C) 1= having a paid job, absence due to CFS/ME and receiving financial compensation under the Sickness Benefit Act; D) 1= 11 of 12 assessed days under score of reference score of 66; E) SIP Sickness Impact Profile; F) DOP daily observed pain, mean; G) FQL Fatigue Quality List, number of positive adjectives *20%; H) FQL, number of frustrating adjectives *20%; I) SES Self-Efficacy Scale with respect to fatigue; J) CIS Checklist Individual Strength, activity subscale.

Table 3 - Hierarchical linear regression with fatigue severity at follow-up as dependent variable.

Predicting physical functioning at long-term follow-up

The baseline and post-treatment assessment of physical functioning were entered in the first block, explaining 34–40% of the variance in physical functioning at long-term follow-up (depending on the MI dataset).

Model				B	p	95% CI for B
1			(Constant)	16·61	<0·001	9·67 to 23·55
	BL	Physical functioning		0·17	<0·001	0·08 to 0·26
	PT	Physical functioning		0·60	<0·001	0·51 to 0·69
2			(Constant)	45·72	<0·001	20·31 to 71·13
	BL	Physical functioning		0·20	<0·001	0·11 to 0·30
	PT	Physical functioning		0·27	<0·001	0·14 to 0·40
	BL	Age (years)		-0·35	<0·001	-0·52 to -0·18
	BL	Sex (1=man)		3·23	0·12	-0·79 to 7·25
	BL	Years of education		-0·03	0·94	-0·78 to 0·72
	BL	Paid job (1=yes)		0·41	0·83	-3·41 to 4·24
	BL	Prior anx. and/ or depr. tr. (1=yes)[1]		-2·13	0·31	-6·26 to 1·99
	BL	Depression (BDI-PC ≥4; 1=yes)[2]		-0·29	0·87	-3·8 to 3·21
	BL	Disablement insurance benefits (1=yes)[3]		0·84	0·70	-3·48 to 5·15
	BL	Number of CDC symptoms		-0·65	0·23	-1·69 to 0·40
	BL	Duration of complaints (years)		-0·16	0·27	- 0·45 to 0·13
	PT	Low activity pattern (actigraphy; 1=yes)[4]		-2·51	0·39	-8·24 to 3·22
	PT	Functional impairment[5]		-0·004	0·11	-0·01 to 0·001
	PT	Self-observed pain level[6]		-0·75	0·06	-1·52 to 0·02
	PT	Pleasant appraisal of fatigue (%; 0-100)[7]		0·04	0·28	-0·03 to 0·12
	PT	Frustrating appraisal of fatigue (%; 0-100)[8]		0·02	0·53	-0·05 to 0·10
	PT	Sense of control over fatigue[9]		0·87	0·008	0·22 to 1·52
	PT	Perceived activity[10]		-0·06	0·81	-0·53 to 0·41
	FU	FU duration from post-treatment (months)		-0·02	0·63	-0·08 to 0·05

	Model 1	Model 2
F range	130·93 to 166·05	19·21 to 23·36
p of F	<0·001	<0·001
Df (regr) (res)	(2) (508)	(18) (491)
R^2 range	0·34 to 0·40	0·43 to 0·47

Notes: BL baseline, PT post-treatment, FU long-term follow-up. Ranges are provided for F and R^2 whereas pooled data was not provided by SPSS. B-values are unstandardized weights.

A) 1= followed pre-existent anxiety and/ or depression treatment; B) 1= a score ≥4 on the BDI-PC; Becks Depression Inventory-Primary Care; C) 1= having a paid job, absence due to CFS/ME and receiving financial compensation under the Sickness Benefit Act; D) 1= 11 of 12 assessed days under score of reference score of 66; E) SIP Sickness Impact Profile; F) DOP daily observed pain, mean; G) FQL Fatigue Quality List, number of positive adjectives *20%; H) FQL, number of frustrating adjectives *20%; I) SES Self-Efficacy Scale with respect to fatigue; J) CIS Checklist Individual Strength, activity subscale.

Table 4 - Hierarchical linear regression with physical functioning at follow-up as dependent variable.

When the other putative predictors were entered in the second block, the model explained 43–47% of the variance (depending on MI dataset). Younger age at baseline, higher sense of control over fatigue at post-treatment together with higher physical functioning at baseline and post-treatment significantly predicted higher physical functioning at LTFU (Table 4).

Post-hoc, we explored whether the addition of fatigue severity at post-treatment would change the significance of the predictor sense of control over fatigue at post-treatment. More sense of control remained a significant predictor of a higher physical functioning at LTFU (*B* = 0.93, 95% CI 0.26 to 1.60, *p* = 0.006), whereas fatigue severity at post-treatment did not significantly predict physical functioning at LTFU (*B* = 0.10, 95% CI -0.18 to 0.38, *p* = 0.48).

Fulfilling criteria of SEID at baseline did not predict physical functioning at LTFU (*B* = 1.37, 95% CI -2.70 to 5.43, *p* = 0.51). However, the predictor pain at post-treatment became significant. Higher pain levels were associated with lower physical functioning at LTFU (*B* = –0.86, 95% CI -1.60 to –0.11, *p* = 0.03). All VIF scores were below the cut-off of 10.

The sensitivity analysis gave similar results except for the variable pain. More severe levels of pain at post-treatment became a significant predictor of lower physical functioning levels at LTFU (*B* = –0.84, 95% CI -1.63 to –0.04, *p* = 0.04).

Model				OR	p	95% CI for OR
1			Constant	11·67	0·008	1·93 to 70·66
	BL	Fatigue severity		0·98	0·32	0·95 to 1·02
	PT	Fatigue severity		0·93	<0·001	0·91 to 0·94
2			Constant	14·07	0·006	2·16 to 91·67
	BL	Fatigue severity		0·98	0·23	0·94 to 1·01
	PT	Fatigue severity		0·95	<0·001	0·92 to 0·97
	PT	Frustrating appraisal of fatigue		0·99	0·04	0·98 to 1·00
	BL	Duration of complaints (years)		0·96	0·06	0·93 to 1·00

	Model 1	Model 2
Omnibus test χ^2 (Df)	90·34 to 106·55 (2)	101·72 to 120·94 (4)
p	<0·001	<0·001
Nagelkerke R^2	0·22 to 0·26	0·25 to 0·29
Hosmer & Lemeshow test χ^2 (Df)	5·92 to 15·72 (8)	4·17 to 19·94 (8)
Pooled *n*	511	511

Notes: BL, baseline; PT, post-treatment. Ranges are provided for χ^2 and R^2 whereas pooled data was not provided by SPSS. OR, odds ratio; CI, confidence interval.

Table 5 - Hierarchical logistic regression with fatigue scores within normal limits at follow up as dependent variable.

Predicting fatigue scores within normal limits at long-term follow–up

The baseline and post-treatment assessment of fatigue severity entered in the first block (Table 5), explained 22–26% of the variance in fatigue severity at LTFU (depending on the MI dataset). Only higher post-treatment fatigue severity significantly predicted lower odds to fatigue scores within normal limits at LTFU, whereas baseline fatigue severity remained non-significant in the prediction of outcome at LTFU.

When frustration in response to fatigue at post-treatment and initial duration of symptoms were entered in the second block, i.e. the significant predictors of the performed linear regression for fatigue, the explained variance (R^2) increased to 25–29% (depending on the MI dataset). Higher fatigue severity at post-treatment together with higher levels of frustration at post-treatment significantly predicted lower odds to fatigue scores within normal limits at LTFU.

The sensitivity analysis gave similar results except for the variable initial duration of symptoms. A longer duration of symptoms became a predictor of significant lower odds to fatigue scores within normal limits at LTFU (OR = 0.96, 95% CI 0.92 to 1.00, *p* = 0.04).

DISCUSSION

The aim of this study was to identify predictors of fatigue severity and physical functioning at LTFU, up to ten years after CBT for CFS/ME. More severe fatigue at LTFU was predicted by a higher level of fatigue at baseline and post-treatment, more frustration in response to fatigue at post-treatment and initial duration of complaints. Sub analyses revealed that a short (initial) symptom duration (0.5 to 2.99 years) and a long symptom duration (>10 years) had respectively a positive and a negative effect on fatigue severity at LTFU. This suggests that a timely diagnosis of CFS/ME and start of CBT can improve long-term outcome. It is not unlikely that a longer symptom duration (>10 years) increases the impact of CFS/ME on the person and his or her functioning. This may be related to a higher likelihood for relapse.

The positive predictive value of a better post-treatment assessment illustrates the importance of the immediate effect of CBT. This finding has direct clinical implications. During treatment, there is considerable variation in the reduction of fatigue between patients [23], but this is not systematically taken into account in the decision when to stop treatment. In most RCT's, treatment duration is fixed and not individually tailored. Instead of a fixed treatment duration, one could extent treatment as long as fatigue severity further improves. For this, regular outcome monitoring during treatment is needed, as is also recommended by others [38].

Clinically, the finding of frustration as a negative predictor of fatigue severity at LTFU stimulates individual analysis that may reveal negative emotionally loaded associations of fatigue, learned during the period patients suffered from severe fatigue. When emotionally loaded associations are activated with the experience of 'normal everyday' fatigue following successful CBT, it may increase chances to relapse. This would imply that treatment strategies to reduce the negative emotional associations with fatigue may result in better long-term outcomes [39].

A better physical functioning at LTFU was predicted by higher physical functioning, a higher sense of control over fatigue (both assessed directly following treatment) and younger age at start of treatment. The age of our cohort ranged from 18 to 67 with a median of 38 years. The finding of a demographic variable predicting outcome was not in line without our hypothesis. Although our group was relatively young, the negative effect of age on physical functioning found in the current

study may indicate a non-specific effect of increasing age on physical functioning [40].

Remarkably, pain at post-treatment was only found to be a predictor of physical functioning at LTFU in the non-imputed dataset. This was not in line with our hypothesis assuming that more severe CFS/ME symptoms at baseline predicted both fatigue and functioning at LTFU. Previous research has shown that pain consistently predicts fatigue directly post-treatment [32,33,41–43]. However, physical functioning at LTFU was predicted by pain at post-treatment when the number of CDC symptoms at baseline was replaced by the fulfilment of SEID at baseline in the regression model. Four CDC symptoms are pain symptoms (i.e. sore throat, multi-joint pain, headaches, and muscle pain) and pain symptoms are not part of the criteria of SEID. This may explain why pain became a predictor of physical functioning when using the SEID criteria. To us this highlights the importance of pain associated to physical functioning at LTFU. Unfortunately, we still lack effective pain interventions, as was also noted by others [33,44,45]. More effective pain interventions may improve both short-term and long-term outcome of CFS/ME patients.

In line with our hypothesis about the cognitive-behavioural perpetuating factors, a higher sense of control over fatigue at post-treatment predicted better physical functioning at LTFU. This was irrespective of fatigue severity at post-treatment. A previous study also found an increased sense of control over fatigue to be related to improvements in physical functioning [46]. This finding can perhaps be explained by assuming that a higher sense of control with respect to physical symptoms generalizes to self-efficacy with respect to resuming activities and overcoming physical limitations. In fact, this is in line with the aim of CBT to teach patients to become gradually more active, irrespective of fatigue levels. The increased sense of control with respect to symptoms also helps to maintain the improvements in physical functioning over time. A lower sense of control over fatigue increases the risk for a deterioration of physical functioning. This underlines the importance of fully maximizing the positive effects of treatment on physical functioning and sense of control over fatigue. For this, regular assessment of both during treatment is needed.

Our sample consisted of two cohort studies (individual CBT), and two RCT's studying CBT in the form of stepped care and group wise. In our previous publication on LTFU in the same sample, we tested the effect of study type on long-term outcome, which was non-significant [6].

A large majority of our CFS/ME sample fulfilled initially also SEID [3]. In the current study, fulfilling SEID was not related to outcome at LTFU. More studies are needed to investigate the different CFS/ME case definitions and their putative association to treatment outcome and follow-up.

Limitations and future research options

We imputed missing data with predictive mean matching, limiting variation within variables and thereby perhaps reducing their predictive value. We found that higher frustration at post-treatment significantly predicted fatigue severity at LTFU in the multiple imputation, but not in the non-imputed dataset. We conducted our statistical analyses using SPSS. SPSS has been reported to underestimate random variation in the imputation process when using predictive mean matching as compared to some other statistical packages [47]. This may have resulted in too small standard errors and too small p-values. Another explanation for the finding that higher frustration at post-treatment significantly predicted fatigue severity at LTFU in the multiple imputation, but not in the non-imputed dataset could be a lack of power due to a smaller sample size in the non-imputed dataset.

With prediction research, no firm conclusions can be drawn about causality as we could not compare outcomes with those of a non-treated control group. The current study was retrospective and long-term outcome was only assessed once. Future studies with a prospective design, with repeated follow-ups for all treated patients may give better insight in the course of CFS/ME symptoms. The predictive value of the variables we selected was limited; a large proportion of variance of the outcome measures remained unexplained. The somatic factor of hypocortisolism might be a predictor of interest as it predicted poor CBT outcome in adult CFS/ME patients [48]. Another study found correlations between cortisol changes to normal during treatment and recovery for adolescent CFS/ME patients [49]. Perhaps these variables may also be relevant for long-term outcome after CBT. Other unknown factors during the FU period may have contributed to our reported outcomes. That is a limitation of our study.

We used actigraphy with an actometer worn around the ankle to assess the level of physical activity [50]. Unfortunately, this device does not track physical activity when the leg is not involved and some types of activity can differentially impact registration. However, generally actigraphy is seen as a valid and reliable measure of the level of objective physical activity [50,51].

The current study was unique for its length of follow-up to ten years after treatment ended, within a large sample of CFS/ME patients, using predictors assessed at baseline and post-treatment. Ideally, treatment would start soon after the beginning of complaints. Based on regular assessments, treatment could be more personalized that may improve treatment outcome and its long-term maintenance. Interventions aimed at maximizing sense of control over fatigue, improving management of pain and influencing the affective quality of fatigue may also benefit long-term outcome after CBT for CFS/ME.

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APPENDIX

		Fatigue severity		Physical functioning		Fatigue within normal ranges	
		Pearson r	p	Pearson r	p	Spear-man's rho	p
FU	**Fatigue severity[A]**			-0·64	<0·001	-0·84	<0·001
FU	**Physical functioning[B]**	-0·64	<0·001			0·57	<0·001
BL	Fatigue severity[A]	0·16	<0·001	-0·11	0·01	-0·09	0·04
BL	Physical functioning[B]	-0·09	0·04	0·36	<0·001	0·040	0·40
BL	Age	0·13	0·003	-0·30	<0·001	-0·07	0·10
BL	Years of education	-0·12	0·009	0·19	<0·001	0·07	0·10
BL	Number of CDC symptoms	0·05	0·25	-0·18	<0·001	-0·05	0·28
BL	Duration of complaints (years)	0·18	<0·001	-0·16	<0·001	-0·17	<0·001
PT	Sense of control over fatigue[C]	-0·39	<0·001	0·46	<0·001	0·33	<0·001
PT	Perceived activity[D]	0·41	<0·001	-0·39	<0·001	-0·35	<0·001
PT	Pleasant appraisal of fatigue (%)[E]	-0·30	<0·001	0·29	<0·001	0·30	<0·001
PT	Frustrating appraisal of fatigue (%)[F]	0·42	<0·001	-0·32	<0·001	-0·38	<0·001
PT	Functional impairment[G]	0·40	<0·001	-0·48	<0·001	-0·35	<0·001
PT	Self-observed pain level[H]	0·29	<0·001	-0·45	<0·001	-0·28	<0·001
PT	Fatigue severity[A]	0·51	<0·001	-0·45	<0·001	-0·43	<0·001
PT	Physical functioning[B]	-0·36	<0·001	0·58	<0·001	0·33	<0·001
FU	FU duration from PT (months)	0·07	0·15	-0·08	0·07	-0·04	0·40
		Spear-man's rho	p	Spear-man's rho	p		p
FU	**Fatigue within normal ranges[I]**	-0·84	<0·001	0·57	<0·001		
BL	Sex (1=man)	-0·01	0·91	0·05	0·24	0·01	0·87
BL	Paid job	-0·14	0·002	0·17	<0·001	0·06	0·18
BL	Prior anx. and/ or depr. tr.[J]	0·03	0·51	0·00	0·94	0·02	0·72
BL	Fulfilling SEID[K]	0·03	0·56	-0·04	0·41	-0·01	0·74
BL	Clinical levels of depression[L]	0·08	0·07	-0·07	0·15	-0·06	0·15
BL	Disablement insurance benefits[M]	-0·06	0·21	0·06	0·15	0·07	0·14
PT	Low activity pattern (actigraphy)[N]	0·15	0·002	-0·18	<0·001	-0·08	0·10

Notes: BL baseline, PT post-treatment, FU long-term follow-up.
A) CIS Checklist Individual Strength, fatigue severity subscale; B) SF-36 Short Form Health Survey, 36 items, physical functioning subscale; C) SES Self-Efficacy Scale with respect to fatigue; D) CIS, activity subscale; E) FQL Fatigue Quality List, number of positive adjectives *20%; F) FQL, number of frustrating adjectives *20%; G) SIP Sickness Impact Profile; H) DOP daily observed pain, mean; I) Score on CIS fatigue severity subscale <35; J) 1= followed pre-existent anxiety and/ or depression treatment; K) SEID: systemic exertion intolerance disease = unrefreshing sleep, post exertional malaise and cognitive problems for at least a couple of times per week; L) 1= a score ≥4 on the BDI-PC; Becks Depression Inventory-Primary Care; M) 1= having a paid job, absence due to CFS/ME and receiving financial compensation under the Sickness Benefit Act; N) 1= 11 of 12 assessed days under score of reference score of 66. Outcome variables are highlighted bold.

Additional Table A - Pearson correlations and Spearman's rho for the dependent variables with the predictors.

First author	Knoop		Tummers		Wiborg		Heins	
Year of publication	2007		2010		2015		2013	
Cohort/ RCT	Cohort		RCT		RCT		Cohort	
Treatment form	Face-to-face		Stepped care		Group		Face-to-face	
n participated in FU of **N**	87/ 96		134/ 169		120/ 135		170/ 183	
Baseline	Mis.	*M (SD)*	Mis.	*M (SD)*	Mis.	*M (SD)*	Mis.	*M (SD)*
Fatigue severity[A]	0	49·94 (5·36)	0	47·88 (6·37)	0	50·83 (4·67)	0	49·96 (5·18)
Physical functioning[B]	1	52·15 (19·26)	0	56·68 (21·45)	0	54·75 (18·54)	0	57·91 (20·09)
Age (years)	1	36·27 (11·26)	5	38·25 (9·88)	0	38·83 (11·84)	0	38·25 (10·91)
Years of education	0	15·05 (2·11)	0	14·44 (2·59)	0	15·48 (2·06)	0	15·14 (2·26)
Number of CDC symptoms	0	7·02 (1·37)	0	7·25 (1·61)	0	6·90 (1·92)	0	7·04 (1·62)
Duration of complaints (years)	2	5·89 (4·40)	15	7·93 (6·04)	7	6·38 (6·3)	13	7·32 (6·62)
		n fulfills variable (%)		*n* fulfills variable (%)		*n* fulfills variable (%)		*n* fulfills variable (%)
Sex (1=man)	0	22 (25)	0	30 (22)	0	30 (25)	0	41 (24)
Paid job	0	47 (54)	0	70 (52)	0	75 (63)	0	123 (72)
Disablement insurance benefits[C]	0	11 (13)	0	17 (13)	0	43 (36)	0	54 (32)
Prior anx. and/ or depr. tr.[D]	11	14 (16)	13	21 (16)	0	31 (23)	1	49 (29)
Systemic Exertion Intolerance Disease (SEID)[E]	1	67 (77)	1	99 (74)	0	99 (83)	1	135 (79)
Clinical levels of depression[F]	0	28 (32)	0	53 (40)	0	48 (40)	1	55 (32)
Post-treatment	Mis.	*M (SD)*	Mis.	*M (SD)*	Mis.	*M (SD)*	Mis.	*M (SD)*
Fatigue severity[A]	0	29·64 (13·90)	8	34·30 (13·21)	19	29·88 (13·59)	0	26·31 (13·48)
Physical functioning[B]	0	77·07 (23·01)	7	74·84 (22·02)	19	80·30 (18·89)	0	83·82 (18·38)
Sense of control over fatigue[G]	0	21·78 (3·68)	33	21·30 (3·83)	21	22·64 (3·37)	1	22·96 (3·83)
Perceived activity[H]	0	8·59 (4·95)	8	9·48 (4·81)	19	8·95 (5·24)	0	7·93 (4·63)
Pleasant appraisal of fatigue (%)[I]	5	23·90 (28·19)	39	22·53 (22·83)	21	28·69 (27·43)	1	28·17 (25·95)
Frustrating appraisal of fatigue (%)[J]	5	23·90 (28·88)	39	29·47 (30·15)	21	34·14 (32·98)	1	24·50 (33·29)
Functional impairment[K]	0	629·86 (567·49)	7	788·89 (622·68)	18	670·17 (653·40)	0	540·78 (542·62)
Self-observed pain level[L]	0	3·63 (2·87)	45	4·33 (3·30)	25	3·53 (2·79)	10	3·40 (2·88)
		n fulfills variable (%)		*n* fulfills variable (%)		*n* fulfills variable (%)		*n* fulfills variable (%)
Low activity pattern (actigraphy)[M]	3	14 (16)	44	11 (8)	23	6 (5)	13	15 (9)
Fatigue within normal ranges[N]	0	56 (64)	8	65 (49)	19	64 (53)	0	126 (74)
Long-term follow-up	Mis.	*M (SD)*	Mis.	*M (SD)*	Mis.	*M (SD)*	Mis.	*M (SD)*
Fatigue severity[A]	0	38·40 (12·40)	0	38·31 (12·33)	0	37·68 (12·87)	0	36·58 (13·24)
Physical functioning[B]	2	72·06 (22·35)	6	71·33 (24·73)	11	74·08 (23·62)	3	74·52 (23·30)
FU duration from post-treatment (months)	0	109·97 (7·56)	7	80·60 (13·00)	18	36·10 (10·01)	0	47·58 (9·59)
		n fulfills variable (%)		*n* fulfills variable (%)		*n* fulfills variable (%)		*n* fulfills variable (%)
Fatigue within normal ranges[N]	0	33 (38)	0	46 (34)	0	46 (38)	0	63 (37)

Notes: Mis. = *n* of missing data.

A) CIS Checklist Individual Strength, fatigue severity subscale; B) SF-36 Short Form Health Survey, 36 items, physical functioning subscale; C) 1= having a paid job, absence due to CFS/ME and receiving financial compensation under the Sickness Benefit Act; D) 1= followed pre-existent anxiety and/ or depression treatment; E) SEID: systemic exertion intolerance disease = unrefreshing sleep, post exertional malaise and cognitive problems for at least a couple of times per week; F) 1= a score ≥4 on the BDI-PC; Becks Depression Inventory-Primary Care; G) SES Self-Efficacy Scale with respect to fatigue; H) CIS, activity subscale; I) FQL Fatigue Quality List, number of positive adjectives *20%; J) FQL, number of frustrating adjectives *20%; K) SIP Sickness Impact Profile; L) DOP daily observed pain, mean; M) 1= 11 of 12 assessed days under score of reference score of 66; N) Score on CIS fatigue severity subscale <35.

Additional Table B - Overview of all used predictor and dependent variables, stratified for each original study.

Chapter 4

Implementation of Stepped Care for Patients with Chronic Fatigue Syndrome in Community-Based Mental Health Care: Outcomes at Post-Treatment and Long-Term Follow-Up

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ABSTRACT

Background: Cognitive behavioural therapy (CBT) is an evidence-based treatment for chronic fatigue syndrome (CFS/ME). Stepped care for CFS/ME, consisting of a minimal intervention followed by face-to-face CBT, was found efficacious when tested in a CFS/ME specialist centre. Stepped care implemented in a community-based mental health centre (MHC) has not yet been evaluated.

Aims: (1) To test the effectiveness of stepped care for CFS/ME implemented in a MHC at post-treatment and at long-term follow-up; and (2) compare post-treatment outcomes of implemented stepped care with treatment outcomes of a CFS/ME specialist centre.

Method: An uncontrolled study was used to test effectiveness of stepped care implemented in a MHC (n = 123). The outcomes of implemented care were compared with the outcomes of specialist care reported in previous studies (n = 583). Data on outcomes from implemented stepped care were gathered at post-treatment and at long-term follow-up. Mixed models were used as method of analysis.

Results: Fatigue decreased and physical functioning increased significantly following implemented stepped care (both $p < 0.001$). The follow-up was completed by 94 patients (78%) within 1–6 years after treatment. Treatment effects were sustained to follow-up. Patients in the MHC showed less improvement directly following stepped care compared with patients in a CFS/ME specialist centre ($p < 0.01$).

Conclusion: Implemented stepped care for CFS/ME is effective with sustained treatment gains at long-term follow-up. There is room for improvement when compared with outcomes of a CFS/ME specialist centre. Some suggestions are made on how to improve stepped care.

INTRODUCTION

Chronic fatigue syndrome (CFS/ME) is characterized by medically unexplained, chronic and severe fatigue that is associated with significant impairment. According to the case definition of the US Centres for Disease Control and Prevention (CDC), patients must also report at least four additional symptoms out of the following eight: muscle pain, sore throat, multi-joint pain, tender lymph nodes, unrefreshing sleep, post-exertional malaise, headaches, and memory and/ or concentration problems [1] [2]. Individual cognitive behavioural therapy (CBT), aimed at changing fatigue-perpetuating cognitions and behaviour, leads to a significant reduction of fatigue and disability [3, 4]. CBT for CFS/ME was developed in tertiary research centres. This is true for most psychological treatments; these treatments are usually tested in specialist treatment centres [5]. To determine if interventions are similarly effective when implemented in routine clinical settings, studies are needed that compare the effects of implemented care with care delivered in specialist centres [5, 6]. Several implementation studies have been published on CBT for CFS/ME. Generally, face-to-face CBT has been successfully implemented [7, 8] with effect sizes comparable to the effect sizes of randomized controlled trials (RCTs) that tested CBT for CFS/ME in research centres [7].

Face-to-face CBT is time intensive, requiring 12–14 sessions. The Dutch healthcare system is under continuous pressure to reduce costs, resulting in budget cuts and limited treatment capacity. The need to use this limited treatment capacity more optimally has stimulated efforts to develop minimal interventions for CFS/ME, based on the protocol of face-to-face CBT. A minimal intervention consisting of a workbook with self-instruction and fortnightly email contact with a trained CBT-for-CFS/ME therapist was first tested in a CFS/ME specialist centre [9]. Subsequently, this minimal intervention was used as a first step in a stepped care model. Patients could step up to a higher intensity of treatment [10] in the form of face-to-face CBT if the minimal intervention did not suffice [11]. Within a CFS/ME specialist centre, the stepped care model was more time efficient and non-inferior compared with face-to-face CBT alone [11].

Subsequently, the minimal intervention was implemented in a community-based mental health centre (MHC). An RCT showed that the minimal intervention was effective, compared with a waiting list [12], with effect sizes comparable to when the intervention was delivered in a CFS/ME specialist centre [9]. Patients who participated in this implementation study were offered stepped care, i.e. the wait list group could start with the minimal intervention; after the minimal intervention patients could step up to face-to-face CBT if needed.

The primary aim of the present study was to evaluate the effectiveness of implemented stepped care in a MHC, both directly following treatment and at long-term follow-up. The secondary aim was to compare post-treatment outcomes of implemented stepped care with treatment outcome of CBT delivered in a CFS/ME specialist centre [13].

METHOD

Participants

In the original minimal intervention study in the MHC, 181 patients were referred for treatment of CFS/ME. Of this group of 181 patients, 123 patients were randomized. Thirty-nine referred patients did not meet the inclusion criteria: 34 did not meet CDC criteria, and five were younger than 18 or older than 65. Of the 142 patients eligible to enter the trial, 14 patients refused participation; four preferred face-to-face contact; four did not believe that treatment would help; three preferred another treatment; and for three patients, the reason for refusal was unknown [12]. All patients were diagnosed with CFS/ME according to the CDC criteria [1, 2]. Patients were severely fatigued, operationalized as scoring ≥35 on the subscale 'fatigue severity' of the Checklist Individual Strength (CIS) [14]. Their fatigue was medically unexplained, present for at least half a year and patients were disabled, operationalized as scoring ≤70 on the subscale 'physical functioning' and/ or the 'social functioning' subscale of the Medical Outcomes Survey Short Form-36 (SF-36) [15]. All patients reported at least four additional symptoms [1, 2].

In the original study, patients were first randomly assigned to the first step of stepped care, consisting of a minimal intervention or a delayed start with the minimal intervention after a waiting period of 6 months [12]. Treatment outcome of the minimal intervention at 6 months post-randomization was previously reported [12]. There was a significant reduction in fatigue following the intervention compared with the waiting list.

The current study used a reference group with CFS/ME patients who met the CDC criteria for CFS/ME and had received CBT in one CFS/ME specialist centre (*n* = 583). Detailed characteristics of the reference group are described in a previous study [13].

Design and procedures

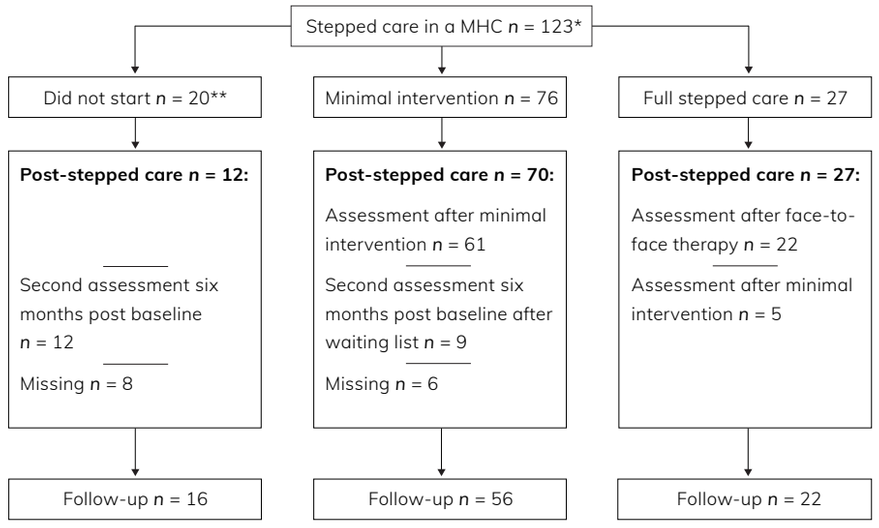
This is a secondary analysis of patients who participated in the original study [12] testing the efficacy of an implemented minimal intervention compared with a waiting list. The study was approved by the ethics committee of the Radboud university medical center. Patients who were still severely fatigued after the minimal intervention, i.e. patients who scored 35 or higher on the CIS fatigue severity subscale [14], were offered face-to-face CBT by trained therapists. The wait-list group was offered stepped care after the waiting period, i.e. a minimal intervention followed by face-to-face CBT if needed (see Figure 1). All patients of the prior RCT [12] were used in the current study and treated as one stepped care cohort. Patients who only completed a baseline assessment were excluded from analysis.

The follow up questionnaires or assessment link was sent again if patients did not return or did not complete them online within two weeks. If only a postal or e-mail address was known, the invitation letter was send without a previous phone call. If no address was known, the municipal registration was checked. When patients refused to fill in questionnaires, they were asked if they were willing to complete the fatigue severity subscale of the CIS by phone.

Of the 123 patients, 20 (16%) did not start treatment. Of those 20 patients, 12 patients had a second assessment that was used for analysis. The remaining eight patients had missing data at the second assessment. Of the 76 (62%) patients who followed the minimal intervention, 70 patients were used for analysis: 61 patients had a post-minimal intervention assessment, nine had a second assessment after the 6-month waiting period and six patients had missing data. Out of the 27 (22%) patients who followed face-to-face CBT after the minimal intervention, 22 had an assessment after CBT and for five patients the last assessment available was the assessment after the minimal intervention.

All 123 patients who participated in the original study [12] were contacted by telephone for a follow-up assessment. If they agreed to participate, they received an invitation letter and questionnaires by post, or e-mail with a link to complete questionnaires online.

CFS/ME patients treated in one CFS/ME specialist centre were the reference group consisting of patients from two cohort studies and two RCTs, all treated following the same protocol [16, 17]. Different treatment formats were applied in the studies of the reference group: individual CBT (*n* = 179) [4, 18], stepped care consisting of a minimal intervention and individual CBT (RCT, *n* = 169) [11] and group CBT (RCT, *n* = 135) [19]. The reference group was treated as one cohort [13].



Notes: The post-stepped care assessment was used for analysis. * half of the stepped care group was randomised to a direct start with the minimal intervention or a delayed start after six months waiting list. **18/ 20 patients were first randomised to the waiting list.

Figure 1 - Study overview of implemented stepped care at post-stepped care and follow-up.

Intervention

The minimal intervention consisted of a booklet with guided self-instruction based on the CBT for CFS/ME protocol. All patients had fortnightly contact with a trained psychiatric nurse via e-mail. Nurses sent a reminder when patients did not respond every 2 weeks. During therapy, patients change cognitions and behaviours that are assumed to perpetuate fatigue and disability.

Psychiatric nurses introduced the minimal intervention booklet and provided instructions to the patient to complete the intervention within 6 months. All patients had a face-to-face evaluation after completion of the second assessment (at 6 months) with the psychiatric nurse who delivered the therapy.

If patients were still severely fatigued, they were referred to a CBT therapist within the MHC for additional face-to-face CBT for CFS/ME. This additional face-to-face CBT was the second step of stepped care. Following the protocol [17], a full therapy would consist of 12 to 14 sessions over a period of 6 months. However, dependent on the progress made during the minimal intervention, the therapist decided which elements of the protocol should be discussed during the face-to-face CBT [11].

The Physical Activity Questionnaire (PAQ) was used to determine the physical activity pattern of patients [20]. Two different physical activity patterns can be discerned, a low active and relative active pattern [21]. The activity pattern is used to tailor treatment. The instructions described in the minimal intervention booklet included personal goal setting, regulating the sleep-wake cycle, reducing the focus on fatigue, and the systematic challenge of dysfunctional fatigue-related beliefs. Relatively active patients, characterized by an alternation of periods of (over)activity and periods of rest, first learned to divide their activities more evenly before gradual increasing their activities. After gradual increase of activities, patients start to accomplish personal goals including full resumption of work or study. Low active patients immediately started with graded activity. Last treatment module contains information about how to let go treatment principles and maintain a normal, healthy lifestyle.

Therapists training and supervision

The minimal intervention was carried out by eight psychiatric nurses. They were trained in four training sessions of 4 hours and received two-weekly supervision [12]. Face-to-face CBT was given by four clinical psychologists who followed a 4-day training in CBT for CFS/ME and received two-weekly supervision. Training and supervision was provided by a clinical psychologist/ cognitive behavioural therapist experienced in delivering the minimal intervention and face-to-face CBT for CFS/ME (HK).

Measures

Fatigue severity

Fatigue severity was measured with the fatigue severity subscale of the CIS. The CIS consists of 20 items. The fatigue severity subscale of the CIS has eight items and each item is scored on a Likert-scale from 1 to 7. The total score ranges from 8 (no fatigue) to 56 (severe fatigue) [14]. The CIS has good psychometric characteristics [14].

Fatigue scores in the normal range

We determined the number of patients ***with a fatigue score in the normal range*** following treatment, defined as a score of less than 35 on the 'fatigue severity' subscale of the CIS. This is below the cut-off for severe fatigue [14].

Physical functioning

Physical functioning was assessed with the physical functioning subscale of the Medical Outcomes Survey Short Form-36 (SF-36). This subscale measures the extent to which health problems interfere with a variety of physical activities. Weighted scores on this subscale range from 0 (no limitations) to 100 (maximum limitations), i.e. higher scores indicate better physical functioning [22]. The SF-36 is considered a reliable and valid instrument [7, 22].

A level of physical functioning comparable to healthy people

Following treatment, we determined the number of patients ***with a level of physical functioning comparable to healthy people*** defined as scoring 80 or higher [4]. Healthy adults without a chronic condition [23] were used as a norm group. The score of 80 is approximately one *SD* (11.7) below the mean of the norm group (mean = 93.1).

Pain

Pain at baseline was measured with self-observation lists in which patients rated pain (0 = no pain to 4 = very severe pain), for 12 days, four times a day. All pain scores per day were averaged into one daily-observed pain (DOP) score (range 0–16). This measure was used in previous studies [24] [25, 26]. The last study found good split half reliability between measures of the first week compared with the second: $r = 0.87$.

Depression

Depression at baseline was assessed with the Beck Depression Inventory-Primary Care questionnaire (BDI-pc, Cronbach's alpha 0.86, seven items, 4-point scale) [27].

CDC symptoms

The ***CDC symptoms*** at baseline (eight in total) [1, 2] were reported on a 4-point scale ranging from 'not at all', 'a few times per month', 'a few times per week' to 'every day'. Symptoms had to be present for at least 6 months.

Additional measures at follow-up

A general questionnaire was used at follow-up that contained items on presence of somatic co-morbidity that occurred since end of treatment and still present, and significant life events in the past year. Mental health and pain at the time of follow-up were assessed with the subscales 'mental health' and 'bodily pain' of the SF-36 [22].

Data analyses

The effect of implemented stepped care

The development over time in fatigue severity and physical functioning was analysed with linear mixed model analyses for the continuous outcomes. Time was added as two categorical variables representing treatment phase from baseline to post-stepped care and the follow-up phase from post to follow-up. The patients who participated in the follow-up study were compared with the group that did not participate in the follow-up study using **t**-tests to determine if both groups were similar with respect to fatigue severity and physical functioning at baseline and post-treatment.

Several covariates, i.e. somatic co-morbidity that occurred since end of treatment and still present; pain and mental health at follow-up; and significant life events within the last year, were added to the mixed model analyses. It was tested if these covariates would change the previous findings of the follow-up phase outcomes. Chi-quadrate tests were used to compare post-stepped care and follow-up for the proportion of patients with fatigue scores in the normal range, and for physical functioning levels compared with healthy people. All data were analysed in IBM SPSS Statistics 22. The threshold for significance was $p < 0.05$ (two-tailed).

Post-treatment outcomes of implemented stepped care compared with CBT in a CFS/ME specialist centre

The contribution of treatment setting (MHC or CFS/ME specialist centre) to treatment outcome was evaluated with the interaction effect of treatment setting × time (baseline up to post-treatment) on fatigue and physical functioning. In the crude model, three variables were added: treatment setting, one categorical dummy variable for time, and its interaction. As patients were not randomized between treatment setting (MHC or CFS/ME specialist centre), we added baseline patient characteristics [i.e. age, gender, number of CDC symptoms, fatigue severity (CIS), physical functioning (SF-36), pain (SF-36) and level of depression (BDI-pc)] to the model to test if this would change the effect of treatment setting. Chi-quadrate tests were used to compare both treatment settings directly following treatment for the proportion of patients with fatigue scores in the normal range, and for physical functioning levels compared with healthy people.

RESULTS

The effect of implemented stepped care

Patient characteristics at baseline are described in Table 1. Following stepped care in the MHC, fatigue severity significantly decreased (–12.6, $p < 0.001$; pre–post Cohen's $d = 1.19$, 95% CI 0.91 to 1.46) and physical functioning significantly increased (17.1, $p < 0.001$; pre–post Cohen's $d = 0.75$, 95% CI 0.48 to 1.01).

		SD/ Range
Baseline (n = 123)		
Mean age at baseline	35·86	17-64
Proportion female, %	78·00	
Median duration of complaints, years	5·00	0·5-52
Mean number of CDC symptoms	7	0-8
Fatigue severity, CIS	51·28	5·41
Physical functioning, SF-36	50·77	22·19
Depression, BDI-pc	3·85	3·45
Pain, SF-36	51·22	24·32
	Numbers	**%**
Follow-up (n = 86)		
Somatic co-morbidity (onset after treatment)	12	14·0
Life events during last year with impact on health	40	46·5

Abbreviations: CDC, US Centers for Disease Control and Prevention; CIS, Checklist Individual Strength; SF-36, Medical Outcomes Survey Short Form-36; BDI-pc, Beck Depression Inventory, primary care.

Table 1 - Patient characteristics of stepped care in a MHC.

From the 123 patients, long-term follow-up data were available for 94 patients (76%); two patients were deceased. Sixteen patients who participated in the follow-up study had not started treatment, 56 patients had followed the minimal intervention and 22 patients had followed full stepped care. The participants in the follow-up study did not differ significantly in fatigue severity and physical functioning scores at baseline and post-stepped care from the patients who did not participate in the follow-up study (data not shown).

From post-stepped care up to follow-up, fatigue severity and physical functioning did not significantly change (mean change fatigue 1.4, $p = 0.32$; mean change physical functioning –1.0, $p = 0.69$; Table 2). The number of patients with fatigue scores in the normal range and physical functioning comparable to healthy people did not significantly change from post-stepped care (fatigue: 36%, 40/ 111; functioning: 40%, 44/ 111) to follow-up (fatigue: 28%, 26/ 94; $\chi^2 = 1.6$, $p = 0.2$; functioning: 35%, 30/ 86, $\chi^2 = 0.5$, $p = 0.49$).

	Fatigue severity			Physical functioning		
	B (SE)	95% CI for B	p	B (SE)	95% CI for B	p
Crude model						
Time						
Categorical, baseline to post*	-12·6 (1·3)	-15·1 to -10·1	<0·001	17·1 (2·3)	12·6 to 21·6	<0·001
Categorical, post to follow-up**	1·4 (1·4)	-1·3 to 4·1	0·32	-1·0 (2·5)	-6·0 to 4·0	0·69
Model with covariates						
Time						
Categorical, from post to follow-up**	-0·2 (1·4)	-2·9 to 2·6	0·91	-1·3 (2·8)	-6·9 to 4·3	0·64
Health status						
Z_Significant life events	0·7 (0·9)	-1·1 to 2·4	0·47	-0·5 (1·9)	-4·3 to 3·3	0·79
Z_Self-reported somatic co-morbidity	1·3 (0·9)	-0·5 to 3·1	0·15	-0·9 (1·9)	-4·7 to 2·9	0·64
Z_Pain (SF-36)	-3·3 (0·6)	-4·4 to -2·1	<0·001	10·8 (1·3)	8·2 to 13·4	<0·001
Z_Mental health (SF-36)	-2·9 (0·6)	-4·0 to -1·7	<0·001	2·2 (1·3)	-0·4 to 4·8	0·10

Notes: * A dummy variable representing the time frame baseline to post-stepped care; ** a dummy variable representing the time frame post-stepped care to follow-up.

Table 2 - The development of fatigue severity and physical functioning from baseline to post-stepped care and from post to follow-up, with adjustment for covariates.

We added the covariates significant life events, somatic co-morbidity, pain and mental health to the model to assess if this would change the non-significant result of outcome during the follow-up phase (Table 2, model with covariates). These covariates have found to be related to fatigue and/ or physical functioning [13,24,25,28] and may influence long-term effects of CBT when they occur in the follow-up phase. Of the patients who participated in the follow-up study, 12/ 94 (13%) reported somatic co-morbidity which had occurred after treatment, and 37/ 94 (39%) reported life events during the last year with an impact on health (see Table 1). The addition of the covariates did not change the non-significant development of our outcomes during the follow-up phase (fatigue: $p = 0.91$ and functioning: $p = 0.64$).

Post-treatment outcomes of implemented stepped care compared with CBT in a CFS/ME specialist centre

There was a significant treatment setting × time interaction ($p < 0.001$) on fatigue severity (additional Figure 1; Table 3). Fatigue severity decreased more when treated in a CFS/ME specialist centre ($B = –19.6$, $p < 0.001$) than with implemented stepped care ($B = –12.6$, $p < 0.001$). There was also a significant setting × time interaction ($p = 0.009$) in physical functioning (additional Figure 2; Table 3). Physical functioning improved more in the CFS/ME specialist centre ($B = 23.2$, $p < 0.001$) than after implemented stepped care ($B = 17.1$, $p < 0.001$). We added covariates to the model to test if this would change the effects for the different treatment settings. Both interactions remained significant when baseline patient characteristics were added as covariates (see model B of Table 3).

Significantly fewer patients after implemented stepped care ($\chi^2 = 25.6$, $p < 0.001$) had fatigue scores in the normal range (36%, 40/ 111) than when treated in the CFS/ME specialist centre (62%, 337/ 543). The same pattern of results was found for the number of patients with physical functioning scores comparable to healthy people (implemented stepped care: 40%, 44/ 111; for a CFS/ME specialist centre: 63%, 340/ 543; $\chi^2 = 20.1$, $p < 0.001$).

	CIS fatigue severity post score			SF-36 physical functioning post score		
A	B (SE)	95% CI for B	*p*	B (SE)	95% CI for B	*p*
Treatment setting post	-8·3 (1·1)	-10·4 to -6·2	<0·001	10·2 (2·2)	5·9 to 14·5	<0·001
Time BL to post	-12·6 (1·3)	-15·1 to -10·0	<0·001	17·1 (2·1)	12·9 to 21·3	<0·001
Time BL to post	-19·6 (0·6)	-20·8 to -18·5	<0·001	23·2 (1·0)	21·3 to 25·1	<0·001
Treatment setting X Time BL to post	-7·1 (1·4)	-9·8 to -4·3	<0·001	6·1 (2·3)	1·5 to 10·7	0·009
B						
Treatment setting post	-8·2 (1·0)	-10·2 to -6·3	<0·001	9·8 (1·5)	6·8 to 12·8	<0·001
Time BL to post	-12·6 (1·3)	-15·1 to -10·1	<0·001	17·2 (1·9)	13·5 to 21·0	<0·001
Time BL to post	-19·5 (·6)	-20·6 to -18·4	<0·001	23·0 (·9)	21·2 to 24·7	<0·001
Treatment setting X Time BL to post **with covariates**	-6·9 (1·4)	-9·7 to -4·2	<0·001	5·7 (2·1)	1·6 to 9·9	<0·007

Notes: Grey shading: the effects for stepped care in a MHC. 95% CI, 95% Confidence Interval; BL, baseline.

Table 3 - Mixed model comparisons between stepped care in a MHC (grey shaded) versus a CFS/ME specialist centre.

DISCUSSION

The first objective of this study was to determine the effectiveness of stepped care implemented in a community-based MHC directly following treatment and at long-term follow-up. Fatigue severity significantly decreased and physical functioning significantly increased after implemented stepped care. Treatment gains were sustained up to 6 years.

The current finding that implemented stepped care is effective is in line with previous studies of stepped care in CFS/ME specialist centres that have also shown significant treatment effects [11, 29]. It is encouraging for implemented CBT that after stepped care patients were able to maintain the gains made on fatigue and physical functioning.

The minimal intervention implemented in the MHC had similar controlled effect sizes on both fatigue and physical functioning when compared with a CFS/ME specialist centre [9, 12]. However, when patients proceed with face-to-face therapy within a stepped care model, therapy in the MHC was less effective than care in a CFS/ME specialist centre, targeting the second objective of this study. This difference between the effects of the implemented ***minimal intervention*** and the effects of implemented ***stepped care*** suggests that the second step in the stepped care model, i.e. face-to-face CBT, has to be improved in the MHC.

Some characteristics of implemented stepped care may have negatively affected outcome. First, shortly after face-to-face CBT had been implemented in the MHC, stepped care was introduced [8]. The newly trained therapists had only limited experience in delivering face-to-face CBT for CFS/ME outside the context of stepped care. It is likely that it is more difficult to deliver CBT to patients who were already unsuccessfully treated with the minimal intervention. Future implementation of CBT for CFS/ME should give therapists enough time to first learn to effectively treat patients with ***regular*** CBT for CFS/ME.

Another relevant implementation factor was the involvement of two different professionals in the delivery of stepped care. Trained nurses performed intakes and carried out the first step of care in the form of the minimal intervention. The second step of care, i.e. face-to-face therapy, was delivered by a CBT for CFS/ME therapist, unknown to the patient. This change of caregiver may have been associated to the fact that only a small group (one-third) of patients with an indication to step up, i.e. still severely fatigued, actually stepped up. If patients do not step up to a higher treatment intensity while they are indicated to do so, this may diminish outcome of stepped care [30]. In contrast, patients in a CFS/ME specialist centre were supported by the same therapist during all steps of care. Here, two-thirds of the still severely fatigued patients proceeded to the second step of care, i.e. face-to-face CBT [11]. The treatment outcome of implemented stepped care may be enhanced if the therapist delivering the second step of treatment is involved early in the diagnostic process and with the evaluation after the minimal intervention.

Lastly, and irrespective of the setting, we highlight two common issues with stepped care: (1) patients who do not start with a minimal intervention, or (2) do not step up to a higher treatment intensity [30]. In the MHC, approximately 15% of patients did not start with the minimal intervention at all (for a similar percentage of non-starters in CFS/ME specialist care, see [9]. In the future, if patients will not start with the minimal intervention in the first 2 weeks, a therapist could contact the patient and discuss the reason for not starting. The outcome of this shared decision making may be that they decide to still start or stop treatment. Stepping up at an early stage is another option, although it is unknown if these patients would benefit from stepping up to a higher treatment intensity at this stage. The second limitation of stepped care was patients who do not step up to a higher treatment intensity. Patients who have started with the minimal intervention and gain minimal benefits may have lost motivation to step up, since they had to wait 6 months until the second step of treatment was provided. A previous process study into face-to-face CBT

showed that patients have different trajectories of change [18]. These trajectories of change are as yet unknown for patients following stepped care. A prospective process study could assess outcome and changes in fatigue perpetuating factors every month to reveal different change trajectories. This knowledge could help to decide when to step up to a higher treatment intensity. More pragmatically, a stepped wedge design [31] can be applied to test the benefit of stepping up to face-to-face CBT earlier than the current 6 months.

In future studies we would propose to randomize early non-responders on the minimal intervention to (1) a control group that will proceed with the minimal intervention or (2) a group that will step up to face-to-face CBT. This randomization procedure can be performed at 3, 4 and 5 months after the start of the minimal intervention. Outcomes of the early non-responders that proceeded with the minimal intervention can be compared with outcomes of the early non-responders that were randomized to face-to-face CBT. Patients who do benefit from the minimal intervention proceed with this treatment until the usual post-treatment assessment at 6 months and will not be randomized. The study may inform us at what point (during non-response to the minimal intervention) it is useful to step up to a higher treatment intensity. One critical note to this design is that it needs a large sample size to test all subgroups with sufficient power.

Limitations

The current study has several limitations. Patients were not randomly assigned to the MHC or to the CFS/ME specialist centre and may therefore differ. The route of referral that patients had followed differed between centres. In the CFS/ME specialist centre, patients were usually referred via the department of internal medicine, whereas in the MHC patients were usually referred by the general practitioner or internal consultant. This may have led to differences in patient characteristics between both settings. However, outcome differences between treatment settings could not be explained by patient's age, gender, number of CDC symptoms, fatigue severity, physical functioning, pain, and level of depression at baseline. This is a relevant finding as there are concerns that RCTs performed in specialist centres use strict inclusion criteria and that patients therefore differ from patients in implementation settings. Moreover, these hypothesized patient differences are assumed to explain the differences in effect sizes between specialist centres and implementation settings [6]. One note to our comparison of treatment outcome between treatment settings was that it had an unbalanced sample size, making the comparison to test for patient differences between settings probably underpowered.

A recent validation study of the Checklist Individual Strength proposed new norms for severe fatigue. The study found a higher cut-off score of 40 to discern severe fatigue of lower scores representing fatigue scores in the normal range [14]. The present study still used 35 as a cut-off to make comparisons with previous studies easier.

One could argue that the comparison between stepped care and different formats of CBT delivered in a CFS/ME specialist centre is a limitation of the present study as it is unclear if these

treatment formats are equally effective. However, a previous analysis showed similar changes in outcome over time for all the different formats of CBT without differences in outcome between stepped care and other formats [13].

Most patients who did not start treatment were first randomized to a 6-month waiting list before they could start with the minimal intervention. This may have reduced the effectiveness of the stepped care [12] and is a limitation of our study design. The absence of a control group and the variety in treatment experiences in the MHC are limitations of our study. Unfortunately, information about the care patients received between post-treatment assessment and follow-up was lacking. This is a further limitation of our study.

Future directions

Significant improved outcomes were found on fatigue and physical functioning after implemented stepped care, although outcomes were less favourable than those of a CFS/ME specialist centre. Treatment gains were maintained at long term. Future research could be directed to study (1) an optimized form of implemented stepped care; (2) evaluating patient change trajectories during stepped care; and (3) determining the right moment for stepping up to face-to-face CBT.

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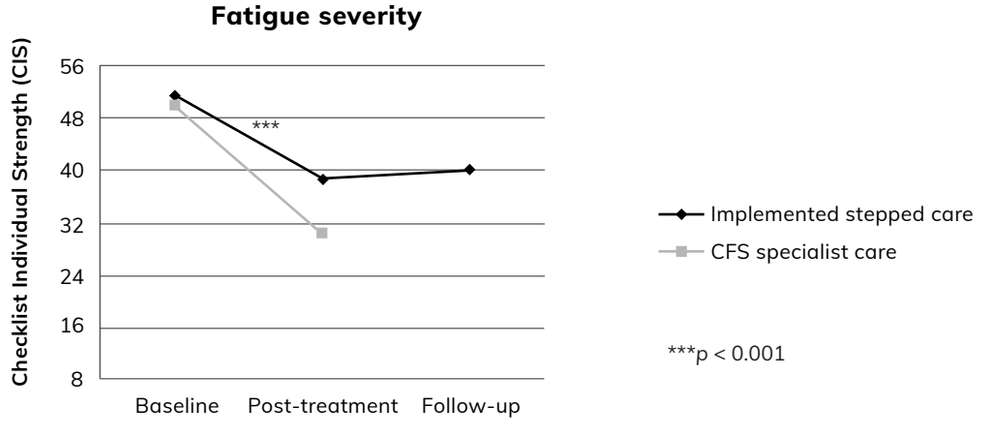
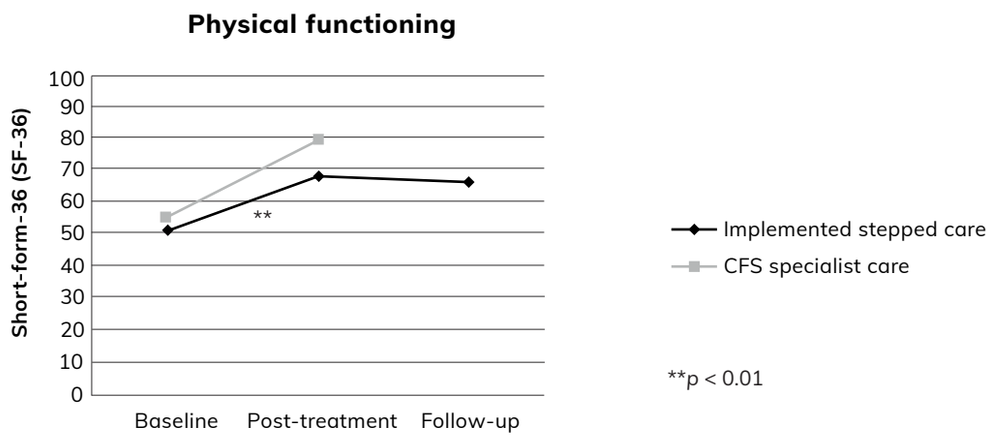
APPENDIX



Additional Figure 1 - Mean fatigue severity over time and the significance level for the interaction of treatment outcome between centres.



Additional Figure 2 - Mean physical functioning over time and the significance level for the interaction of treatment outcome between centres.

Chapter 5

The Efficacy of Guided Self-instruction for Patients With Idiopathic Chronic Fatigue: A Randomized Controlled Trial

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ABSTRACT

Objective: To determine the efficacy of a cognitive–behavioural intervention for patients meeting U.S. Centers for Disease Control and Prevention (CDC) criteria for idiopathic chronic fatigue (ICF). ICF is thought to be a less severe disorder than chronic fatigue syndrome (CFS/ME). The intervention consisted of a booklet with self-instructions combined with e-mail contact with a therapist.

Method: Randomized controlled trial conducted at an outpatient facility. All patients suffered from severe and persistent fatigue with moderate impairment levels or fewer than 4 additional symptoms. Patients were randomly allocated to either guided self-instruction or a wait-list control group. Primary outcome measures were fatigue severity assessed with the Checklist Individual Strength and level of overall impairment assessed with the Sickness Impact Profile. Outcome measures were assessed prior to randomization and following treatment or wait-list control group.

Results: One hundred patients were randomly allocated to the intervention or a wait-list control group and 95 completed second assessment. An intention-to-treat analysis showed significant treatment effects for fatigue severity (-8.98, 95% confidence interval [CI] [-13.99 to -3.97], Cohen's d = 0.68, p < 0.001) and for overall impairment (-317.19, 95% confidence interval [CI] [-481.70 to -152.68], Cohen's d = 0.53, p < 0.01) in favour of the intervention. The number of additional symptoms and overall impairment at baseline did not moderate post-treatment fatigue severity. Baseline overall impairment moderated post-treatment impairment.

Conclusions: Patients with ICF can be treated effectively with a minimal intervention. This is relevant as ICF is more prevalent than CFS/ME and treatment capacity is limited.

INTRODUCTION

Fatigue is a frequently reported symptom by patients who visit general medical care settings [1]. Although in most patients fatigue is only a temporary phenomenon, a substantial number of patients will continue to experience fatigue [2]. Only a few patients will meet the criteria for chronic fatigue syndrome (CFS/ME) as formulated by the U.S. Centers for Disease Control and Prevention (CDC) [3,4]. CFS/ME is characterized by medically unexplained severe fatigue, which leads to *significant* disability in daily life and persists 6 months or longer. Four or more of the following eight additional symptoms must also be present: unrefreshing sleep, post-exertional malaise, headaches, muscle pain, sore throat, multi-joint pain, tender lymph nodes, and memory and/ or concentration problems [3,4]. Several randomized controlled trials have shown that cognitive behaviour therapy (CBT) and graded exercise therapy (GET) can lead to a significant reduction of fatigue and disability in CFS/ME [5-7].

The diagnosis *idiopathic chronic fatigue* (ICF) is assigned when patients suffer from "clinically evaluated, unexplained chronic fatigue that fails to meet criteria of CFS/ME" [3, p. 956]. In our study, we interpreted this as medically unexplained severe fatigue that persisted for 6 months or longer but where patients reported fewer than four additional symptoms and/ or less impact of fatigue on their daily functioning than CFS/ME patients. ICF is a problem for both patients and the health care system, as medically unexplained symptoms like fatigue are associated with poorer quality of life [8], more health care and complementary medical therapy use [9] and work related costs [10,11]. A recent meta-analysis showed that the general population prevalence rate of CFS/ME is 0.76% [12]. Based on the definition of ICF one would expect the prevalence of ICF to be much higher. ICF prevalence rates varied between studies from 3% [13] to 15% [14]. Variation in prevalence rates is probably at least partly caused by the use of different operationalisations of ICF [2,15,16]. Even though there are substantially more patients with ICF than there are patients with CFS/ME, most intervention trials are aimed at reducing fatigue in patients meeting criteria of CFS/ME (e.g., [5]).

The CDC criteria are widely used internationally. When diagnostic systems with broader criteria for defining CFS/ME are used—for example, Oxford criteria [17]—patients with ICF will be classified as CFS/ME [18]. As far as we know, the efficacy of interventions for the subgroup of patients with ICF was not determined. As a consequence, little is known about how to treat patients effectively who meet criteria for ICF.

Because ICF has been conceptualized as less severe than CFS/ME, a minimal (behavioural) intervention might suffice for many of the patients diagnosed with ICF. Several minimal or self-help interventions were developed and tested specifically for patients with CFS/ME [19,20], CFS/ME patients aged 11–18 year [21], and for chronically fatigued patients in general practice [22,23,24]. Following these interventions, fatigue levels and/ or impact of fatigue on daily functioning were significantly reduced. All these studies included only CFS/ME patients or patients with CFS/ME were always part of the total group of the included patients. Chalder et al. [22], also included

patients with a medical or psychiatric condition that could explain the fatigue, and Ridsdale et al. [24], included patients who were fewer than 6 months fatigued or unimpaired. None of the studies was specifically aimed at patients with ICF.

In this study, we tested the efficacy of a minimal cognitive–behavioural intervention in patients with ICF. This intervention was originally developed for and tested on patients with CFS/ME. It consists of guided self-instruction in the form of a self-help workbook plus e-mail contact with a trained therapist. Guided self-instruction is based on the protocol of face-to-face CBT for CFS/ME [25] and has been shown to reduce fatigue severity and disability in patients with CFS/ME [19,20,26]. We also tested whether the number of additional symptoms and the level of disability moderated the treatment response of ICF patients. Fewer than four additional symptoms and/ or moderate levels of disability differentiate ICF patients included in this study from CFS/ME patients included in previous studies. A previous study in CFS/ME patients showed that the level of disability was a moderator of treatment outcome—more severely impaired CFS/ME patients profited less from guided self-instruction [19].

We hypothesized that patients with ICF would profit from guided self-instruction in the form of a significant reduction in the primary outcome measures fatigue severity and level of disability at the end of 6 months of treatment compared with a wait-list control group of 6 months. We further hypothesized that the level of disability and number of additional symptoms would moderate the treatment response in ICF patients.

METHOD

Participants

Patients were referred to the Expert Centre for Chronic Fatigue of the Radboud university medical center, an outpatient treatment facility. Consultants of the department of internal medicine evaluated the medical records of referred patients and—if needed—physically examined the patient to rule out medical explanations for fatigue. Trained cognitive– behavioural therapists at the treatment centre ruled out psychiatric comorbidity as potential explanation for the fatigue with a clinical interview. Recruitment took place between January 2009 and July 2012 among referred patients. Patients were eligible for the study if they were at least 18 years old (there was no maximum age for participation);

- were able to speak, read, and write Dutch;
- had experienced for at least 6 months severe fatigue, operationalized as having a score of 35 or higher on the subscale “fatigue severity” of the Checklist Individual Strength (CIS) [27]; a fatigue severity score of 35 is two standard deviations above the mean of healthy controls; [28];
- had moderate levels of overall impairment operationalized by a total score on the Sickness Impact Profile (SIP8; [29,30] between 450 and 700; and/ or

- had fewer than four additional CDC symptoms that is, unrefreshing sleep, post-exertional malaise, headaches, muscle pain, sore throat, multi-joint pain without swelling or redness, tender lymph nodes, and memory and/ or concentration problems [3,4].

Following the CDC definition, the criteria of presence of additional symptoms and/ or a moderate level of disability reported by patients (SIP) were used to distinguish between patients with CFS/ME and ICF. Patients with a score below 450 on the SIP8 were excluded regardless of the number of additional CDC symptoms (i.e., no clinically relevant overall impairment). The additional symptoms were assessed with a standardized questionnaire in which patients had to indicate for each of the symptoms if it was present.

Patients were temporarily excluded when they were engaged in a legal procedure concerning disability-related benefits, as being engaged in a legal procedure is known to predict poor therapy outcome in CFS/ME patients [31].

Design and procedures

This study was a parallel group randomized trial with an intervention condition consisting of guided self-instruction. The ethical committee of the Radboud university medical center approved the trial. The trial is registered at the Netherlands Trial Registry under number NTR1660. Eligible patients received verbal and written information. If they wanted to participate, they were asked to sign an informed consent form. They were randomized to either guided self-instruction or a wait list after given informed consent and baseline assessment. All patients were requested not to start another treatment for fatigue while following the intervention or during the waiting period. After 6 months, all patients were assessed again.

Assessment of ICF

Before referral to our treatment centre consultants of the outpatient clinic of the department of internal medicine assessed the medical status of all patients and decided whether patients had been sufficiently examined to rule out a medical explanation for the fatigue. If patients had not been sufficiently examined, they were seen for anamnesis, full physical examination, case history evaluation and laboratory tests following the National CFS/ME guideline as is used at the department of internal medicine and is according to the guidelines of the CDC [4,32,33]. When consultants concluded that patients met CDC criteria for ICF, they were referred to our treatment centre. Psychiatric comorbidity that can explain the presence of fatigue was ruled out by a clinical interview by a therapist trained in delivering CBT for CFS/ME. The clinical interview was part of baseline assessment, which is part of clinical routine for all referred patients.

Baseline assessment

The assessment consisted of two intake sessions with a CBT therapist and two test sessions in which the patient filled in questionnaires. Patients also wore an actometer (a device that measures physical activity) for two weeks to assess the pattern of physical activity and they registered their sleep-wake pattern.

Randomization

A statistical advisor, from another department and independent of the study, ensured concealed allocation by coding numbered and sealed opaque envelopes according to a computer-generated list of random numbers in blocks of four. A psychological test-assistant not involved in the treatment or study performed the randomization. The assistant handed the envelope to the therapist who opened it in the presence of the patient and the test-assistant. Both patients and therapists were unblinded for condition.

Therapists

Licensed cognitive–behavioural therapist trained in individual CBT for CFS/ME, responded to e-mails of the patient. The therapists had on average 5.2 years (range 1–20 years) experience with CBT for CFS/ME. Aside from general postdoctoral training in CBT, all therapists followed an additional 4-day training for individual CBT for CFS/ME. This was followed by one year of weekly individual supervision. Before the start of the study therapists (*n* = 16) followed one day of training in writing e-mails. Therapists were advised to begin with a compliment for relevant and new behaviour in the context of the intervention. This was followed by affirmation of the most relevant target cognitions or target behaviours for example commitment to fixed bedtimes or the gradual increase of activity. The content of e-mail could contain explanations of certain aspects of the treatment that were relevant for the individual patient or suggestions regarding how to proceed with the treatment. Several guidelines were offered on how to write short messages aimed at motivating patients to continue with the program. The therapists received weekly supervision (group size *n* = 5) from GB or HK where e-mails of patients and answers written by therapists were discussed.

Intervention

The therapist explained to patients who were randomized to the intervention condition how to use the booklet and how to e-mail. The booklet was introduced to the patient together with information about his or her physical activity pattern. Patients were requested to send an e-mail within the first week and from then on e-mail fortnightly to report on their progress. Patients were allowed to e-mail more often if they wanted. The expected time-investment was not specified, as it is a (guided) self-help intervention. When patients asked about the expected time-investment, therapists were instructed to respond by encouraging to practice as much as possible because a better outcome was expected when the patient was able to practice more. In the introduction text of the booklet, patients were instructed to complete treatment within 6 months. Patients in both conditions received a Web-based assessment following the waiting period or the intervention of 6 months. After randomization, all patients made an appointment for a face-to-face session after second assessment. In this session, results of the second assessment was discussed and therapists asked if patients had followed other treatments in the previous 6 months. After this session, the wait-list group could start with guided self-instruction.

The intervention consisted of a booklet with information and assignments divided in 13 successive modules. Patients could work on their own pace through the booklet modules and could skip modules if they were not applicable to their situation. The treatment is based on the protocol of face-to-face CBT for CFS/ME [25]. The cognitive–behavioural model for CFS/ME for this intervention is based on the assumptions that fatigue-related cognitions and behaviour perpetuate fatigue [34]. Patients learn to change these cognitions and behaviours.

Patients started with formulating their personal goals for therapy. Achievement of these goals should, when attained imply that the patient was recovered (i.e., no longer severely fatigued and no longer disabled by the fatigue). Next, the CBT model with precipitating and perpetuating factors was explained after which patients learned how to (re)set a fixed sleep wake cycle. Fatigue-related beliefs such a catastrophizing responses were challenged. In order to reduce the focus on fatigue patients learned to shift their attention away from the fatigue. Patients were instructed to no longer discuss their fatigue with others and learned to cope with negative or overprotective responses of significant others. Patients then started with gradually increasing their physical activity. Two different physical activity pattern can be discerned, a low active and relative active pattern [35]. The activity pattern is used to tailor treatment. The individuals' activity pattern was based on the 12 daily physical activity scores. Physical activity was assessed with an actometer, a motion-sensing device worn at the ankle for 14 days. The average daily physical activity scores of low active patients stay below the general mean physical activity of CFS/ME patients in at least 11 of 12 days. Relatively active patients score at least 2 of 12 days above the mean physical activity score of CFS/ME patients. Relatively active patients, characterized by an alternation of periods of (over)activity and periods of rest, first learned to divide their activities more evenly. After this, they gradually increased their level of physical activity by walking or cycling. Patients with a low-active activity pattern started immediately with gradually increasing their physical activity level.

If applicable, patients were invited to make a plan for returning to work and/ or study. After gradually increasing physical activity, patients gradually increased their mental and social activities. Patients then attained their goals as formulated at the start of the treatment, step by step, including returning to work. Finally, patients learned how to further improve self-control for retaining a healthy lifestyle while they no longer considered themselves to be a patient.

Primary outcome measures

Fatigue severity

Fatigue severity was assessed with the subscale "fatigue severity" of the Checklist Individual Strength (CIS) [28]. The CIS has a good internal consistency and is sensitive to change [19]. The subscale "fatigue severity" consists of eight items that have to be answered on a 7-point scale asking for a judgment about the last two weeks. Scores range from 8 to 56, with a higher score indicating more severe fatigue.

Overall impairment

Overall impairment was measured with the Sickness Impact Profile (SIP8) [29,30]. The SIP8 consists of eight subscales, which assess functional impairment on the following domains of daily life: home management, mobility, alertness behaviour, sleep/ rest, ambulation, social interactions, work, and recreation and pastimes. A weighed total score was computed from the scores on the eight subscales (range 0–5799). Higher scores are indicative of more severe overall impairment.

Secondary outcome measures

Physical and social functioning

Physical and social functioning was assessed with the subscales "physical functioning" and "social functioning" of the Medical Outcomes Survey Short Form-36 (SF-36) [36]. Scores on both scales range from 0 (maximum limitations) to 100 (no limitations). The SF-36 is a reliable and valid instrument to assess self-reported health status [36,37].

Psychological distress

Psychological distress was measured with the Symptom Checklist 90 (SCL-90) [38]. A total of 90 items are answered on a 5-point Likert scale. Total scores range from 90 to 450, with higher scores indicating more psychological distress.

Clinical significant improvement in fatigue

Clinical significant improvement in fatigue was defined as having a reliable change index of >1.96 and a score of less than 35 on CIS fatigue severity at second assessment [26,37].

Recovery

For fatigue severity, a healthy level of fatigue for ICF patients was defined as a CIS fatigue score of 27 or lower at second assessment. This score is the mean plus 1 SD of a norm group of healthy adults [28]. By choosing the mean plus the range of 1 SD of a healthy norm group, ICF patients who score within this range cannot be differentiated from healthy adults. Norm scores of healthy people

were also used to set a criterion for healthy functioning on the other outcome measures [see 35].

Full recovery Full recovery was defined as a combination of a CIS fatigue score of 27 or lower, a SIP8 score of 203 or lower, a SF-36 physical functioning score of 80 or higher and a SF-36 social functioning score of 75 or higher at second assessment [39].

Sample size calculation

Sample size calculations were performed for both primary outcome variables: CIS-fatigue and SIP8 total score. In order to detect a clinical significant difference on the CIS-fatigue of 6 points in the change scores of the treatment and control group, with an alpha of 0.025, a power of 0.80, a standard deviation of 9.1, and a dropout rate of 10%, 50 patients were needed in each condition. For a clinical relevant change [40] of 150 points [19] on the SIP8 total score, with an alpha of 0.025, a power of 0.80, a standard deviation of 225, and a dropout rate of 10%, a total of 50 patients per group sufficed as well. As there were two primary outcome measures a significance level of $p = 0.025$ was used ($p = 0.05$ divided by two).

Treatment integrity and treatment adherence

An integrity check was performed by analysing the content of 5% of all e-mails sent by therapists. Two authors (AJ, HK) coded the interventions of therapists. We discerned interventions according to protocol and interventions not described in the protocol. In case of disagreement, the item was discussed until consensus was reached. Treatment adherence was studied by counting the number of e-mails sent by the patient and the therapist. Patients were classified as adherent to the intervention when they at least had e-mailed every other week.

Statistical analysis

Treatment effects were analysed using analysis of covariance (ANCOVA) with the outcome measure at second assessment as dependent variable, baseline score of the outcome measure as covariate and condition as fixed factor [41]. Cohen's *d* effect sizes were computed for our primary outcome measures. Cohen's *d* outcomes were interpreted as small ≥0.20, medium ≥0.50 and large ≥0.80, following Cohen's guidelines [42]. All analyses were based on intention-to-treat for all randomized patients. Multiple imputation was used on the basis of the assumption that data were missing at random with full conditional specification and five imputations. The imputation method used was predictive mean matching for missing data in primary and secondary outcome measures. Aside from condition we used the following variables assessed at baseline to generate the imputations: duration of complaints, number of CDC symptoms, depression score measured with the Beck Depression Inventory (BDI), and baseline primary and secondary outcome measures and causal attribution of fatigue [27].

One sensitivity analysis was carried out. The last observation carried forward method was used for missing data in the guided self-instruction group and for the wait-list control group the

mean improvement of that group was imputed [43].

We analysed e-mail data to determine if treatment outcome was related to the communication between patient and therapist. Correlations coefficients were calculated between the number of e-mails sent by therapists or patients, the mean number of words per e-mail and the change score in fatigue severity and overall impairment. First, data of all patients allocated to the guided self-instruction with complete outcome measures were analysed. Second, the correlation analysis was repeated with the subset of patients who had started treatment, that is, had sent more than one e-mail to their therapist. Chi-square tests were used to test differences in the frequency of clinically significantly improved or recovered patients between the intervention and the control group.

We used multiple regression to determine if the number of symptoms or level of disability moderate treatment outcome. Two consecutive models were tested [44]. In the first model, we entered the number of additional symptoms or overall impairment and the baseline value of the outcome measure together with treatment. In the second model, the previous variables were entered and the proposed moderator by treatment condition interaction term was added. This regression analysis was done separately for fatigue severity and overall impairment as dependent variables. In the case of overall impairment as dependent variable, the baseline measure was also the proposed moderator. Analyses were carried out using IBM SPSS (Version 20). Significance level in the analyses of the effects of treatment on the primary outcome measures was $p < 0.025$; for all other analyses, $p < 0.05$.

RESULTS

During the inclusion period, 127 patients who met our inclusion criteria were referred to our treatment unit (see Figure 1). Twenty-seven patients (21%) did not participate in the trial. One patient declined treatment, seven patients already participated in other research and for 19 patients the reason for not participating in the trial was not recorded. Fifteen of these 19 patients were eligible on basis of the CDC additional symptom criteria. We compared this subgroup with the subgroup of patients included in the study who also had fewer than four additional symptoms. The 15 patients were significantly more fatigued but not more impaired (data not shown).

One hundred patients were randomly assigned to either guided self-instruction (n = 50) or the wait-list control group (n = 50). Based on verbal report of patients, none of them was involved in a legal procedure concerning disability benefits. Each patient was allocated a single therapist who also had conducted the initial assessment. Two patients were allocated to another therapist because the therapist who did the initial assessment went on maternity leave. In total, 95 patients completed the second assessment. Of the five patients who did not complete the second assessment, three were in the treatment group and two were from the wait-list control group. The three patients from the treatment group did not e-mail with their therapist. One patient found the information in the treatment booklet not applicable to his situation and one patient did not start treatment because he was diagnosed with colon cancer (shortly after randomization) and refused to fill in the questionnaires because it would reflect the consequences of the illness. Of the third patient, the reasons for not starting treatment were unknown. The two patients from the wait list with missing data started with another treatment for fatigue and refused to fill in the questionnaires.

In the wait-list control group, one patient decided to follow CBT for fatigue at another centre (and was recovered at second assessment). Two included patients were mistakenly included with a SIP score that was lower than the cut-off of 450 (one in the treatment condition with a score of 426 and one in the wait-list control group with a score of 371). Based on the intention-to-treat principle, we included the three aforementioned patients in our main analysis.

Characteristic	Guided self-instructions (n = 50)		Wait list control group (n = 50)		t	p
Median age in years	37	(18-63)	31	(18-62)	-1·47	0·15
Median duration of complaints in years	6·0	(1-61)	4	(0·5-26)	-1·88	0·06
Male/ Female	18/ 32		14/ 36		$\chi^2 = 0{\cdot}74$	0·39
Fatigue severity[A]	46·82	(5·58)	46·58	(4·89)	-0·23	0·82
Overall impairment[B]	854·46	(477·99)	769·90	(410·93)	-0·95	0·35
Physical functioning[C]	69	(20·45)	74·6	(15·81)	1·53	0·13
Social functioning[C]	56·25	(24·26)	54·71	(20·44)	-0·34	0·73
Psychological distress[D]	134·88	(29·14)	133·06	(19·42)	-0·37	0·71
Median number of additional CDC symptoms	4	(0-9)	5	(0-9)	0·62	0·53
Number of eligible patients						
<4 add. symptoms and SIP score <700	5			5		
<4 add. Symptoms and SIP score >700	18			14		
≥4 add. Symptoms and SIP score <700	27			31		

Notes. Numbers in parentheses are standard deviations/ range. CDC = Centers for Disease Control and Prevention A) CIS Checklist Individual Strength; B) SIP8 Sickness Impact Profile; C) SF-36 Medical Outcomes Survey Short Form–36; D) SCL-90 Symptom Checklist-90

Table 1 - Baseline characteristics of guided self-instruction versus wait list control group (n = 100).

Baseline characteristics

Baseline characteristics for the randomized sample are shown in Table 1.

Treatment integrity and adherence

For the integrity check, 35 e-mails were evaluated (5%). The e-mails contained a mean of 8.5 interventions. Of all interventions, 93% were according to protocol. Seven percent of interventions were not described in the protocol. Eighteen patients (36%) had e-mailed at least fortnightly with their therapist and adhered to the prescribed e-mail regime. Patients who adhered did not

significantly differ in change scores in fatigue severity and disability from the patients who did not adhere to the prescribed e-mail regime (data not shown).

Analysis of treatment effects

In Table 2, the results of the analysis of the change in the outcome measures are presented. Patients who received the guided self-instruction were significantly less fatigued—$F(1,97) = 12.39$, $p < 0.001$; CIS fatigue $M = 32.77$, SD = 14.82 vs. $M = 41.60$, SD = 11.09 —and disabled—$F(1,97) = 11.40$, $p = 0.001$; SIP $M = 458$, SD = 577 vs. $M = 732$, SD = 455—at second assessment compared to patients in the wait list control group. Patients who received the guided self-instruction had significantly higher scores— $F(1,97) = 6.28$, $p = 0.012$; SF-36 social functioning— on social functioning ($M = 71.70$, SD = 26.83 vs. $M = 59.19$, SD = 22.22) and less psychological distress at second assessment —$F(1.97) = 11.73$, $p = 0.001$; SCL-90 —than patients in the wait list control group ($M = 116.44$, SD = 26.17 vs. $M = 131.86$, SD = 27.36). No significant difference —$F(1,97) = 2.57$ $p = 0.110$; SF-36 physical functioning— was found on physical functioning between the guided self-instruction group ($M = 81.86$, SD = 18.00) and the wait list participants ($M = 79.76$, SD = 14.23). Second, we did a "modified intention-to-treat analysis" [45]. We repeated the analysis after removing the two patients with SIP scores lower than 450 who did not meet all eligibility criteria [46]. It did not result in meaningful changes in the treatment effects (data not shown).

Moderate controlled effect sizes were found for the primary outcome measures fatigue severity (Cohen's $d = 0.68$) and for overall impairment (Cohen's $d = 0.53$). The sensitivity analysis confirmed results from our main analysis. We imputed the missing values with the last observation being carried forward in case of missing values in treatment group and the mean improvement of the wait list for missing values in the wait list. Patients in guided self-instruction were still significantly less fatigued—$F(1,97) = 11.12$, $p = 0.001$, Cohen's $d = 0.64$; CIS fatigue—and disabled—$F(1.97) = 10.93$, $p = 0.001$, Cohen's $d = 0.52$; SIP—at second assessment compared to patients in the wait list control group.

To determine if differences between patients in time to second assessment introduced a bias in the results we analysed the relationship between time to second assessment and outcome in an additional post hoc analysis.

First, we tested if there was a significant difference between the guided self-instruction group and the wait list with respect to time to second assessment from baseline ($t = -1.579$, $df = 93$, $p = 0.12$). Second, we calculated Pearson correlations between the change in primary outcomes and time to second assessment (CIS fatigue: $r = 0.101$, $p = 0.331$; SIP: $r = 0.088$, $p = 0.394$). Lastly, we repeated the ANCOVA analysis with the completers ($n = 95$) and added time to second assessment as a covariate in the model. The covariate time to second assessment did not yield significance. We still found significant treatment effects for fatigue severity (-9.2; -14.6 to -3.8; $p = 0.001$), level of disability (-324; -524 to -125; $p = 0.002$), social functioning (11.0; .8 to 21.3; $p = 0.035$) and psychological distress (-16.8; -27.2 to 6.3; $p = 0.002$). The treatment effect on physical functioning (4.6; -1.4 to 10.5; $p = 0.130$) remained non-significant.

E-mail contact

Forty-seven patients in the treatment group had complete outcome data. The mean number of e-mails sent by the patients was 11 (SD = 7) with a mean number of 360 words (SD = 316). The mean number of e-mails sent by the therapist was 13 (SD = 7) with a mean number of 184 words per e-mail (SD = 81). There was a positive and significant correlation between the mean number of words written by the patient (Spearman's *rho* = 0.288, $p = 0.049$) and the change in fatigue severity but not with change in impairment. The number of e-mails sent by therapist of patient, and the number of words used by the therapist did not correlate with change in fatigue or impairment at second assessment. We repeated the correlation analysis with those patients who did start treatment ($n = 44$), and the change in fatigue severity correlated positively with the mean number of words used by the therapist (Spearman's *rho* = 0.414, $p = 0.005$) but not with the number of words used by the patient. The change in impairment did not correlate with any of the e-mail variables.

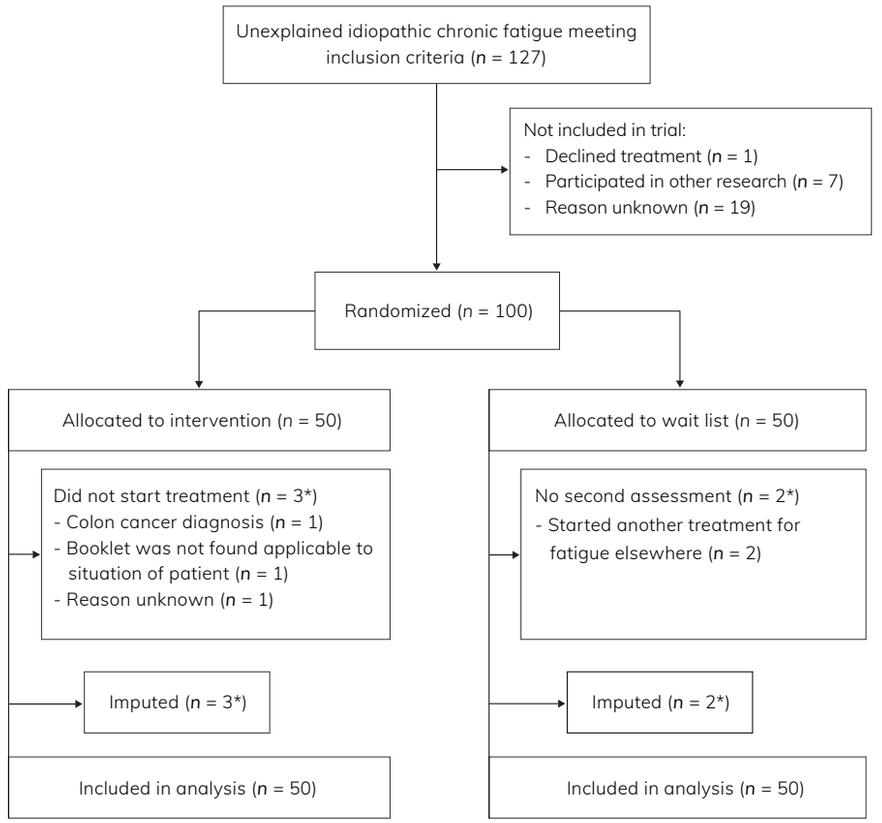

Figure 1 – Participant flow.

Outcome measure	Guided self- instruction (*n* = 50) Baseline *M* (SD)	Guided self- instruction (*n* = 50) Second assessment *M* (SD)	Wait list control group (*n* = 50) Baseline *M* (SD)	Wait list control group (*n* = 50) Second assessment *M* (SD)	Difference *M*	95% CI	*p*	Cohen's *d*
Fatigue severity[A]	46·82 (5·58)	32·77 (14·82)	46·58 (4·89)	41·60 (11·09)	-8·98	[-13·99, -3·97]	0·000	0·68
Overall impairment[B]	854·46 (477·99)	458·36 (576·88)	769·90 (410·93)	731·58 (455·34)	-317·19	[-481·70, 152·68]	0·001	0·53
Physical functioning[C]	69·00 (20·45)	81·86 (18·00)	74·60 (15·81)	79·76 (14·23)	4·58	[-1·04, 10·20]	0·110	0·13
Social functioning[C]	56·25 (24·26)	71·7 (26·83)	54·71 (20·44)	59·19 (22·22)	12·20	[2·63, 21·77]	0·012	0·51
Psychological distress[D]	134·88 (29·14)	116·44 (26·17)	133·06 (19·42)	131·86 (27·36)	-16·33	[-25·71, -6·96]	0·001	0·58

Notes: SD = standard deviation; 95% CI = 95% confidence interval; A) CIS Checklist Individual Strength; B) SIP8 Sickness Impact Profile; C) SF-36 Medical Outcomes Survey Short Form–36; D) SCL-90 Symptom Checklist-90

Table 2 - Effects of guided self-instruction on primary and secondary outcome measures based on intention-to-treat (n = 100).

Clinical significant improvement in fatigue and recovery of ICF

Clinical significant improvement in fatigue and recovery rates per condition is presented in Table 3. Rates were based on the original dataset with missing data being filled in with a 0 on the dependents (*n* = 100). Significantly more patients in the treatment condition were improved at second assessment compared with patients in the wait list, 48% vs. 20%; $\chi^2(1, n = 100) = 8.73$, $p = 0.003$, odds ratio (OR) = 3.69. More patients were fully recovered after guided self-instruction than after the waiting period; 28% versus 4%; $\chi^2(1, n = 100) = 9.78$, $p = 0.009$, OR = 4.47.

Outcome measures	Guided self-instruction (*n* = 50)	Wait list control group (*n* = 50)	Odds ratio	95% CI	χ^2	*p*
Clinical significant improvement[A]	24 (48%)	10 (20%)	3·69	[1·52 to 8·97]	8·73	0·003
Recovery[B]	14 (28%)	4 (8%)	4·47	[1·36 to 14·76]	9·78	0·009

Notes: A) Reliable change >1.96 on the Checklist Individual Strength (CIS) fatigue combined with a score of <35; B) CIS fatigue ≤27, Medical Outcomes Survey Short Form (SF-36) physical functioning ≥80, SF-36 social functioning ≥75, Sickness Impact Profile version 8 ≤203

Table 3 - Comparing proportions of patients with clinical significant improvement in fatigue and who were recovered at second assessment.

Moderation Analysis of Number of Additional Symptoms and Overall Impairment

There were no significant interaction effects with treatment condition for number of additional symptom and overall impairment in the analysis with fatigue severity at second assessment as dependent variable (symptoms: *B* = -1.50, *t* = -1.39, *p* = 0.16, 95% confidence interval [CI] [-3.61 to 0.61]; impairment: *B* = 0.006, *t* = 1.10, *p* = 0.27, 95% CI [-0.005 to 0.018]. The interaction terms in the analysis with overall impairment at second assessment as dependent variable resulted in non-significant effect for CDC symptoms (*B* = -26.33, *t* = -0.67, *p* = 0.51, 95% CI [-103.79 to 51.14]) and a significant interaction for overall impairment (*B* = 0.62, *t* = 3.00 *p* = 0.003, 95% CI [0.27 to 0.97]. Patients with a higher level of overall impairment profited less from the intervention.

DISCUSSION

The purpose of this study was to test the efficacy of guided self-instruction for patients with ICF. As far as we know this was the first time that the efficacy of a cognitive–behavioural intervention was determined for this substantial group of patients with severe, chronic and debilitating fatigue who do not meet all CDC criteria for CFS/ME. Our study showed that following guided self-instruction patients were significantly less fatigued and impaired compared with the wait-list control group. Their social functioning improved significantly more and they reported significantly less psychological distress. We found the same significant treatment effects with a modified intention-to-treat analysis and in our sensitivity analysis. We conclude that including patients who did not meet the inclusion criterion with respect to level of disability did not result in meaningful changes in the effect of treatment. Removing these did not make our study underpowered, as the dropout rate remained lower than the assumed 10%.

Effect sizes for the treatment effects were moderate. In previous studies testing the efficacy of guided self-instruction for CFS/ME moderate effect sizes were also found for the reduction in fatigue [19,20]. The effect size for fatigue severity in the present study was within the 95% CI interval of the effect sizes of previously conducted trials with CFS/ME patients. This indicates that despite differences in the number of symptoms and level of disability, patients with ICF can profit as much from this treatment as CFS/ME patients can.

Patients with ICF do not only show a significant reduction of fatigue and overall impairment, a substantial subgroup recovers following the intervention. This means that guided self-instruction is sufficient for a substantial number of ICF patients. The fact that about half of the patients show a clinically significant improvement in fatigue following a minimal intervention is promising. The fact that 28% of patients had scores that could not be distinguished from general population scores underscores the effectiveness of this treatment option for patients with ICF. Given frequent reports about the substantial costs that are associated with medically unexplained symptoms [10,11,47], this finding is also promising from a societal point of view.

A recent implementation study showed the practical value of this intervention. Tummers et

al. [20] found that guided self-instruction can also be delivered by trained psychiatric nurses in a community-based mental health care centre instead of cognitive–behavioural psychologists in a tertiary treatment centre. This study also showed that instead of actigraphy, a questionnaire can be used for determining the activity pattern of patients [20]. Furthermore, we showed in another study that the minimal intervention requires less therapist time than regular face-to-face CBT [26]. For us, the aforementioned shows that guided self-instruction is an intervention that can be of practical value for the management of fatigue in patients with ICF.

There was no positive effect of the intervention on physical functioning. We think that this can be explained by the fact that the ICF patient already scored high (*M* = 71.8, SD = 18.4) on this scale at baseline, compared with the norm score for healthy adults without a chronic condition (*M* = 93.1, SD = 11.7; [48]. This indicates that a substantial number of patients do not experience many problems in their physical functioning and room for improvement is limited. In previous studies testing the effect of guided self-instruction in CFS/ME patients, a significant increase in physical functioning was found [19,20]. In the latter study, a significant increase in physical functioning was only found in a subgroup, with lower scores on the physical functioning subscale at baseline. Our findings are in line with those of an RCT testing the efficacy of a self-management program in primary care for medically unexplained fatigue in patients who had relatively good baseline physical functioning scores and did also not significantly improve on physical functioning following the intervention [23]. The inclusion criteria of our study most resembled the latter study, although Friedberg and colleagues also included CFS/ME patients. In the study of Friedberg, the effects of the intervention in CFS/ME patients were compared with those in ICF patients, and they did not find a difference between both subgroups. However, most likely this study was underpowered to detect differences between treatment effects in both groups.

The number of additional symptoms did not moderate our treatment effect on fatigue severity and overall impairment. We conclude from this that for ICF patients the number of additional symptoms does not seem to be relevant for the effect of a cognitive–behavioural intervention. Functional impairment at baseline was a moderator for the effect of the intervention on the level of impairment after the intervention. This indicates that baseline overall impairment predicts whether patients profit from the minimal intervention, which is a replication of previous findings [19] in CFS/ME patients. Knoop et al. also found that patients with high overall impairment profited less from guided self-instructions. Patients with higher levels of impairments may benefit more from starting with face-to-face therapy, although it is difficult to determine a proper cut-off score. In the light of possible diminished motivation in a face-to-face therapy or lower self-efficacy after an unsuccessful first step for patients, it seems relevant to determine a proper cut-off score to be allocated to the intervention from which the patient is most likely to profit [49].

It has been suggested that on the continuum of clinically relevant fatigue patients with ICF can be conceptualized as less severely fatigued than patients with CFS/ME [50]. Fewer than four additional symptoms and/ or moderate levels of functional impairment differentiate the ICF

patients of the present study from the CFS/ME patients in the previous studies. Classifying cases into different categories of severity—as is common in the classification and management of other psychological disorders such as depression—could help to guide clinical decision-making [51]. It is likely that within the group of patients meeting criteria of ICF subgroups can be identified (e.g., on the basis of symptoms). However, despite the heterogeneous character of ICF our study shows that a cognitive–behavioural intervention aimed at fatigue is effective.

We suggest that the definition of ICF as described by the CDC could be used as clinical rule of thumb to select patients with clinically relevant fatigue for guided self-instruction (or another minimal intervention) as first intervention. There are indications that problems with fatigue are underestimated and GP's are more likely to attribute medically unexplained fatigue to psychosocial problems [52]. Implementing this program for ICF patients in primary care delivered by mental health care nurses could form a next step in the development of the intervention and could enhance care for ICF in primary care. A previous study showed that nurses in a community mental health care centre were able to effectively deliver guided self-instruction for CFS/ME patients [20]. Some CFS/ME patients seem to profit from face-to-face therapy as a second step after they have followed guided self-instruction [26]. Face-to-face therapy could be considered as a second step of care for patients with ICF who do not profit from guided self-instructions.

Limitations

Our study has several limitations. Some eligible patients were not included in our trial. No reliable data were collected as to why these patients were not included. Because this subgroup was significantly more fatigued than the included patients, we could have introduced a potential bias that may limit the generalizability of our findings. In addition, second assessments were not always as planned done at a standard time point from baseline assessment. However, we consistently did not find a relationship between variations in time to second assessment and effects of the intervention.

We used two primary outcome measures. At the time the research proposal was formulated CONSORT statements were used to aid the designing of the study and did not state that only one primary outcome measure should be used [53,54]. In later statements, it was recommended to use only one primary outcome measure because multiple testing makes the interpretation of results more difficult [55]. We used an adjusted *p* value to correct for multiple testing.

A further limitation of our study was that patients were asked to report on their progress with the self-instructions, and most did, but six patients did not communicate their progress by e-mail. These six patients did not adhere to the treatment protocol, as they did not send e-mails to the therapist. We did not evaluate the effects of the intervention without these patients as is done in a per-protocol analysis because it would inflate treatment outcomes and will most likely not correspond with clinical practice.

Treatment adherence was studied by counting e-mails sent by the patient and therapist.

Patients who e-mailed at least fortnightly did not achieve better treatment result than patients who did not. The number of e-mails may not be a valid reflection of assessing adherence to the treatment protocol.

Patients with better outcomes regarding fatigue had received longer e-mails of their therapists. This finding is not in accordance with previous research were no significant correlation was found with treatment outcome [20]. Our finding is not easy to interpret, but could suggest that giving elaborate feedback on the progress of the patient helps them benefit from the intervention. It would be interesting to determine the added value of coaching by a therapist. This question could be answered in a study where guided self-instruction is compared with self-instruction—that is, the booklet without e-mail contact with a therapist. A meta-analysis in depression showed that guided self-help was more effective than self-help without support [56]. However, the main aim of our study was to determine the efficacy of the treatment for ICF patients—not the role of the therapist. In a study we are currently conducting, we investigate the role of the therapist in a CBT Internet intervention for CFS/ME patients based on the guided self-instruction booklet [57]. Working in a highly specialized treatment facility with weekly supervision makes it unlikely that there is treatment outcome variation between therapists. This presumption is also based on previous research that found no meaningful variation in treatment outcome between therapists within a CFS/ME treatment centre [58]. We did not assess the therapist's time needed to deliver the intervention. However, prior research showed that therapist spent less time on patients following guided self-instruction surplus face-to-face when needed, than on patients following face-to-face CBT only [26]. Nonspecific factors or placebo effects such as the bond between the therapist and the patient of the intervention could have influenced the outcome of this intervention. However, prior research suggested that factors such as the perceived bond between therapist and patient do not seem to predict treatment outcome in patients with CFS/ME [58]. Later study found that outcome expectations of the patient were related to outcome, but mainly because they facilitated the change in fatigue perpetuating beliefs and behaviours. In a meta-analysis of the treatment effects for CFS/ME, better controlled treatment effects were reported for trials with care as usual as an active control condition than studies with a wait-list control condition [7]. This finding might suggest that it is unlikely that factors such as "disappointment" for allocation to the wait list are responsible for the observed outcomes. Another possible limitation is the fact that we did not measure any safety outcomes. However, several studies found that CBT for CFS/ME is a safe intervention that does not produce more harm than any of the control conditions included in trials [59,60]. Our intervention was based on the same principles.

A further limitation is the lack of follow-up data. A follow-up assessment could have provided insight into the sustainability of the effects of the intervention. Unfortunately, controlled follow-up data were not available as patients from the wait-list control group were treated following the waiting period as it was considered unethical to have those patients wait longer for treatment. By using a structured diagnostic interview for assessing comorbidity such as the Mini International Neuropsychiatric Interview (MINI) [61] further uniformity in the exclusion of psychiatric disorder can be attained. The assessments could have more precisely been fixed on 6 months as was originally planned and communicated with the patient. In future research additional treatment seeking should be systematically assessed. Finally, data of cost-effectiveness should be gathered.

In conclusion, our findings suggest that guided self-instruction, based on the principles of CBT for CFS/ME, is an evidence-based treatment option for the large group of patients with ICF. In the context of constant health care budged cuts and limited treatment capacity, being able to offer an effective, low intensive treatment for impaired chronic fatigued patients is highly relevant.

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Chapter 6

Testing the Efficacy of Web-based Cognitive Behavioural Therapy for Adult Patients with Chronic Fatigue Syndrome (CBIT): Study Protocol for a Randomized Controlled Trial

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ABSTRACT

Background: Cognitive behavioural therapy (CBT) is an effective treatment for fatigue and disabilities in patients with chronic fatigue syndrome (CFS/ME). However, treatment capacity is limited. Providing web-based CBT and tailoring the amount of contact with the therapist to the individual needs of the patient may increase the efficiency of the intervention. Web-based CBT for adolescents with CFS/ME has proven to be effective in reducing fatigue and increasing school attendance. In the proposed study, the efficacy of a web-based CBT intervention for adult patients with CFS/ME will be explored. Two different formats of web-based CBT will be tested. In the first format named *protocol-driven feedback*, patients report on their progress and receive feedback from a therapist according to a pre-set schedule. In the second format named *support on demand*, feedback and support of the therapist is only given when patients ask for it. The primary objective of the study is to determine the efficacy of a web-based CBT intervention on fatigue severity.

Method/ Design: A randomized clinical trial will be conducted. Two-hundred-forty adults who have been diagnosed with CFS/ME according to the US Centers for Disease Control and Prevention (CDC) consensus criteria will be recruited and randomized to one of three conditions: web-based CBT with *protocol-driven feedback*, web-based CBT with *support on demand*, or wait list. Feedback will be delivered by therapists specialized in CBT for CFS/ME. Each of the web-based CBT interventions will be compared to a wait list condition with respect to its effect on the primary outcome measure; fatigue severity. Secondary outcome measures are level of disability, physical functioning, psychological distress, and the proportion of patients with clinical significant improvement in fatigue severity. Outcomes will be assessed at baseline and six months post randomization. The web-based CBT formats will be compared with respect to the time therapists need to deliver the intervention.

Discussion: As far as we know this is the first randomized controlled trial (RCT) that evaluates the efficacy of a web-based CBT intervention for adult patients with CFS/ME.

Trial registration: NTR4013

BACKGROUND

Chronic fatigue syndrome (CFS) i.e. often also named ME (myalgic encephalomyelitis/ encephalopathy) by patient groups is characterised by medically unexplained, severe, and persisting fatigue that leads to substantial disability. Following the widely used US Centers for Disease Control and Prevention (CDC) consensus criteria for CFS/ME, patients not only suffer from fatigue for six months or longer but also report four or more of eight additional symptoms: unrefreshing sleep, post-exertional malaise, headaches, muscle pain, sore throat, multi-joint pain, tender cervical or axillary lymph nodes, impaired short-term memory, and/ or concentration problems [1,2]. A recent meta-analysis comparing the prevalence rates of CFS/ME from studies conducted in different countries found a mean prevalence rate of about 1% [3]. Cognitive behavioural therapy (CBT) for CFS/ME is an effective treatment [4], leading to a significant reduction of fatigue and disabilities. A subgroup of patients fully recovers following treatment [5,6].

The cognitive behavioural model for CFS/ME is based on the assumption that fatigue and disability are perpetuated by fatigue related beliefs and behaviours. CBT is aimed at changing these beliefs and behaviours. Individual CBT for CFS/ME is an intensive treatment, requiring between 13 to 16 sessions over a period of six to eight months depending on the protocol used [7–10]. Treatment capacity and budgets for delivering treatment are limited. More *efficient* interventions are needed to both increase treatment capacity and reduce the costs of treatment. One way of achieving this is to develop a minimal intervention for the subgroup of CFS/ME patients who do not need intensive CBT. Our research group developed one such a minimal intervention—guided self-instruction [11]. Guided self-instruction consists of a booklet with instructions combined with fortnightly email contact with a therapist. The information and instructions in the booklet are based on the protocol for individual CBT for CFS/ME [8]. It has been repeatedly shown that guided self-instruction leads to a significant reduction of fatigue and disabilities [11–12]. For a subgroup of about 25 to 30% of CFS/ME patients, the level of fatigue was within normal limits following the intervention. This is less than in face-to-face CBT. Guided self-instruction was also applied in a stepped care model for CFS/ME. Stepped care started with guided self-instruction and, if insufficient, was followed by regular face-to-face CBT. Stepped care was as effective as face-to-face CBT but more time efficient as therapists had to invest less time per patient [13].

Although guided self-instruction is effective, fewer patients benefit from this intervention than from face-to-face therapy. Further development of guided self-instruction should be aimed at improving the efficacy of the intervention without substantially increasing the time therapists need to treat a patient. A possible way of achieving this is to design a web-based version of this intervention; CBIT (cognitive behavioural Internet therapy). The Internet has proved to be an effective medium for delivering CBT in a range of disorders [14]. Online therapy for CFS/ME in adolescents—FITNET (Fatigue In Teenagers on the InterNET)—has proved to be as effective as face-to-face CBT in adolescent CFS/ME patients [15].

Using online platforms for therapy offers new opportunities for interaction. Compared to the booklet used in guided self-instruction, online platforms provide more ways of communication, for example chat sessions or text-alerts via sms. Assignments can be interactive and patients can be given access to interview excerpts with patients that illustrate essential elements of the therapy. Therapists can get access to and offer feedback on the completed homework of patients so that they are able to follow the progress of the patient.

Although online CBT has shown to be effective in several disorders and also in adolescents with CFS/ME, its efficacy in adult CFS/ME patients has not yet been shown. We developed a web-based CBT for CFS/ME based on the guided self-instruction and will test its efficacy in the proposed study. As little is known about the optimal form and amount of feedback delivered by the therapist [16], we developed two formats of the intervention.

In the first format, patients are asked by their therapist to report on their progress by email according to a schedule. In response, the therapist offers feedback. This format is named ***protocol-driven feedback***. Asking patients to email regularly and providing regular feedback according to a fixed schedule makes online CBT time consuming for therapists, possibly without increasing its efficacy. Patients may also report on their progress with respect to parts of the web-based CBT they do not need therapist input for. An alternative way of providing sup-port is to tailor it to the needs of the patient and only give feedback when the patient asks for it. We assume that this will be more time efficient—i.e., requiring less therapist time to deliver, —than giving support according to the pre-set schedule. We named this second for-mat of the web-based CBT ***support on demand***. The efficacy of both web-based CBT interventions will be determined by comparing each web-based CBT format to a wait list control group with respect to its effect on the primary outcome measure: fatigue severity. Subsequently, we will determine if both forms of web-based therapy lead to a reduction of disability, improved physical functioning, less psychological distress and/ or a higher proportion of patients with a clinically significant improvement in fatigue compared to a wait list condition. Furthermore, the effect on treatment outcome of how and when feedback is delivered to patients will be determined in an exploratory analysis by comparing the efficacy of the two web-based CBT formats with each other with respects to its effect on primary and secondary outcome measures. We will also compare therapists' time needed to deliver the intervention. We hypothesize that:

1) Fatigue severity will be significantly lower at second assessment following web-based CBT compared to the wait list control group.

2) Patients who receive web-based CBT will report significantly less disabilities and psychological distress and significantly more often show clinical significant improvement in fatigue compared to the wait list control group.

3) Patients who received ***protocol-driven feedback*** web-based CBT will report a significantly larger decrease in fatigue severity, level of disability, psychological distress and report more often a clinical significant improvement than patients who received web-based CBT with ***support on demand***.

METHODS

Study design

The efficacy of the web-based CBT will be determined in a randomized controlled trial (RCT) with a follow-up six months after randomization (T_1). All patients will start with two intake sessions with a therapist and a baseline assessment (T_0), which is part of clinical routine for CFS/ME patients referred to our CFS/ME treatment centre. At the second intake session, eligible patients will receive written information about the study from their therapist and will be asked to participate. Eligible patients who give written informed consent will be randomized into one of three conditions (see Figure 1):

1) Web-based CBT with ***protocol-driven feedback***,

2) Web-based CBT with ***support on demand*** or

3) A wait list condition.

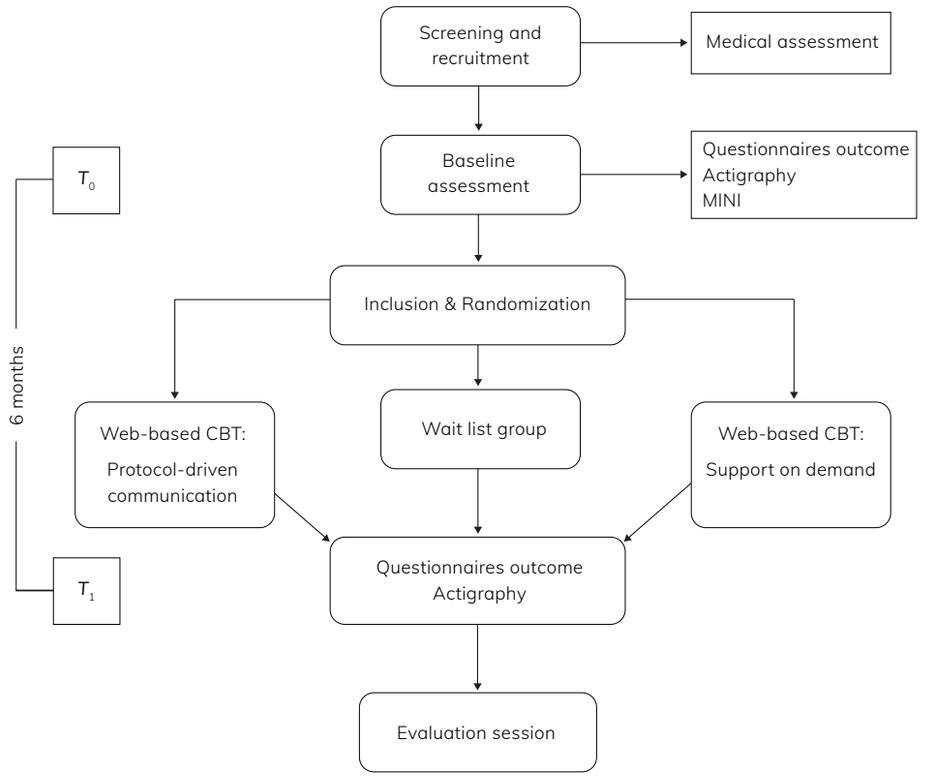

Figure 1 - Flowchart of study.

Patients in the wait list condition will wait for six months. After the evaluation session at T_1, all patients from the wait list condition directly start with face-to-face CBT. They will not receive web-based CBT.

The primary endpoint of the study is fatigue severity at six months post-randomization (T_1). Secondary outcome measures are level of disabilities, physical functioning, psychological distress, and proportion of patients with clinically significant improvement in fatigue. In the main analysis, both conditions of the web-based CBT will be compared with a wait list condition with respect to the effect on fatigue severity. Subsequently, the effects of each of the treatment conditions on the secondary outcomes will be compared with the wait list control group.

Study population

In total 240 patients will participate in the study. All patients are referred to the Expert Centre for chronic Fatigue (ECCF), a tertiary treatment centre for chronic fatigue of the Radboud university medical center in the Netherlands. All patients will meet CDC consensus criteria for CFS/ME [1,2]. They will all be severely fatigued with a score 35 or higher on the subscale fatigue of the Checklist Individual Strength (CIS). According to the consensus criteria, the fatigue must be associated with significant disabilities. The latter is operationalized as scoring 700 or higher on the Sickness Impact Profile 8 (SIP8 total score). The other inclusion criteria are described in Table 1. Patients will be (temporarily) excluded when engaged in a legal procedure concerning disability-related financial benefits or when participating in other research [17]. We will assess the presence of psychiatric disorders using the MINI and clinical assessment and exclude patients who do not meet the inclusion criteria of the CDC with respect to current psychiatric disorders and/ or having a medical history with psychiatric disorders.

Ethical approval

This study will be carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments that involve humans. This study has been reviewed and approved by the Medical Ethical Committee of the Radboud university medical center (reference NL42543.091.12) and has been registered in the Dutch Trial Register (trial number: NTR4013). Patients will receive verbal and written information about the study and will be asked to sign a written informed consent form before randomization. They were requested not to follow other treatments for fatigue during participation in the study. Patients will receive written information about the study results when the paper reporting on the study has been published.

	Inclusion criteria	References
1)	≥18 years.	
2)	Able to speak, read, and write Dutch.	
3)	Able to use a computer and have access to Internet.	
4)	CFS/ME diagnosis according to the CDC consensus criteria:	[1,2]
5)	Severe fatigue is assessed with the subscale fatigue severity of the Checklist Individual Strength (CIS). Severe fatigue is operationalized as scoring ≥35.	[24]
6)	Disabilities; Disability is assessed with the total score of the Sickness Impact Profile (SIP8). Severe disability is operationalized as a total score ≥700 on the SIP8.	[28,42]
7)	Given written informed consent.	
	Exclusion criteria	
1)	Engaged in a legal procedure concerning disability-related financial benefits.	
2)	Participating in other CFS/ME research.	

Table 1 - Inclusion and exclusion criteria.

Randomization and blinding

Patients will be randomly allocated to one of the three conditions. This web-based randomization was computer-generated by creating blocks of 12 patients. Patients are contacted one week later to ask them if they want to participate in the study. An administrative assistant will call the patient and will perform randomization during this phone call. If patients do not need time to think about their decision and decide to participate, randomization will take place immediately at the second intake session. This will be performed by an administrative assistant in the presence of the therapist and patient. After randomization, therapists and patients will be able to read the randomization result on the screen i.e. ‘1) Internet therapy’ or ‘2) Internet therapy’ or ‘wait list’. Patients will not be informed that there are two web-based CBT treatment conditions. Knowledge of the two different treatment arms could affect the behaviour of the patient while following the web-based CBT. During the second intake session, the therapist will explain that the therapist will be available to support them during the web-based CBT without specifying the frequency of support. In an instruction on the first page of the web-based application, only available after randomization, participants can read how to contact their therapist and when their therapist will contact them. The cognitive behavioural therapist who performs the intake will also deliver the web-based CBT. Test assistants will do all assessments. Therapists and test assistants are not blinded with respect to condition. This will most probably not introduce a bias, as there is no contact between test assistants and patients following randomization. The test assistant sends a link via email to the patient, patients will fill in the questionnaires at home.

Assessments

All patients have been medically examined prior to referral and somatic explanations for the fatigue will be ruled out either at the outpatient clinic of the department of internal medicine of the Radboud university medical center or by the referring general practitioner. The baseline assessment consists of two intake sessions and two test sessions at our treatment centre. Questionnaires are completed during both test sessions. Between test sessions, patients will wear an actometer and register their activities and symptoms in a diary. The actometer is a motion-sensing device worn at the ankle for 12 consecutive days and nights [18]. Trained cognitive behavioural therapists will perform the intake. They are all psychologists specialized in treating patients with CBT for CFS/ME. During the first intake session with a therapist, the Mini International Neuropsychiatric Interview (MINI) will be completed to assess the presence of psychiatric disorders [19]. At the half-year post randomization assessment, patients fill in the same questionnaires as at T_0. Patients will also wear the actometer again and complete the diary. After randomization, patients will receive a letter with the second assessment date and the face-to-face session with their therapist for evaluation of the web-based intervention or start of treatment for the wait list controls. Patients will receive reminders when questionnaires are not completed within one week. When patients do not want an evaluation session, the researcher will contact the patient with the request to complete the assessment as previously agreed. When a patient does not want to complete the full assessment, he or she will be requested to only fill in the questionnaire that assess the primary outcome measure.

We did not use a data monitoring committee for this study. All data will be monitored by a data-manager of the department who is not part of the research team. All participants have a study number in the data file. The file connecting study numbers with identifying personal data is separately stored and protected with a password that is only known to the principal investigator. All authors will have access to the final dataset.

Intervention

Both web-based CBT interventions have a maximum duration of six months. All patients will receive a private user-name and password, ensuring private communication with their therapist. After patients accept the general terms of the web-based treatment, patients will get their unique username and password (by email) necessary for logging in on the portal.

The web-based CBT is based on the protocol for face-to-face CBT for CFS/ME [8]. The protocol consists of several modules or subparts (see Table 2).

After completion of the first Getting started and goal setting-module, the following modules—from ‘Regulate sleep-wake cycle’ to ‘Reaching my goals step by step’—will be available to the patient. After completion of the sixth module, the last module ‘Evaluation and the future’ will be available. Patients can send emails and have chat sessions with their therapists.

Module title	Content of module
Getting started and goal setting	Psycho education about the cognitive-behavioural model of CFS/ME and CBT, signing treatment contract and establish goals that if attained implies that a patient no longer has CFS/ME.
Regulate sleep-wake cycle	Regulating sleep-wake cycle i.e., fixed bedtimes, no sleeping or lying down during the day
Helpful beliefs about fatigue	Formulate helpful beliefs
	Divert attention away from fatigue towards other activities and the environment
How to communicate with others about CFS/ME	Change the communication about CFS/ME with significant others
Gradually increasing my activities	Determine activity pattern
	Graded activity program for relative active patients (first divide activities evenly, followed by graded activity)
	Graded activity program for low active patient
	Pain: helpful beliefs for dealing with pain during graded activity
	Solve problems with the graded activity program
Reaching my goals step by step	Work resumption
	Increase mental activities
	Increase social activities
	Achieve my goals step by step
Evaluation and the future	Letting go of the rules of therapy (e.g., sleep in late, do a lot of activities from time to time)
	No longer being a CFS/ME patient
	Having healthy levels of fatigue and learn how to stay healthy

Table 2 - Module titles and specific subparts of the web-based CBT for patients with CFS/ME.

Patients can also view inter-view excerpts with recovered CFS/ME patients who share their experiences with web-based CBT. In these excerpts, patients explain the different elements of the treatment and talk about their experience with the intervention. Patients can print all texts and assignments.

During development of the intervention, before the start of the study, seven patients were asked to evaluate the usability of the intervention. The think aloud method was used in this pilot and improvements have been made to the Internet program. Three out of these seven patients were interviewed. Excerpts of these interviews were reported in this trial paper. After the pilot study, the intervention will only be available to patients participating in the study and allocated to one of the treatment arms. Therapists have access to the assignments and registration forms that are filled in by patients. In a box at the bottom of each completed assignment, therapists can give feedback. In both conditions, the therapist will respond within five working days after the patient sent an email. When practical problems with the program occur or when communication between therapist and patient is not sufficient to resolve a specific problem via email or by chatting, telephone contact will be offered to the patient. All data of patients—i.e., assignment, forms, and communications with the therapist—will be encrypted and securely stored on the mainframe of the Internet portal supplier.

Low active versus relative active

With data from the actometer, two activity patterns can be discerned: a low activity pattern and a relatively active pattern. The individuals' activity patterns will be based on the 12 daily physical activity scores [18]. Two physical activity patterns can be discerned. The average daily physical activity scores of low active patients stay below the general mean physical activity of CFS/ME patients in at least 11 of 12 days. Relative active patients score at least 2 of 12 days above the mean physical activity score of CFS/ME patients. Relative active patients have fluctuating activity levels with bursts of activity followed by (prolonged) periods of rest [18]. In case of missing actometer data at baseline, therapists will determine the activity pattern by using a structured interview [21].

In accordance with the CBT protocol for face-to-face therapy, we developed a low active and a relatively active variant of the two web-based CBT formats. Low active patients will start with a graded activity program early in therapy. Relatively active patients will first learn to spread their activities more evenly before starting the graded activity program. Following Stulemeijer [22] we do not expect different treatment outcomes for low or relatively active patients.

Web-based CBT—protocol-driven feedback

Patients following web-based CBT with *protocol-driven feedback* will be asked by the therapist to report on their progress according to a schedule set by the therapist. The therapist asks the patient to email at least weekly in the first four weeks and once every two weeks in the next eight weeks. After this period, the therapist will propose a schedule dependent on the progress being made. We expect this will likely be once every two or three weeks until the end of the program. Therapists will send reminders if patients do not follow the schedule. Patients can book chat sessions with their therapists. Phone support will only be provided when needed urgently.

Web-based CBT—support on demand

Patients who will follow the web-based CBT with sup-port on demand will only receive feedback if they ask for it. Patients will not receive any reminders from the therapist if they do not report on their progress via email.

Training and supervision of therapists

The therapists delivering the web-based CBT are psychologists and cognitive behavioural therapists who are trained and experienced in delivering CBT for CFS/ME. They will receive weekly group supervision regarding the web-based CBT. All therapists received training to improve their online communication skills with patients. The therapist will aim to write the emails in such a way that it motivates patients to follow the instructions of the intervention.

Adherence, dropout, and treatment integrity

Patients are assumed to have started with the treatment after they logged in on the Internet portal three times or more and have established goals for therapy on the goal sheet of the first module. We will assess how patients have used the web-based CBT by registration of 1) the number of times logged on; 2) the total duration of all sessions in minutes; 3) the number of opened treatment modules 4) and the number of sent emails and chat sessions. These variables will be reported.

We assume that a patient adheres to the web-based CBT with *protocol-driven feedback* if:

- He or she at least fortnightly emailed to the therapist, and
- has opened at least each module of the web-based intervention once.

We assume that a patient adheres to the web-based CBT with *support on demand* if:

- They have opened at least each module of the web-based intervention once.

Treatment integrity will be determined by evaluating a random selection of five percent of the emails send by the therapist. Two experienced therapists (HK; AJ) will independently score to what extent the feedback given to the patients is according to the protocol for CBT for CFS/ME (Knoop & Bleijenberg, 2010). We will register to what extent therapists have followed the pre-set schedule in the '*protocol-driven feedback*' condition.

Outcomes

All outcome measures are listed in Table 3. See Figure 2 for a schedule of enrolment, interventions and assessments.

	STUDY PERIOD	
	Enrolment	**Post-allocation**
Timepoint	T_0	T_1
Enrolment		
Eligibility screen	X	
Informed consent	X	
Allocation	X	
Interventions		
CBIT: protocol-driven feedback		
CBIT: feedback on demand		
Wait list control group		
Assessments		
Age, sex, duration of complaints	X	
Fatigue severity, disability level, physical functioning, social functioning, psychological well-being	X	X
Assessment of activities and symptoms (diary), actiography, number of additional CDC symptoms	X	X

Figure 2 – Schedule of enrolment, interventions, and assessments.

Primary outcome measure

Fatigue severity

Fatigue severity will be assessed with the subscale fatigue severity of Checklist Individual Strength [23]. This subscale consists of eight items assessing fatigue severity over the past two weeks. Scores range between eight (no fatigue) and 56 (severe fatigue). The cut-off score for severe fatigue is 35. This is two standard deviations above the mean of healthy controls [24]. The CIS is a reliable and valid instrument for the assessment of fatigue in CFS/ME patients [23–25]. The Cronbach's alpha reliability coefficient for the subscale fatigue severity is 0.88 [23]. This outcome measure and cut-off point was also used in previous trials assessing the efficacy of a minimal intervention for CFS/ME [26].

	Instruments
Primary outcome measure	
Fatigue severity	Checklist Individual Strength, (CIS) subscale fatigue severity
Secondary outcome measures	
Level of disabilities	Sickness Impact Profile-8, (SIP8) total score
Physical functioning	Medical Outcomes Survey Short Form-36, (SF-36) subscale physical functioning
Psychological distress	Symptom Checklist 90items, (SCL-90) total score
Clinical significant improvement in fatigue	Checklist Individual Strength, (CIS) subscale fatigue severity < 35 and a reliable change index > 1.96

Table 3 - Outcome measures.

Secondary outcome measures

Level of disability

Level of disability will be measured with the total score of the Sickness Impact Profile (SIP8) [25]. The SIP8 assesses functional disability on the following eight domains: ambulation, home management, mobility, alertness behaviour, sleep and rest, work, social interactions, and recreation and pastimes. A weighted total score is computed from the scores on the eight subscales [12,27]. This widely used measure has good reliability [27] and validity [5,11].

Physical functioning

Physical functioning will be assessed with the Medical Outcomes Survey Short Form-36 (SF-36) [28]. The subscale 'physical functioning' will be used. Scores on both scales range from 0 (maximum limitations) to 100 (no limitations). The SF-36 is a reliable and valid instrument to assess self-reported health status in CFS/ME patients [28,29].

Psychological distress

Psychological distress will be assessed with the total score of the Symptom Checklist 90 (SCL-90) [30]. In total 90 items are answered on a five-point Likert scale. Total scores range from 90 to 450, with higher scores being indicative of more psychological distress. This widely used measure has good reliability and discriminating validity [31].

Clinical significant improvement in fatigue

Clinical significant improvement in fatigue is defined as a reliable change index >1.96 [32] and a score of <35 on the CIS 'fatigue severity' subscale at second assessment.

Other study parameters

Based on the CBT for CFS/ME model several fatigue related behaviours and cognitions will be assessed [33,34]. The therapist will register invested therapist time for each patient. Actigraphy will be used to assess the level of physical activity. The actometer has been shown to be a reliable and valid instrument for the assessment of physical activity in CFS/ME [18].

The presence of psychiatric disorders will be assessed using a structured diagnostic interview, the Mini International Neuropsychiatric Interview (MINI) screen test [19].

Adverse events

Adverse events will be assessed six months post randomization. Patients will be asked if they experienced new symptoms or an increase of existing symptoms during therapy or wait period. Patients who have received treatment will be asked if therapy in their opinion had negative side effects. Previous treatment studies have shown that regular face-to-face CBT and guided self-instructions for CFS/ME are safe [35,36].

Statistical analysis

To determine whether web-based CBT leads to a reduction of fatigue severity compared to a wait list condition ANCOVA will be used. The second assessment of the primary outcome measure fatigue severity is the dependent variable in this analysis, with baseline CIS score as covariate, and condition as fixed factor. In RCTs ANCOVA yields greater power than other statistical methods [37]. Analyses will be based on intention to treat. Multiple imputation using fully conditional specification will be used to handle missing observations. The number of imputations will be at least equal to the percentage of missing data of the outcome measure. The assumption is made that data are missing at random [38]. A priori contrasts will be defined for the factor condition comparing web-based CBT with *protocol-driven feedback* versus wait list and *support on demand* versus waiting list. When statistical significant differences are found, a sensitivity analysis will be performed based on different assumptions about the values of missing data.

For the secondary outcome measures disabilities, physical functioning, psychological distress and the pro-portion of patients with clinical significant improvement in fatigue severity, the same analysis will be repeated, but with the secondary outcome measures at the second assessment

as dependent variable, and the scores of these measurements at baseline as covariate. Statistical significance will be assumed at $p < 0.025$ (0.05 corrected for two comparisons: web-based CBT with *protocol-driven feedback* versus waiting list and web-based CBT with *support on demand* versus wait list) for the analysis of the results with respect to the primary outcome measure fatigue and $p < 0.05$ for secondary outcome measures. We will use a chi-square test to determine if the proportion of patients with a clinical improvement out-come significantly differ between treatment arm and wait list condition. We will also use ANCOVA to explore possible differences between the two web-based CBT formats with fatigue severity as dependent variable, baseline score as covariate and condition as fixed factor. Mean therapist time needed per patient in each web-based CBT format will be compared with an independent

Sample size calculation

Based on a previous study with guided self-instructions [11] we expect a mean difference on the CIS fatigue severity score between each web-based CBT format and the wait list condition of 6.7. The standard deviation in this study at second assessment was 12.1 in the treatment condition and 8.7 in the wait list condition. In order to answer the primary objective of this study to detect a difference of 6.7 points on the CIS fatigue between each of the web-based CBT formats and the wait list condition, assuming the same standard deviations as in the aforementioned study, with a two sided alpha of 0.025 and a, power of 0.95, 76 patients are needed in each of the three conditions at T_1. This number is based on a *t*-test. Because an ANCOVA with baseline assessment as covariate will be used (which increases statistical power) this sample size has been multiplied with ($1–0.342^2$) [39]. The correlation between the baseline CIS-fatigue score and the score at second assessment was 0.342 in the aforementioned study. After correction, 68 patients with complete data per condition are needed. Assuming a drop-out rate of 15%, based on previous trials testing the guided self-instruction [11, 12] we will have to include 80 patients in each group to have 95% power to detect the expected difference of 6.7 points on the CIS fatigue between each of the CBT formats and the wait list condition.

In an exploratory analysis, we will determine whether there is a difference in efficacy between web-based CBT with *protocol-driven feedback* and web-based CBT with *support on demand*. On the basis of the calculated sample size of 68 patients with complete data per treatment arm, a power of .80 and a two sided significance level of 0.05 we will be able to detect a difference between both conditions that corresponds with an effect size (Cohen's *d*) of 0.48 (moderate size effect size).

DISCUSSION

The CBIT trial outlined in this article will be the first randomized clinical trial testing the efficacy of a web-based CBT for adults with CFS/ME. It will determine if web-based CBT leads to a significant reduction of fatigue. Secondary outcome measures are disabilities, physical functioning, psychological distress, and clinically significant improvement in fatigue severity. If this CBIT study shows that on-line CBT is an effective treatment for severe fatigue and disability, it can be a first choice treatment for patients with CFS/ME as web-based interventions can reach also those patients who are unable to visit our treatment centre due to geographical location or other circumstances that com-plicate face-to-face interventions in an outpatient clinic. The web-based CBT will be time efficient for patients. Therapists can be more flexible in their daily scheduling, as there are no face-to-face sessions with a fixed timeslot.

In an exploratory analysis, we will determine whether there is a difference in efficacy when patients receive *support on demand* or when they interact with the therapist according to a schedule. However, given the relatively small sample size a considerable difference between both conditions has to be present in order to detect it. In-formation about the amount of time of the therapist needed to deliver the two formats of web-based CBT could have implications for the decision which of the web-based interventions could best be implemented in clinical practice.

This study has some potential limitations. We have no controlled follow-up assessment in our study. We will not be able to determine if the expected positive effects of the web-based intervention are sustained over a longer period. A longer follow-up period is not possible as our study will be continued as a randomized non-inferiority trial comparing the two forms of web-based CBT followed by face to face CBT if patients have not profited from the internet intervention (stepped care) with care as usual, i.e. face to face CBT following the waiting list. This randomized non-inferiority trial is registered in the Netherlands trial register (NTR4809). Second potential limitation is that the treatment effects cannot be controlled for non-specific factors of the interventions. As this study will be continued as a randomized controlled non-inferiority trial, an active control was not possible. Previous research has shown that CBT is significantly more effective than other active interventions, like guided support groups and specialist medical care [42,43].

Although we expect that the web-based CBT will be more effective than guided self-instruction, it is possible that some patients do not profit from web-based CBT and they could benefit from additional face-to-face CBT. In a follow-up study we will test whether stepped care, consisting of a form of web-based CBT followed by individual CBT if a patient has not benefited from the web-based CBT, is as effective but more efficient than face-to-face CBT. The results of this follow-up study could help to further broaden treatment possibilities for adults with CFS/ME.

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Chapter 7

Efficacy of Web-based Cognitive–behavioural Therapy for Chronic Fatigue Syndrome: Randomised Controlled Trial

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ABSTRACT

Background: Face-to-face cognitive–behavioural therapy (CBT) leads to a reduction of fatigue in chronic fatigue syndrome (CFS/ME).

Aims: To test the efficacy of internet-based CBT (iCBT) for adults with CFS/ME.

Method: A total of 240 patients with CFS/ME were randomised to either iCBT with protocol-driven therapist feedback or with therapist feedback on demand, or a waiting list. Primary outcome was fatigue severity assessed with the Checklist Individual Strength (Netherlands Trial Register: NTR4013).

Results: Compared with a waiting list, intention-to-treat (ITT) analysis showed a significant reduction of fatigue for both iCBT conditions (protocol-driven feedback: $B = -8.3$, 97.5% CI −12.7 to −3.9, $p < 0.0001$; feedback on demand: $B = -7.2$, 97.5% CI −11.3 to −3.1, $p < 0.0001$). No significant differences were found between both iCBT conditions on all outcome measures ($p = 0.3–0.9$). An exploratory analysis revealed that feedback-on-demand iCBT required less therapist time (mean 4 h 37 min) than iCBT with protocol-driven feedback (mean 6 h 9 min, $p < 0.001$) and also less than face-to-face CBT as reported in the literature.

Conclusions: Both iCBT conditions are efficacious and time efficient.

INTRODUCTION

Cognitive–behavioural therapy (CBT) [1-4] has been shown to significantly reduce fatigue severity and functional impairment in patients with chronic fatigue syndrome (CFS/ME). However, face-to-face CBT is an intensive treatment [1] and treatment capacity is limited. Internet-based CBT (iCBT) might help to lower the threshold for seeking help and reduce the burden of the intervention for patients. iCBT makes treatment easier to access for more patients [5] and might promote self-efficacy. However, iCBT for CFS/ME has only been tested in adolescents, [6] where it was found to be effective. But, as adolescents are more inclined to use e-health, [7] these outcomes cannot automatically be translated to adults. Guided variants of internet treatment are more effective than unguided variants, [8] but require therapist time to deliver them. Most guided variants require patients and therapists to respond at pre-set intervals determined by a protocol. We tested the efficacy of iCBT with this type of guidance in a protocol-driven feedback condition. We also tested the efficacy of iCBT in which guidance was only given when patients asked for it, i.e. a feedback-on-demand condition. Both interventions were compared with a waiting-list condition and to each other. We also considered the therapist time needed to deliver the intervention for both forms of iCBT [9].

METHOD

Trial design

The efficacy of iCBT was determined in a three-arm parallel randomised controlled trial (RCT), using randomisation with two versions of iCBT and a waiting list (1:1:1) comparing baseline outcomes to those obtained in a second assessment (T_1) 6 months post-randomisation. Six months was the regular waiting time before patients could start with routine clinical treatment. The study has been described in a protocol paper [9] and registered with the Netherlands Trial Register (NTR4013).

Participants

A total of 240 patients participated in the study. They were consecutively referred [9] to the Expert Centre for Chronic Fatigue, a tertiary treatment facility for chronic fatigue at a university hospital. Before referral, consultants at the outpatient clinic of the department of Internal Medicine assessed their medical status to decide whether they had been sufficiently examined to rule out a medical explanation for their fatigue. If their medical evaluation was deemed insufficient, patients were seen again for anamnesis, full physical examination, case-history evaluation and laboratory tests following the national CFS/ME guidelines, [10] which are in accordance with the Centers for Disease Control and Prevention (CDC) guidelines. [11,12] If patients met the CDC criteria for CFS/ME, they were referred to our centre. Psychiatric comorbidity that could explain the fatigue was

ruled out using the Mini International Neuropsychiatric Interview.[13]

After referral, all eligible patients were informed and invited to participate in the trial during the standard clinical assessment. Patients were eligible if they met the following inclusion criteria: (a) aged 18 years or older; (b) being severely fatigued as indicated by a score of 35 or higher on the fatigue subscale of the Checklist Individual Strength (CIS); [14,15] (c) being severely disabled, operationalised as a score of 700 or higher on the Sickness Impact Profile 8 (SIP8); [16] (d) able to speak, read, and write Dutch; (e) able to use a computer and having access to the internet. Exclusion criteria were: (a) being involved in legal procedures concerning disability benefit claims; (b) participating in other CFS/ME research. All patients were asked to refrain from seeking treatment for their fatigue elsewhere for the duration of the study.

Interventions, treatment adherence and treatment integrity

The two iCBT conditions tested in this trial are based on a face-to-face CBT for CFS/ME protocol [17]. The cognitive–behavioural model of CFS/ME assumes that fatigue-related behaviours and beliefs perpetuate fatigue and impairment (for further details of the treatment see appendix). The treatment is tailored to a patient's current activity pattern as assessed with actigraphy. Patients received a private username and password, ensuring private communication with their therapist. ICBT consisted of seven modules aimed at change of fatigue-related behaviours and beliefs [9]. The iCBT modules were opened when patients had read general treatment information and had set their personal goals. The times at which their therapist would contact them were given on the first page of the portal. The final treatment module that covered relapse prevention became accessible after patients had completed the digital evaluation assignment.

Therapist guidance was manipulated in that in the protocol-driven feedback condition, patients were asked by their therapist to report on their progress by email according to a prescribed schedule of at least fortnightly. The therapist provided feedback and sent reminders if the schedule was not adhered to. Therapist adherence to the feedback schedule was monitored (at least fortnightly for 6 months with a minimum of 12 messages).

In the second treatment arm, the feedback-on-demand condition (referred to as support on demand in the protocol paper), support was tailored to the individual needs of the patient in that feedback was only provided when the patient indicated a need for advice. Patients did not receive any reminders.

Treatment-adherence criteria for the patients allocated to the protocol-driven condition were strict. It was verified whether all treatment modules had been accessed and whether email contact was made at least fortnightly. For the patients following the feedback-on-demand condition monitoring was restricted to checking whether each module had been opened. An integrity check was performed and for this the content of 5% of all emails the therapists had sent were evaluated. Two authors (A.J. and H.K.) coded treatment delivery dichotomously, discerning interventions delivered according to protocol and interventions not delivered according to protocol. In cases of

disagreement, the item was discussed until consensus was reached. Finally, how the web-portal was used was assessed by recording the number of times patients logged in, mean duration of sessions, number of opened treatment modules and number of emails sent.

Therapists

All 12 therapists delivering the interventions were experienced clinical psychologists trained in treating patients with CBT for CFS/ME [9].

Outcome measures

Primary outcome measure

Fatigue was assessed with the fatigue severity subscale of the CIS, which consists of eight items scored from 1 to 7, with subscale scores varying between 8 and 56. A score higher than 35 indicates severe fatigue. The CIS has proven to be a reliable and valid instrument in patients with CFS/ME [14,15].

Secondary outcome measures

Level of functional impairment was assessed with the total score of the SIP8. The SIP8 gauges overall functional impairment in the following eight domains: ambulation, home management, mobility, alertness behaviour, sleep and rest, work, social interactions and recreation and pastimes. A weighted total score was computed from the scores on the eight subscales, (range 0–5799). Higher scores are indicative of more severe overall impairment. This widely used measure has good reliability [16] and validity [18].

Physical functioning was assessed with the physical functioning subscale of the Medical Outcomes Survey Short Form-36 (SF-36) [19] where scores also range from 0 (maximum limitations) to 100 (no limitations). The SF-36 is a reliable and valid instrument to assess self-reported health status in patients with CFS/ME [19].

Psychological distress was assessed with the Symptom Checklist 90 (SCL-90), [20] whose 90 items are answered on a five-point Likert scale. Total scores range from 90 to 450, with higher scores being indicative of more psychological distress. The SCL-90 has good reliability and discriminating validity [21].

Fatigue scores in the normal range were defined as a score of <35 on the CIS fatigue severity subscale at second assessment, together with a reliable change index (RCI) >1.96.

Invested therapist time in hours and minutes per patient, was recorded by therapists on an excel sheet for comparison with CBT provided face-to-face or by telephone, for which a mean of 12 h is reported in the literature [1,22]. Additionally, 2 h of time was added to the therapist time spent per patient representing the two diagnostic assessment sessions that are part of clinical routine.

Adverse events were assessed 6 months post-randomisation (T_1). All participants were asked if they had experienced new symptoms or an increase of existing symptoms during therapy or the waiting period. Patients who received iCBT were asked if they had experienced negative side-effects of the therapy. The adverse-event assessment was added to the test battery after an update of the internet portal in March 2014. Clinically significant exacerbation was computed for fatigue severity, level of functional impairment, physical functioning and psychological distress. Indicating an RCI >1.96 between two measurements, we set clinically significant exacerbation at a RCI <–1.96 [23] (for visual illustration see additional Figure 1).

After trial registration but before the start of the study, we added the Chalder Fatigue Questionnaire (CFQ) [24] and Work and Social Adjustment Scale (WSAS) [25] to the assessment battery as both instruments are often used in CFS/ME intervention studies. Adding them, aids comparison of treatment effects between studies (see also Worm-Smeitink et al) [26]. Another deviation of the original study protocol was the decision not to determine quality-adjusted life-years; because of limited resources we were unable to perform a cost-effectiveness study. The quality of life questionnaire (the EQ-6D) [27] was, however, still part of the assessment battery.

Sample size

We expected a mean difference on the CIS fatigue severity score between each web-based CBT format and the waiting-list condition of 6.7 points with a standard deviation of 12.1 for the iCBT conditions and 8.7 for the waiting-list condition [28]. Assuming a power of 0.95 and a two-sided alpha of 0.025, 76 patients were needed in each study condition when a *t*-test was used. This sample size could be multiplied with ($1–0.342^2$) for using ANCOVA [29]. This meant that 68 patients with complete data were needed per condition. Assuming a dropout rate of 15%, a sample size of 80 patients was needed per study condition. In an exploratory analysis, we determined whether there was a difference in efficacy between both iCBT conditions. Based on 68 patients with complete data per condition, a two-sided *p*-value of 0.05 and a power of 0.80, a difference between both iCBT conditions could be detected, corresponding to a moderate effect size (Cohen's *d* of 0.48).

Randomisation

All patients attended two therapist-conducted intake sessions and completed a baseline assessment (T_0) as part of the clinical routine in our treatment centre. If eligible and willing to participate at the second session, patients were asked to give their written consent to the therapist who performed the intake sessions, after which they were randomly allocated (computer-generated; in blocks of 12, which was only known to the researcher and the statistician) to one of the three trial conditions. The randomisation was performed by a study assistant in the presence of the patient and therapist.

Patients were not informed about the existence of the two iCBT treatments to avoid contamination between the two treatment arms. Further contact between the study assistant and the patients was restricted to one standardised email containing the link to the T_1 assessment. Patients allocated to the waiting list started face-to-face CBT after T_1. Statistical analysis was performed on locked data files masking the researchers for allocation to condition. The analysis was done by an independent researcher. Post-analysis, the data manager unmasked the data to enable the authors to interpret results.

Statistical methods

It was hypothesised that both iCBT conditions would lead to improvements in fatigue and secondary outcomes compared with a waiting-list control. ANCOVA was performed with the CIS fatigue scores at T_1 as the dependent variable, its T_0 score as covariate, and condition as fixed factor. Differences in the proportion of patients with fatigue scores in the normal range were assessed using chi-squared tests. We also used ANCOVA for our secondary outcome measures and for comparisons between the iCBT conditions. The latter analysis was exploratory as was already mentioned in the protocol paper [9] because there were no previous findings to determine the power needed to test our hypothesis. However, we expected more improvement in primary and secondary outcomes following iCBT with protocol-driven feedback than following iCBT with feedback on demand. We also expected that more therapist time would be needed to deliver iCBT with protocol-driven feedback.

Difference in therapist time between both iCBT conditions was analysed with an independent *t*-test and additional bootstrap procedure if the therapist times were too skewed. We conducted *post hoc* ANCOVAs for the CFQ, the WSAS and the assessment of physical activity using actigraphy to determine the effects of the intervention. Furthermore, we used ANCOVA with T_0 assessment and gender as covariate and CIS fatigue at T_1 as dependent in testing the potential correlation to outcome. The number of patients per study arm reporting adverse events and/ or clinically significant symptom exacerbation was compared using chi-squared tests.

Our outcome analyses were based on ITT with multiple imputation (20 imputed data sets) for missing observations in primary and secondary outcomes, assuming that data were missing at random. Separate from the imputation, we performed two stand-alone sensitivity analyses for missing data on our primary outcome: (a) we hypothesised the mean change in the control group for missing data in that group and hypothesised no change for missing data in the iCBT conditions; (b) we hypothesised an improvement for the control group and deterioration for the iCBT conditions. Specifically, the progression of the iCBT conditions was used for missing data in the waiting-list condition and the maximum score on the CIS fatigue subscale was used for missing iCBT data.

A per-protocol analysis was performed for fatigue severity including completers only, i.e. patients who had started treatment and had complete data without receiving treatment elsewhere. There was no data-monitoring board, but data entry was checked by an independent data manager who was also responsible for data encryption and storage. IBM SPSS statistics (version 22) were used for all statistical analyses.

RESULTS

We assessed 398 patients between 24 April 2013 and 24 June 2015 who were consecutively referred to our clinic because of severe fatigue and impairment and met CDC criteria for CFS/ ME. Of these 398, 240 eligible patients remained and were randomly allocated to the three study conditions (Figure 1).

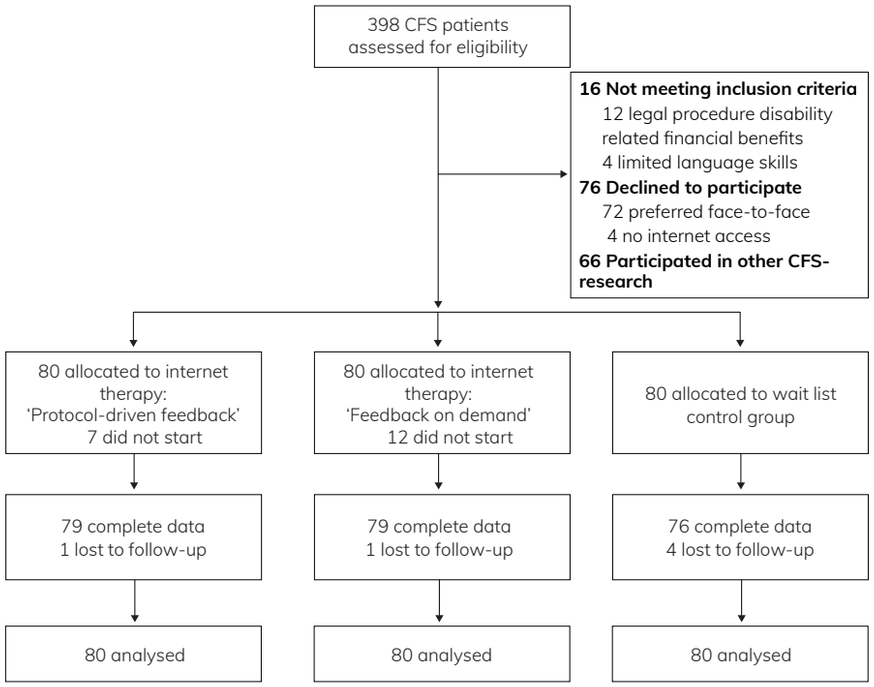


Figure 1 - Flow of patients through the study.

The primary outcome measure was completed by 234 patients (97.5%). See Table 1 for the baseline patient characteristics. With independent *t*-tests, chi-squared tests or Mann–Whitney *U*-tests we tested potential baseline differences between all study conditions. Patients on the waiting list had a significantly higher education level ($p = 0.0022$) than patients from the feedback-on-demand iCBT group. Significantly more patients reported unrefreshing sleep in the protocol-driven iCBT than in the feedback-on-demand group ($p = 0.0125$).

Six patients were included with less than four CDC symptoms (one being randomised to the waiting list and five to the on-demand treatment). Twenty-five patients started another treatment for CFS/ME during the study (*n* = 8/ 8/ 9; equally spread over conditions with medical, psychological and alternative treatments). Median treatment length was 27 weeks for both iCBT conditions and mean waiting time was 26 weeks for the waiting list.

	Protocol-driven feedback iCBT	Feedback-on-demand iCBT	Waiting-list control group
	(*n* = 80)	(*n* = 80)	(*n* = 80)
Age in years (SD)	36·6 (12·8)	36·4 (12·4)	39·9 (12·9)
Female, n/ N (%)	54/ 80 (68)	46/ 80 (58)	45/ 80 (56)
Education level, years: mean	15·3	14·9	15·9
Paid job, n/ N (%)	51/ 78 (65)	56/ 79 (71)	53/ 78 (68)
Duration of complaints in years, median (IQR)	4 (7·8)	4·5 (9·5)	6·5 (7·8)
Fatigue severity, mean (SD)[A]	50·7 (5·3)	49·9 (4·9)	49·5 (5·3)
Overall impairment, mean (SD)[B]	1452·0 (519·6)	1495·9 (543·5)	1607·9 (619·7)
Physical functioning, mean (SD)[C]	62·4 (21·1)	62·9 (17·7)	62·3 (19·2)
Psychological distress, mean (SD)[D]	152·5 (30·9)	157·3 (36·8)	159·8 (37·7)
Clinically relevant depressive symptoms, *n*/ N (%)[E]	25/ 80 (31)	23/ 80 (29)	33/ 80 (41)
Pain, mean (SD)[C]	59·7 (25)	61·1 (25·3)	59·9 (25·1)
No current psychiatric diagnosis, *n*/ N (%)	65/ 80 (81)	70/ 80 (88)	67/ 80 (84)
Any depressive disorder, *n*/ N (%)	9/ 80 (11)	7/ 80 (9)	8/ 80 (10)
Any anxiety disorder, *n*/ N (%)	7/ 80 (9)	5/ 80 (6)	5/ 80 (6)
Other psychiatric disorder, *n*/ N (%)[F]	1/ 80 (1)	1/ 80 (1)	3/ 80 (4)
CDC symptoms, median number (IQR)	7 (2)	7 (2)	7 (2)
Memory and/ or concentration problems, *n*/ N (%)	76/ 80 (95)	71/ 80 (89)	76/ 80 (95)
Sore throat, *n*/ N (%)	38/ 80 (48)	37/ 80 (46)	39/ 80 (49)
Tender lymph nodes, *n*/ N (%)	31/ 80 (39)	37/ 80 (46)	30/ 80 (38)
Muscle pain, *n*/ N (%)	63/ 80 (79)	63/ 80 (79)	66/ 80 (83)
Multi-joint pain, *n*/ N (%)	57/ 80 (71)	58/ 80 (73)	64/ 80 (80)
Headaches, *n*/ N (%)	61/ 80 (76)	61/ 80 (76)	55/ 80 (69)
Unrefreshing sleep, *n*/ N (%)	80/ 80 (100)	74/ 80 (93)	78/ 80 (98)
Postexertional malaise, *n*/ N (%)	73/ 80 (91)	69/ 80 (86)	75/ 80 (94)

Notes: Test statistics were: the independent *t*-test where variables are mean (SD); chi-squared for *n* (%); and the Mann–Whitney *U*-test for median (IQR). Percentages were rounded to whole numbers.

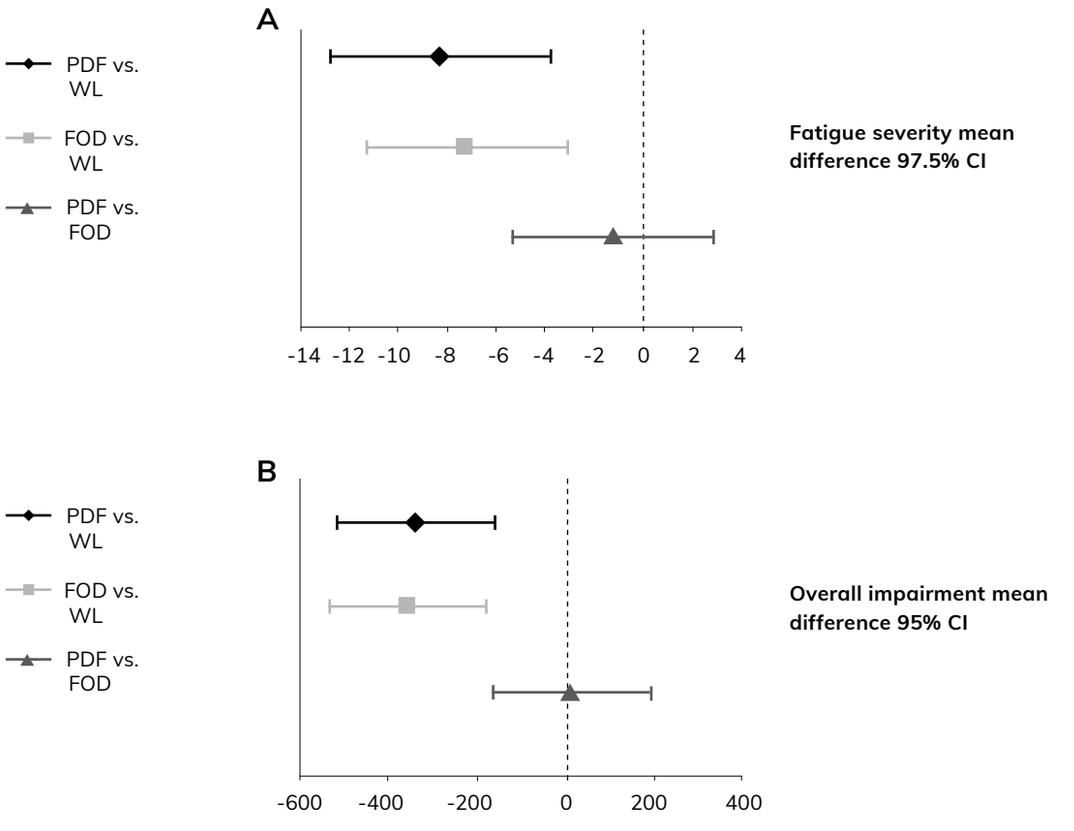
A) CIS Checklist Individual Strength; B) SIP8 Sickness Impact Profile; C) SF-36 Medical Outcomes Survey Short Form–36; D) SCL-90; Symptom Checklist-90, E) BDI-PC Beck Depression Inventory-PC, total score ≥4; F) body dismorfic disorder (mild), boulimia nervosa, obsessive compulsive disorder, somatisation disorder, conversion disorder.

Table 1 - Baseline patient characteristics per study condition.

At T_1, patients who followed protocol-driven iCBT were significantly less fatigued than those awaiting treatment (CIS fatigue; Table 2 and Figure 2). The two sensitivity analyses and per-protocol analysis confirmed this finding (additional Table 1).

Compared with waiting-list controls, patients reported less overall functional impairment (SIP8), less psychological distress (SCL-90) but no significant improvement on physical functioning (SF-36) following protocol-driven iCBT. Significantly more patients had fatigue scores in the normal range following protocol-driven iCBT than controls (protocol-driven 29/ 80 (36%) v. waiting list 12/ 80 (15%): $\chi^2(1, n = 160) = 9.5$, $p = 0.0021$; number needed to treat (NNT) = 4.7) (additional Figure 1).

At T_1, patients that followed on-demand iCBT were significantly less fatigued than those awaiting treatment (Table 2 and Figure 2). The two sensitivity analyses and per-protocol analysis confirmed this result (additional Table 1).



Notes: In each pair of comparison, treatment differences are in favour for the first study condition. In 'A' the Checklist Individual Strength, fatigue severity subscale was used and in 'B' the Sickness Impact Profile, total score. For our primary outcome measure we used a 97.5% confidence interval for comparisons with the waiting list. PDF, internet-based cognitive behavioural CBT with *protocol-driven feedback*, WL: waiting-list control group, FOD: iCBT with *feedback on demand*.

Figure 2 - Treatment differences for fatigue (A) and overall impairment (B) at six months.

Compared with waiting-list controls, patients reported less overall functional impairment, significant improvement in physical functioning and less psychological distress following feedback-on-demand iCBT. The covariate gender was added to the model and all aforementioned analyses were repeated. This did not change the pattern of results; the covariate gender did not reach significance. Significantly more patients had fatigue scores in the normal range following treatment than the controls (on demand 34/ 80 (43%) v. waiting list 12/ 80 (15%): $\chi^2(1, n = 160) = 14.8$, $p = 0.0001$; NNT = 3.6) (additional Figure 1).

	Protocol-driven feedback (n = 80)					**Feedback on demand (n = 80)**					**Waiting-list control group (n = 80)**
	2nd assess-ment	Difference compared to controls				2nd assess-ment	Difference compared to controls				2nd assess-ment
Outcome measures	*Mean (SD)*	*Mean*	97.5% CI	*p*	Cohen's *d*	*Mean (SD)*	*Mean*	97.5% CI	*p*	Cohen's *d*	*Mean (SD)*
Primary											
Fatigue severity[A]	36·3 (14·6)	-8·3	-12·7 to -3·9	<0·0001	0·60	37·0 (13·1)	-7·2	-11·3 to -3·1	<0·0001	0·58	43·9 (10·5)
Secondary			95% CI					95% CI			
Overall impairment[B]	867·8 (670·4)	-338·3	-514·7 to -161·9	0·0002	0·66	885·0 (658·9)	-356·0	-530·0 to -182·0	<0·0001	0·64	1322·5 (720·8)
Physical functioning[C]	73·3 (25·9)	2·4	-3·6 to 8·4	0·4348	0·11	77·0 (21·3)	5·8	0·6 to 11·0	0·0297	0·29	70·8 (21·0)
Psychological distress[D]	135·0 (36·4)	-14·2	-24·7 to -3·8	0·0075	0·47	140·3 (45·0)	-12·6	-23·6 to -1·6	0·0247	0·31	154·8 (47·6)

Notes: SD = standard deviation; 95% CI = 95% confidence interval; A) Checklist Individual Strength; B) Sickness Impact Profile 8; C) Medical Outcomes Survey Short Form–36; D) Symptom Checklist-90

Table 2 - Effects for the iCBT-treated patients and the controls based on intention-to-treat analyses.

We found no significant differences on all outcome measures between both iCBT formats (fatigue: $B = -1.2$; $t(157) = -0.6$, $p = 0.5589$; overall functional impairment $B = 11.2$; $t(157) = 0.1$, $p = 0.9027$ (Figure 2); physical functioning $B = -3.4$; $t(157) = -1,1$, $p = 0.2628$; psychological distress $B = -1.6$; $t(157) = -0.3$, $p = 0.7466$ and with fatigue scores in the normal range $\chi^2(1, n = 160) = 0.6$, $p = 0.4392$). With this small treatment outcome difference between both formats on fatigue severity (Cohen's $d = 0.04$, 95% CI −0.03 to 0.11), a large number of patients ($n > 10\,000$) would have needed to participate in order to reach significance.

The independent t-test indicated a significant difference in therapist time between both iCBT conditions ($t = -4.13$, $p < 0.0001$). The bootstrap procedure confirmed this result, i.e. protocol-driven iCBT required significantly more time to deliver than feedback-on-demand iCBT (mean 6 h 9 min, s.e. = 2 h 17 min and mean 4 h 37 min, s.e. = 2 h 23 min, respectively; mean difference: −92; bias, −0.45, bias-corrected and accelerated (Bca) 95% CI = −132 to −51, $p = 0.001$).

No serious adverse events were reported. Some patients indicated adverse events: 4 of 38 (11%) patients in the protocol-driven condition, 7 of 39 (18%) in the on-demand condition, and 12 of 46 (26%) in the control condition (see additional Table 2 for details and the patients' perception of iCBT side effects). The chi-squared analysis revealed no significant differences for the three conditions in the proportion of patients reporting an exacerbation of symptoms and/ or functional impairments.

Our integrity check showed that 90.3% of the interventions were delivered according to protocol with an interrater reliability (Cohen's Kappa) of 0.96. A total of, 4 of 80 (5%) patients in the protocol-driven condition and 6 of 80 (8%) in the on-demand condition did not start the intervention. Without taking the relapse module into account, 39 (49%) patients in the protocol-driven condition were adherent to following our criteria of emailing fortnightly and having opened all modules. Of the patients in the on-demand condition, 74 (93%) were adherent to following our criterion of having opened all modules. When the relapse module was taken into account, this percentage dropped considerably to 16 and 19%, respectively (see additional Table 3). Finally, the *post hoc* analyses revealed that CFQ scores and social impairment (WSAS) were significantly reduced and objectively assessed activity was significantly increased following the iCBT conditions compared with the waiting list (additional Table 1).

DISCUSSION

Main findings

To our knowledge, this study is the first RCT to report on the efficacy of iCBT for adults with CFS/ ME. Comparing iCBT outcomes with those of patients allocated to the waiting list, we found a significantly larger reduction of fatigue severity, overall impairment and psychological distress in the treatment groups, with approximately 40% of completers reporting fatigue scores within the normal range. Our results are in line with the findings of studies testing the efficacy of web-based interventions for mental disorders (e.g. depression, post-traumatic stress disorder and anxiety disorders) [31].

Comparison of feedback-on-demand with protocol-driven iCBT

Having therapists providing feedback according to a protocol, requiring at least fortnightly patient–therapist email interactions or on demand, resulted in a significant reduction of therapist time compared with the time needed to deliver CBT face-to-face or by telephone (mean therapist time in our study 6 h 9 m and 4 h 37 m, respectively *v.* 12 h reported in the literature). Furthermore, the therapists needed significantly less time for the on-demand treatment than they did for the protocol-driven treatment without the former treatment being less efficacious. Outcomes for the two iCBT conditions did not significantly differ. Our hypothesis that protocol-driven feedback would be more effective than feedback on demand did not hold. We clearly overrated the influence

of set guidance by a therapist over feedback on demand. With the present effect size of Cohen's *d* = 0.04 between iCBT conditions, the sample size was too small to detect a significant difference between iCBT conditions. However, we think this difference and its confidence interval is of little clinical relevance. One might argue that feedback on demand is superior to the protocol-driven iCBT condition when one takes therapist time spent into account. However, other aspects might be equally or even more important, such as patient satisfaction or being able to plan therapist workload in advance.

Safety of CBT for CFS/ME

Internet makes evidence-based interventions more accessible to more patients, especially those living far from healthcare facilities and those whose mobility is compromised by their condition. There is an ongoing debate in the literature and among patient advocacy groups that challenge the efficacy and safety of CBT for CFS/ME. First, in line with previous studies this study has shown that a subgroup of patients with CFS/ME were able to reduce their fatigue severity to healthy proportions and reduce their overall impairment and improve psychological well-being [18,32]. Second, this study has shown, in line with previous research, that CBT is a safe intervention [33,34]. Unfortunately, only half of the patients in our trial were asked to report on the occurrence of adverse events as this evaluation was not added until a portal update halfway through the study. Still, the available data did not show more patients with adverse events in the iCBT conditions compared with the waiting-list condition and none of the adverse events reported were serious. Furthermore, we found no evidence of a higher prevalence of clinically significant exacerbation in fatigue and other outcomes in the treatment conditions.

One could argue that the use of a waiting-list control does not control for non-specific therapy factors and limits the external validity. However, a meta-analysis that studied active placebo conditions for CFS/ME did show low responses [35], as was also true for standardised specialist medical care [34]. If face-to-face CBT was added as a third arm instead of a waiting list, the trial would have shifted toward an effectiveness trial. If iCBT was shown to be less effective than face-to-face therapy, we would not have been able to conclude that the more efficient iCBT is an efficacious treatment for a substantial subgroup of patients.

Impact of iCBT on physical functioning

One iCBT condition did not result in a significant increase in physical functioning. This seems remarkable as previous studies did find positive effects of face-to-face CBT on physical functioning (for example White et al) [34]. Previous studies, however, often used compromised physical functioning as an inclusion criterion, excluding patients who score within the 'normal range' on physical functioning. In our study these patients could be included if they reported severe impairments in other domains of functioning, like work or social functioning, as assessed with the SIP8. The fact that our study did not select on the level of physical functioning will make it

more difficult to find an effect of iCBT on physical functioning. It would be interesting to directly compare iCBT and face-to-face CBT in a sample of patients with CFS/ME with a compromised physical functioning scoring below a cut-off on the SF-36 to determine if the interventions differ in their effect on physical functioning. A *post hoc* analysis showed that objectively assessed physical activity significantly increased after iCBT. However, this might be an accidental finding, taking the amount of missing data into account and previous research that did not find an increase in physical activity following CBT [36].

Limitations

The effects of iCBT were only assessed 6 months post-randomisation as the medical ethical committee considered it unethical to let patients wait longer than the regular waiting period for start of treatment in usual care. Moreover, step two of our (stepped care) study consisted of face-to-face therapy if patients were still fatigued at the second assessment, therefore ruling out a controlled follow-up. More men participated in this study as compared with other CBT for CFS/ME trials. This can be explained by the inclusion criteria of another study that only included female patients with CFS/ME [22] out of the same pool of patients. There were no indications that gender was correlated with treatment outcome. As to our strict adherence criteria, a substantial number of patients did not fully adhere to the interventions. Adherence might be improved by sending standardised automatic emails or mobile text reminders.

Face-to-face CBT seems to result in superior fatigue effect sizes (up to $d = 1.0$) [4,26] compared with our study results of iCBT with a medium effect size of $d = 0.6$. This suggests that stepped care may help to optimise treatment effects [37]. We are currently performing a noninferiority trial with comparison of a stepped care intervention combining iCBT as a first step and face-to-face CBT as an optional second step (see NTR 4809) with face-to-face CBT only.

Implications

Our current trial was a first attempt to develop and test a web-based CBT for adults with CFS/ME. We think that treatment results can be further optimised, for example by communication via video conferencing and using physical activity apps with affirmative feedback. In the Western world, healthcare budgets are overstretched and psychological treatments are increasingly delivered digitally to reduce the costs of intervention. This web-based CBT programme, offers adults with CFS/ME a new and efficacious treatment option.

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APPENDIX

Treatment content of iCBT for CFS/ME

Cognitive behaviour therapy (CBT) is based on a model of perpetuating factors [A]. This model assumes that fatigue and disability are maintained by fatigue related beliefs and behaviour. CBT is aimed to change these cognitive-behavioural factors with recovery as highest attainable goal [B,C].

ICBT for CFS/ME is adapted from the face-to-face CBT protocol [D].

ICBT for CFS/ME consists of several modules. After general information about how to progress with iCBT, the cognitive behavioural model of CFS/ME is explained. Thereafter, patients first start to formulate treatment goals aimed at recovery that contains future activities assuming a patient is no longer severely fatigued and impaired. Secondly, patients start to regulate their sleep-wake pattern with fixed bedtimes and without sleeping or lying down during the daytime. Information is provided on how to reduce 'catastrophizing' and non-accepting fatigue beliefs', and patients formulate more helpful beliefs in response to fatigue. Furthermore, patients learn how to shift their attention away from fatigue towards other activities or the environment to reduce the focus on fatigue. The next module addresses the perceived lack of social support and how to communicate about CFS/ME with significant others.

Dependent on the activity pattern of patients [E] that was assessed at baseline, tailored information was provided on how to proceed with a graded activity program. Two patterns can be discerned: a low active and a relative active pattern. Patients with a low active activity pattern, characterized by an extremely low level of physical activity, immediately start to gradually increase their activity with walking or cycling. Relative active patients, characterized by an 'all-or-nothing pattern' of activity, first have to learn to divide their activities more evenly across the day before they start with graded activity. For patients with a high impact of pain, information was provided on how to deal with pain by formulating helpful beliefs. All patients learn how to solve problems with the graded activity program. The graded activity was followed by a step-by-step realisation of goals. This included work or study resumption, increasing mental and social activities and other goals.

The last CBT module was on how to learn to 'deregulate' oneself again, e.g. by having peaks of activity or going to bed late at night again. In this phase patients determine if they are recovered from CFS/ME and how they can maintain the gains they have made.

References of additional treatment information

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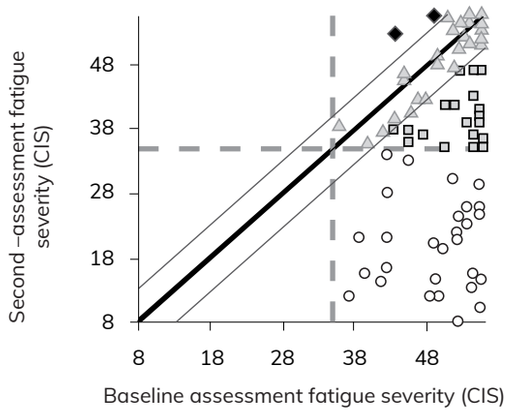
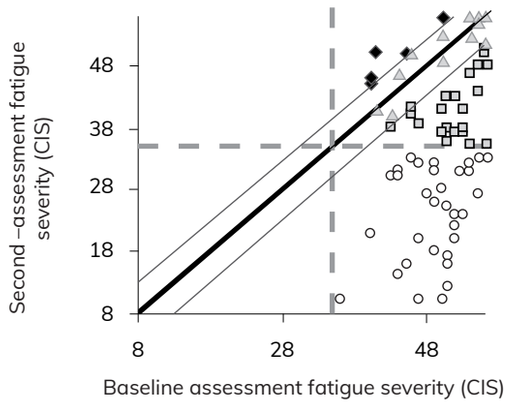
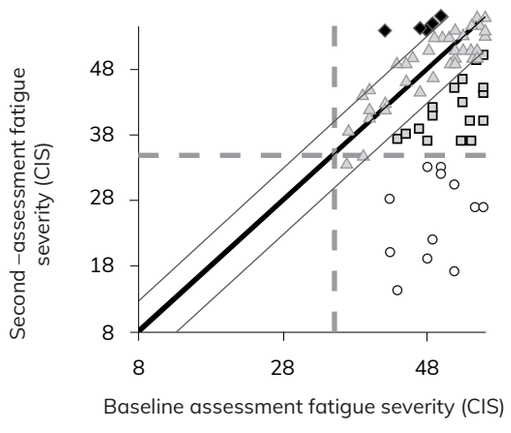
Protocol driven feedback



Feedback on demand



Waiting list



Diamond: Deterioration;
Triangle: No change;
Square: Only reliable change;
Circle: Reliable and clinical significant change

Notes: The diagonal line represents no change from baseline to second assessment, the upper and lower diagonal lines represent the bounds of the 95% CI of the Reliable Change Index and the horizontal and vertical lines represent the CIS fatigue cut-off score of 35. Normal fatigue is defined as a score of <35 at second assessment plus meeting the criterion for reliable change. Reliable change on CIS fatigue severity subscale; protocol driven feedback: >-5.10, *n* = 79; feedback on demand: >-4.71, n = 79; waiting list: >-5.14, n = 76.

Additional Figure 1 - Baseline and second assessment fatigue severity scores of all individual patients.

Outcome measure	Feedback on demand						Waiting-list control group		
	Baseline	2nd assess-ment	Difference compared to waiting list				Base-line	2nd assess-ment	n per condition
	Mean (SD)	Mean (SD)	Mean	95% CI	p		Mean (SD)	Mean (SD)	n
CIS fatigue severity[A]									
Sensitivity analysis 1	49·9 (4·9)	37·1 (13·2)	-7·0	-10·6 to -3·5	0·0001		49·5 (5·3)	43·9 (10·1)	80/ 80/ 80
Sensitivity analysis 2	49·9 (4·9)	37·1 (13·2)	-6·6	-10·2 to -3·1	0·0003		49·5 (5·3)	43·5 (10·4)	80/ 80/ 80
Per-protocol analysis	49·4 (5·2)	35·2 (13·3)	-8·7	-12·5 to -4·8	<0·0001		49·5 (5·3)	44·1 (10·3)	65/ 56/ 76
Chalder fatigue questionnaire, completers	24·0 (5·1)	17·5 (7·5)	-3·0	-5·2 to -0·8	0·0073		24·7 (5·0)	20·8 (7·3)	75/ 77/ 76
Work and social adjustment scale, completers	22·2 (6·3)	15·4 (9·3)	-5·1	-7·6 to -2·7	<0·0001		23·0 (6·9)	20·8 (9·2)	73/ 74/ 75
Actigraphy, mean waken score,	70·7 (17·6)	78·8 (21·7)	9·3	4·0 to 14·6	0·0008		67·6 (18·1)	66·4 (21·5)	59/ 68/ 60
Completers									
Protocol-driven feedback									
CIS fatigue severity[A]									
Sensitivity analysis 1	50·7 (5·3)	36·5 (14·7)	-8·1	-12·0 to -4·3	<0·0001				
Sensitivity analysis 2	50·7 (5·3)	36·5 (14·7)	-7·8	-11·6 to -3·9	0·0001				
Per-protocol analysis	50·4 (5·4)	37·0 (15·0)	-7·5	-11·6 to -3·4	0·0004				
Chalder fatigue questionnaire, completers	23·5 (5·7)	16·7 (8·6)	-3·4	-5·7 to -1·0	0·0048				
Work and social adjustment scale, completers	23·6 (6·7)	16·2 (10·4)	-5·3	-7·9 to -2·6	0·0001				
Actigraphy, mean waken score,	65·4 (17·5)	73·2 (20·7)	5·8	0·5 to 11·0	0·0324				

Notes: SD = standard deviation; 95% CI = 95% confidence interval; A) CIS Checklist Individual Strength; Patients included in per-protocol analysis: at least four CDC symptoms, started treatment, complete data, no other treatments for fatigue during study.

Addtional Table 1 - Sensitivity analysis, per-protocol analysis and post-hoc analysis of outcome on CFQ, WSAS and actigraphy.

	Protocol-driven feedback	Feed-back on demand	Waiting list	Proto-col-driven feedback versus waiting list, p (χ^2)	Feedback on demand versus waiting list, p (χ^2)	Missing data, *n*
Fatigue severity[A]	2/ 78 (2·6%)	5/ 79 (6·3%)	5/ 76 (6·6%)	0·25	0·95	2/ 1/ 4
Overall impairment[B]	2/ 75 (2·7%)	3/ 77 (3·9%)	6/ 76 (7·9%)	0·15	0·30	5/ 3/ 4
Physical functioning[C]	6/ 76 (7·9%)	2/ 77 (2·6%)	3/ 76 (2·6%)	0·30	0·65	4/ 3/ 4
Psychological distress[D]	8/ 75 (10·7%)	6/ 77 (7·8%)	12/ 75 (16%)	0·62	0·29	5/ 3/ 5
						Not assessed
N with self-reported adverse events	4/ 38 (10·5%)	7/ 39 (17·9%)	12/ 46 (26·1%)	0·14	0·75	42/ 41/ 34
Fatigue	0	1	1			
Pain	4	2	5			
Distress	0	3	2			
Other	0	1	4			
Patient-reported ICBT side effects*	3/ 37 (8·1%)	3/ 38 (7·9%)	^^	-	-	43/ 42

Notes: A) CIS: Checklist Individual Strength, B) SIP: Sickness Impact Profile, C) SF-36 physical functioning subscale, D) SCL-90: Symptom Checklist-90 items. Clinically significant change criterion was defined as RCI <- 1.96; *4/ 75 were temporary complaints; of the remaining two patients, one reported headaches and one lost her job during ICBT; ^^not assessed in the control (waiting-list) group

Additional Table 2 - Number of patients with symptom exacerbation at second assessment.

Internet variables	Protocol-driven feedback	Feedback on demand
M login frequency	37	39
*M login time in minutes	17	19
Started treatment, n/ N (%)	76/ 80 (95%)	74/ 80 (93%)
Full adherence, n/ N (%)	13/ 80 (16%)	15/ 80 (19%)
Adherence without opening the 'preventing relapse' module, n/ N (%)	39/ 80 (49%)	74/ 80 (93%)

Notes: Full adherence to protocol-driven feedback format: Opened all treatment modules and sent at least 12 emails. Full adherence to feedback-on-demand format: Opened all treatment modules. *Note: Data was lost of 11 patients (four from the protocol-driven feedback condition; 7 from the feedback on demand condition) and could not be traced.

Additional Table 3 - Internet login variables per ICBT condition.

Chapter 8

General Discussion

Chronic fatigue syndrome (CFS), also known under the name Myalgic Encephalomyelitis (ME) is a debilitating condition from which only about 5% of patients spontaneously recover [1]. This makes evidence-based treatments highly relevant.

An often used case definition for CFS/ME is that of the US Centers for Disease Control and prevention (CDC) revised in 2003 [2,3]. According to this case definition, CFS/ME patients are severely fatigued for at least 6 months with substantial impairment in daily life. Patients must report at least four additional symptoms [2,3]. The cognitive behavioural model of CFS/ME assumes that symptom related behaviours and beliefs perpetuate the syndrome. With cognitive behavioural therapy (CBT) for CFS/ME, patients learn how to change these perpetuating behaviours and beliefs.

The studies in this thesis focused on the treatment of CFS/ME with CBT, one of the few evidence based interventions for CFS/ME. CBT was studied in different groups (patients with CFS/ME and idiopathic chronic fatigue), different treatment settings (specialist care and implemented care), different treatment formats (guided self-help, stepped care, CBT via internet) and with outcomes assessed at different moments in time (directly following treatment and at long-term follow up). We will discuss who profits from treatment and how treatment outcome might by optimized.

Which patients profit from CBT?

CFS/ME patients are a heterogeneous group. A substantial subgroup of patients profits from CBT, but a large group of patients does not. Unfortunately, not much is known about which patients benefit. We will discuss the predictive value of different case definitions and the predictors of long-term outcome.

Does fulfilling case criteria for CFS/ME predict the response to CBT?

To diagnose CFS/ME, different case definitions are being used [4]. The CFS/ME case definitions are important as these are being adopted by national guidelines prescribing treatment for a certain group of patients [5]. Furthermore, research into the management of fatigue is often limited to the groups meeting the criteria. There are, however, many persons suffering from persistent medically unexplained fatigue without fulfilling case definitions of CFS/ME. For example, fatigue with a duration >6 months was found in 15% of the normal population in the UK [6]. For the patients who do not fully meet the case definition, but nevertheless suffer, the efficacy of interventions for fatigue will not be studied and no treatment will be prescribed by national guidelines. This is the case for the group of idiopathic chronic fatigue (ICF) patients (as described in chapter 5), which is not referred to in the Dutch national guideline on CFS/ME [5]. ICF is characterised by severe medically unexplained fatigue leading to considerable impairment - but not to impairment severe enough to warrant the diagnosis CFS/ME - and/ or less than four additional symptoms. This thesis showed that CBT was also effective in this group (chapter 5). Therefore, one can conclude that CBT for CFS/ME is effective in a larger group of severely fatigued patients than the group of patients meeting CDC criteria of CFS/ME only.

Only two studies determined the relation between meeting a specific case definition of CFS/ME and the outcome of behavioural interventions. They did not find a relation between outcome and case definition [7,8].

Also for the latest proposed case definition Systemic Exertion Intolerance Disease (SEID) (Institute of Medicine (US) Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome & Institute of Medicine (U.S.). Board on the Health of Select Populations, 2015), we could not find evidence that it was associated with different outcomes of CBT (see chapter 2 and 7). This is in line with a recent other study that found similar treatment outcomes after CBT for patients fulfilling the CDC criteria only and the subset of patients also fulfilling the SEID criteria [9]. Previous studies have shown that there is a substantial overlap between different case definitions and therefore most patients fulfil more than one case definition [4,10]. It seems likely that case definitions are too broad categories to discern different patient groups with respect to their response to treatment.

We assume that at least chronic fatigue leading to impairment needs to be present to be eligible for CBT for fatigue as described in treatment manuals for CFS/ME. Fatigue with disability is common to all case definitions of CFS/ME and also present in the less severe groups such as ICF. Severe fatigue leading to impairment is also prevalent in other conditions such as diabetes, neuromuscular disease, multiple sclerosis and in cancer survivors. CBT for fatigue tailored to these fatigued patient groups was also effective in reducing fatigue and impairment [11-15]. This is not surprising, as the main aims of this therapy are a reduction of fatigue and disability. Although CBT is adapted to the specific patient group, it seems that when the condition of patients is characterized by both fatigue and disability, patients can profit from CBT aimed at fatigue [16].

In sum, case definitions do not seem to discern patients that profit from treatment with CBT for CFS/ME. Case definitions have a potential disadvantage. Chronically fatigued patients with considerable impairment but insufficient symptoms to fulfil the CFS/ME case definition, are not included in treatment studies or national guidelines on CFS/ME. However, we showed that these patients could benefit from CBT like the patients for whom this treatment was originally designed.

Predicting long term outcome of CBT

At long-term assessment, up to 10 years post-CBT we found that *one out of three* patients was no longer severely fatigued. That a substantial subgroup profits from therapy and maintains treatment gains over such a long period is remarkable. During natural course without treatment, only one patient out of twenty improves on fatigue and/or functioning [1].

On the other hand, 50% of the patients who initially profited from therapy relapsed over time. This relapse rate seems not unique for CFS/ME as similar relapse rates were found in fatigued cancer survivors and fatigued type 1 diabetes patients that followed CBT for fatigue [17,18].

For the first time, outcome was studied for such long period post-CBT (chapter 2). Furthermore,

we explored predictors of outcome at long-term follow up (chapter 3). Our study had limitations. The long-term follow up study was uncontrolled and cross-sectional. In future, longitudinal studies are needed to replicate our findings. With the long-term follow up study reported on in chapter 2, we only knew the severity of fatigue at one point during follow up, which we assumed to be chronic. Repeated measurements during the follow up period would give insight into the development of complaints over time in individual patients.

We will focus in our discussion of the predictors of long-term outcome on the findings with respect to *symptom duration* and *frustration in response to fatigue* at post-CBT and indicate how these findings may be used to improve treatment.

A longer symptom duration at start of CBT was related to higher fatigue severity at long-term follow up. Remarkably, most previous studies did not find a relation between symptom duration and fatigue severity at post-treatment [19-24]. Only two studies found a shorter symptom duration to be related to better treatment outcome: one to improved physical functioning [25] and one to less severe fatigue [26] immediately after treatment. Thus far, no study determined the predictive value of symptom duration for treatment outcome with a follow-up of longer than twelve months.

In most Dutch CBT studies, symptom duration before start of treatment is long i.e. about 5 years (see for example chapter 5 and 7; [27]). General practitioners (GP's) play a key role in the diagnosis of CFS/ME and referral for treatment. Knowing that CFS/ME can be diagnosed after half a year, it is important that GP's diagnose CFS/ME earlier [28]. This issue still requires more attention. If patients would be diagnosed earlier (as soon as they have symptoms for more than 6 months and fulfilling the criteria for CFS/ME) and are referred immediately for CBT, we might enhance long-term benefits of treatment. Furthermore, when treatment is provided earlier, it reduces the burden of the syndrome for patients and perhaps it may reduce the societal costs caused by the symptoms.

More frustration in response to fatigue at post CBT was associated with higher fatigue severity at long-term follow up, independent of the fatigue severity level at post treatment. This is remarkable as changing negative emotional reactions as a response to fatigue, is part of treatment. We may assume that feelings of frustration were insufficiently treated. Perhaps the treatment of this negative emotional response can be optimized. Frustration might be a conditioned response (CR) to fatigue that refers to the activation of memories to previous unpleasant experiences. Presumably, this makes relapse more likely. During the period of CFS/ME, many patients will have had negative experiences associated with fatigue such as loss, social rejection or being misunderstood. In the current Dutch CBT for CFS/ME protocol, there is no specific intervention directed to reprocess adverse memories. The adversity of these memories may be neutralized with the help of Eye Movement Desensitization and Reprocessing (EMDR) [29]. The potential benefits of additional EMDR to a reduction of negative emotional responses to fatigue needs to be studied. An effective intervention for feelings of frustration in reaction to fatigue might improve long-term outcome.

Another hypothesis about frustration is that processes of evaluative learning took place. At the end of treatment, patients may have learned that fatigue (CS) is not followed by increased symptoms or disability (US). However, some studies indicate that even when patients have learned that CSs are not followed by USs i.e. extinction has taken place, the CS is still being disliked [30,31]. For CFS/ME, this would mean fatigue may have been 'contaminated' with some unpleasantness of the previously connected US (i.e. increased symptoms or disability). Therefore, fatigue itself would still be perceived as frustrating. This negative evaluation might be treated with contra conditioning. With contra conditioning, fatigue (CS) is repeatedly being associated with a reward (S+). It is assumed that contra conditioning would make the evaluation of the CS less negative, as was previously shown in chronic pain patients [32]. Patients may reward themselves when being fatigued after exercise. Perhaps this procedure can be applied to CFS/ME and might be beneficial to prevent relapse.

<u>Interventions that may prevent relapse after CBT</u>

For CFS/ME, relapse prevention programs do not yet exist. Interestingly, for several mental problems relapse prevention programs already have been developed in the form of maintenance CBT i.e. a continuation of the same CBT [33-36], therapy via internet [37,38], or mindfulness based cognitive therapy (MBCT) [39-41]. With MBCT [40] an open and non-judging relation to fatigue can be developed. Patients will learn to take an observatory stance towards their own (emotional) experiences without fusing with the experience. The option of MBCT may seem appealing to prevent relapse in CFS/ME, however convincing evidence for the efficacy of MBCT in CFS/ME patients is still lacking [42,43].

Maintenance CBT for CFS/ME might be a more promising option to investigate in future. We found fatigue severity at post-CBT to be the main predictor of fatigue severity at long-term follow up. Based upon this result, one might argue we must continue therapy to the point where fatigue does not further decrease to a lower severity. However, this treatment will require a considerable investment of (sparse) therapist time and will also be offered to patients who will not relapse anyway. Therefore, it might be argued to wait for relapse and then provide (some) CBT again. The CBT after relapse would consist of a rehearsal of treatment principles.

An option *to prevent* relapse might come from another treatment strategy from positive psychology, such as well-being therapy [44]. Well-being therapy does not aim to reduce symptoms further, as the absence of symptoms does not necessarily imply a general feeling of well-being [45]. Well-being is broadly described by a sense of autonomy and a positive attitude toward oneself, the capacity to manage one's life, positive interpersonal relationships, personal growth, self-acceptance and the belief that life is meaningful [46]. It is assumed that high levels of well-being make people more resilient [47-50]. It would be interesting to assess the general feeling of well-being at the end of CBT. Those patients with low well-being at the end of CBT may be more vulnerable to relapse. For these patients, additional well-being treatment might be useful.

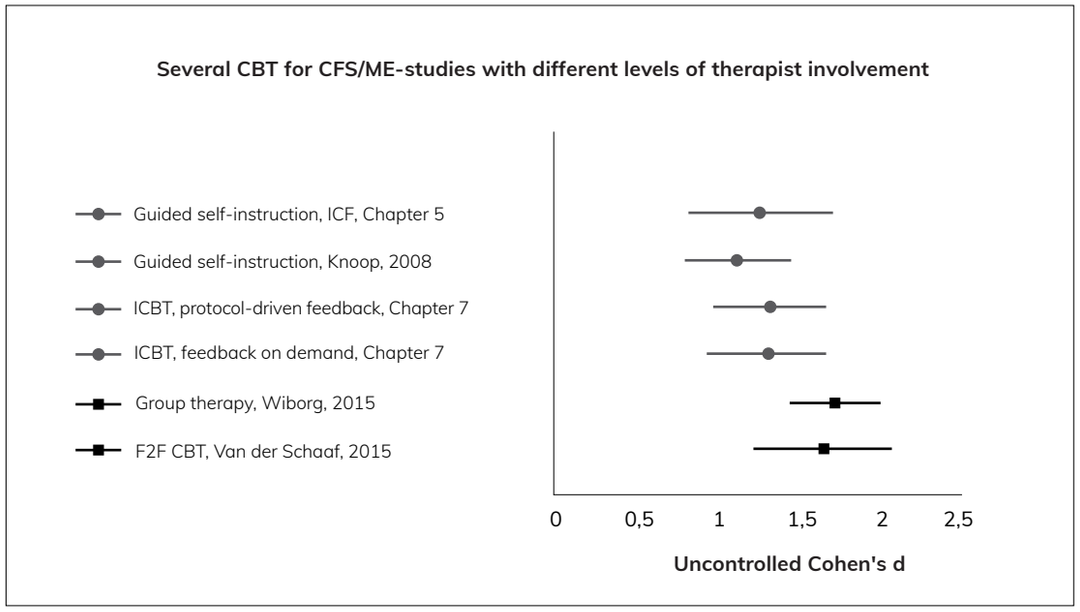
Future perspectives on how to improve Internet-CBT for CFS/ME

Internet-CBT (ICBT) asks for a different approach to treatment of both patients and therapists. As the current version of ICBT was the first version for adult patients, there are many opportunities to further improve the intervention. We will discuss several options to optimize treatment.

The effectiveness of CBT with different levels of therapist involvement

Generally, CBT for CFS/ME is an effective therapy with uncontrolled effect sizes of >1.0 for the Dutch studies performed in specialist care (see Figure 1). Data from Figure 1 suggests that face-to-face therapy [51,52] is more effective than minimal interventions (chapter 5 and 7; [53]. It has to be noted that the different treatment formats are not directly being compared to each other and the confidence intervals of effect sizes overlap due to the small sample sizes.

However, the assumption that face-to-face CBT is more effective makes intuitively sense as there is greater involvement of the therapist. It is known from other psychological treatments that interaction with a therapist lead to better treatment outcomes than when no therapist is involved [49,50]. For CFS/ME, fully self-guided treatments have not been tested, but only interventions that differ in the level of therapist involvement (i.e. intensity). Limited therapist resources make improvements to save therapist time highly relevant. On the other side, a more efficient therapy must not reduce the effectiveness of the intervention or increase the burden for patients.



Abbreviations: ICF = Idiopathic chronic fatigue; ICBT = CBT via internet; F2F CBT = Face-to-face CBT

Figure 1 - Uncontrolled effect sizes of fatigue severity of specialist care studies for CFS/ME and ICF.

CBT via internet versus CBT face-to-face

Based on the aforementioned, it seems that interventions with limited help of a therapist such as ICBT (chapter 7) are less effective than face-to-face therapy [9]. ICBT is different from face-to-face CBT. The most outspoken difference is patients have less interaction with a therapist. Remember that the mean invested therapist time for ICBT was approximately half of that of face-to-face CBT as reported in the literature. The limited time investments of therapists consequentially ask from patients to do more by themselves when following ICBT. This may bring some challenges for patients who follow ICBT as well as for therapists who provide ICBT.

<u>How to change dysfunctional beliefs?</u>

A consequence of less therapist interaction might be that it is more difficult to change dysfunctional beliefs that perpetuate symptoms. A CBT for CFS/ME-therapist is trained to ask, pinpoint and help patients to change dysfunctional thoughts. It is not easy for patients to go through this process by themselves after reading instructions. With the traditional face-to-face conversation, the therapist aims to help the patient to gain insight in this/ her own beliefs that may be dysfunctional or unhelpful. The use of email in the current version of ICBT, may hamper this process, resulting in dysfunctional beliefs remaining unaware to patients (and therapists).

We suggest to add some therapist interaction during the ICBT modules aimed at changing unhelpful/ dysfunctional beliefs and the graded activity program [54]. Research has shown the importance of the *perceived* activity level instead of the *actual* activity level [55,56] for treatment outcome. The graded activity program is aimed at gathering evidence for the belief that patients can increase their ability to become active. Video calls i.e. calling via internet that enables visual communication, can be used to communicate online with a therapist. When the patient-therapist communication is more like the communication in face-to-face therapy, the effect of the intervention may increase. A future study is needed to test whether video calls will indeed increase the effectiveness of the intervention.

<u>How to tailor treatment to the individual patient?</u>

A possible problem with the web-portal for CFS/ME tested in this thesis was that everyone was exposed to the treatment content with the same texts/ explanation. In face-to-face therapy, a therapist will tailor generic treatment content to the individual patient, for example by using diagnostic information about a patient. Tailoring is defined as an "*assessment-based approach in which data from or about a specific individual and related to a given health outcome are used to determine the most appropriate information or strategies to meet that person's unique needs*" p.184 [57].

It was already shown in the nineties that tailoring to individual needs and concerns helped to increase physical activities better than when general health messages were given [57,58].

Recently, personalised treatment content was found to be related to higher engagement with online psychological interventions [59]. However, with ICBT, the patient himself had to translate or apply generic information to his own situation.

Automated tailoring can be applied when patient data - gathered during the diagnostic phase - can be used during treatment. For example, when a patient has ticked the unhelpful belief "I have an illness and whatever I do, it will not change my situation", this specific belief may automatically be presented as an example of an unhelpful belief in the explanatory text of "How to formulate helpful beliefs?" Other personal diagnostic information or written content may later come back during the intervention such as registered sleep-wake cycle, activity pattern or personal targets for therapy (such as resuming work or social activities). When the system does this automatically, internet treatment will become more similar to face-to-face CBT and therefore perhaps more effective.

How to get patients exposed to treatment?

With less therapist interaction with ICBT, it becomes less certain that patients get exposed to the content of treatment. This is in contrast to face-to-face sessions, where the therapist takes care of explaining the treatment content. When patients do not adhere to treatment as intended, therapy will likely be less effective [60]. In our ICBT-sample, we tested whether adherence was significantly correlated to treatment outcomes directly post-CBT. More opened treatment modules (as operationalization of adherence) was positively associated with lower fatigue severity and lower overall impairment at the follow-up assessment (data not shown). Therefore, we assume that improving adherence might improve the efficacy of ICBT.

Improvements to ICBT with the help of persuasive system design

Patients might better adhere to a treatment, when a web-portal is persuasive to use it. We think the current version of ICBT still is a rather static booklet displayed on the internet. The importance of a persuasive system design for increasing adherence or engagement with treatment is repeatedly being emphasized [61-63]. Persuasive system design (PSD) is defined as an "*interactive computing system, designed to change people's attitudes or behaviours*" (p. 1) [64,65]. Several web-based treatments aimed at improving mental health had better outcomes when PSD principles were applied [66].

Improvements to ICBT with the help of modern technology

The current ICBT version was not yet available via smartphone, but the next version will be. The smartphone will ease sharing of real life data while following ICBT. One could think of sharing activities performed or bedtimes. More data creates new research challenges for collecting, interpretation and relating this to treatment outcome [62].

Automated feedback

Besides challenges, data sharing provide also opportunities to reinforce patient behaviour sooner (as soon as it emerges). When patients would share real-time data on their graded exercise program i.e. a couple of minutes walking or cycling, automated feedback may directly reinforce the performance. With automated feedback i.e. feedback sent automatically without therapist involvement, the reinforcement would come temporally closer to the intended behaviour. New behaviour with positive consequences tends to be strengthened or repeated [67]. A swift automated reinforcement would presumably make repetition of the intended behaviour more likely.

Chatbots

An advanced way of providing automated feedback is a chatbot i.e. software that simulates human conversation. Chatbots may be used to respond on shared data from patients. Main advantage of chatbots is their 24/7 availability and functioning [68]. Although there are still many challenges left to resolve, some of the work previously been done by therapists, will most likely be performed by chatbots in the near future. Responses may also come from avatars (a picture that represent a virtual person) that may react real time with the help of software that is able to use speech pattern, eye movements, body language and facial expressions (for example [69].

Serious gaming

Serious gaming may stimulate patients to practice certain new behaviours as intended by the therapy. An existing example of serious gaming that helped to increase physical activity in adolescents is Pokémon Go [70,71]. With this game, real world places are augmented with virtual items that need to be collected. In short: you need to get out and become active to play the game. For CBT for CFS/ME, an augmented reality (like Pokémon Go) may help to increase the incentive for gradually increasing physical activity. In addition, virtual reality [72] has the ability to make practicing more attractive [73,74] as it could help to reduce the focus on symptoms. The latter is known to be a perpetuating factor of fatigue and a decrease in the focusing on symptoms mediates the reduction in fatigue brought on by CBT [75].

Other research designs than RCT's

When patients are sharing more data during treatment, it gives the opportunity to test treatment outcome of separate elements of the intervention instead of pre and post intervention. Traditional forms of evaluation such as RCT's take too much time against the background of a rapid changing technological landscape. Other or additional research designs could be applied to use and test new developed treatment parts [62]. One specific design –called sequential, multiple, assignment, randomized trial (SMART)– has the potential to test different modules or new treatment tools within one study [76]. In a SMART-design, patients can repeatedly be randomised to different sub-conditions or parts of treatment [62].

The role of the future therapist

The therapist is expected to be a manager of the options he or she has for guiding the patient during therapy (email, chat, video call or traditional face-to-face). Some guidance during therapy will be partly taken over by artificial intelligence (automated feedback, chatbots, reminders). The (future) therapist is needed for complex situations in which the therapist can adjust the intervention to a wide range of different patient characteristics and situations. It is likely that some form of human-to-human contact will remain the basic ingredient to all psychological interventions, irrespective of the technological developments the future will bring.

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Appendices

Cognitive Behaviour Therapy for Chronic Fatigue Syndrome: Long-Term Follow-Up and Internet-based Treatment

Summary

Chronic fatigue syndrome (CFS), also known as Myalgic Encephalomyelitis (ME) is a debilitating condition from which about only 5% of patients spontaneously recover. Case definitions, mainly based on symptoms reported by patients, are used to diagnose CFS/ME as there are no known somatic markers. An often-used case definition is that of the US Centers for Disease, Control and prevention (CDC) which was revised in 2003. According to this case definition, CFS/ME patients are severely fatigued for at least 6 months with substantial impairment in daily living. In addition, patients need to report four out of the following eight symptoms: unrefreshing sleep, muscle pain, multi-joint pain, post-exertional malaise, sore throat, headaches, tender lymph nodes, and impaired memory and/ or concentration problems.

The Health Council of the Netherlands estimated in 2005 the number of CFS/ME patients at 30.000 to 40.0000 patients. Compared to international prevalence rates, the Dutch estimate seems conservative.

CFS/ME is often seen in less severe forms without meeting the additional symptom criteria or with only moderate levels of impairment. The CDC does refer to this chronically fatigued group with the term idiopathic chronic fatigue (ICF). The prevalence rates of ICF are much higher than of CFS/ME.

The cognitive behavioural model of CFS/ME assumes that behaviour and beliefs perpetuate symptoms and disability. Cognitive behavioural therapy (CBT) aims to change these perpetuating behaviours and beliefs and has shown to lead to a significant reduction of fatigue and disability.
The CBT for CFS/ME protocol studied in this thesis starts with formulating treatment goals. Patients then learn to maintain a fixed sleep-wake pattern, formulate helpful beliefs in response to fatigue, shift their attention away from symptoms and change the way they communicate about CFS/ME. This is followed by a graded activity program in which patients gradually increase physical activity. If they succeed, they resume work or study and realise other personal goals step by step.

In this thesis outcomes of CBT were studied in different groups (patients with CFS/ME and ICF), different treatment settings (tertiary treatment centre vs care implemented in a community mental health care centre), different treatment formats (self-help booklet, stepped care, CBT via internet) and at different moments in time (directly following treatment and at long term follow-up).

Long-term outcome of CBT for CFS/ ME

Chapter 2 described patients fatigue and physical functioning up to 10 years after treatment with CBT. Follow-up studies are needed to determine whether the effects of CBT for CFS/ME are sustained at long term. From the literature, it was known that up to 1,5 years after end of treatment, treatment gains were generally sustained. The study of chapter 2 addressed the question to what extent the effects of treatment were maintained up to 10 years after end of therapy.

Participants (*n* = 583) of four previously published studies on the effects of CBT for CFS/ME were contacted for a long-term follow-up assessment. Of this group, 511 completed a follow-up assessment between 21 and 125 months (*M* = 64.97, SD = 28.56) after finishing CBT (response rate 88%). They completed questionnaires assessing the main outcomes fatigue severity (Checklist Individual Strength, CIS, fatigue severity subscale) and physical functioning (Short Form Health Survey, SF-36, physical functioning subscale). At long term follow-up still 37% of the patients had fatigue scores within normal limits compared to 64% directly post-treatment. 70% of the participants were not impaired in physical functioning at long-term follow-up compared to 81% directly following treatment.

We concluded that positive effects of CBT for CFS/ME on fatigue and physical functioning were partly sustained at long term follow-up. A substantial subgroup of patients however, reported again severe fatigue. It was concluded that further research should inform us what predicts relapse or sustainment of effects of CBT. This information may be used to improve treatment and prevent relapse.

Predictors of long-term outcome after CBT for CFS/ME

In **Chapter 3** we explored which variables predicted long-term outcome after CBT for CFS/ME in a group of patients (*n* = 511) who participated in the study reported on in chapter 2. We used demographic variables, cognitive-behavioural variables thought to maintain fatigue, and variables assessing CFS/ME symptoms as predictors for outcomes at long term follow-up. The objective of the study was to predict fatigue severity, fatigue severity within normal limits, and physical functioning levels at long-term follow-up after CBT for CFS/ME.

Outcomes at long term follow-up were primarily predicted by outcomes directly post-treatment. Additionally, lower fatigue severity at long term follow-up was predicted by a shorter duration of CFS/ME symptoms and lower fatigue levels at baseline, and lower frustration in response to fatigue directly post-treatment. Fatigue scores within normal limits at follow-up was predicted by lower fatigue severity and lower levels of frustration in response to fatigue, both assessed directly post-treatment. Better physical functioning at follow-up was predicted by higher sense of control over fatigue, and better physical functioning at post-treatment, and being younger.

The positive relation between outcomes at long term follow-up and the same outcomes at post-treatment *highlights* the importance of fully maximizing the positive effects of CBT. Augmenting sense of control and lowering frustration in response to fatigue before treatment ends might help long-term sustainment of treatment outcomes. Furthermore, starting treatment sooner after diagnosing CFS/ME might be beneficial for long-term outcome.

Long-term outcome after stepped care for CFS/ME in a mental health care centre

Chapter 4 described stepped care for CFS/ME patients implemented in a community-based mental health care centre (MHC). Stepped care comprised a minimal intervention as first step, and face-to-face CBT as second step when needed. Patients were assessed pre and post stepped care and at long term follow-up.

The first objective of the study was to evaluate the effectiveness of stepped care directly following treatment and at long term follow-up. The second objective was to compare the outcomes directly following stepped care in the MHC with those of a CFS/ME specialist centre.

In the MHC sample (*n* = 123), fatigue decreased and physical functioning significantly increased following implemented stepped care. The follow-up was completed by 94 patients (78%), between 1-6 years after treatment (*M* = 4.31). Treatment effects were sustained at long term follow-up. Patients in the MHC were less improved directly following stepped care than patients in a CFS/ME specialist centre were. After stepped care, 36% (40/ 111) had fatigue scores within normal limits compared to 62% (337/ 543) in the specialist care group.

Both steps of stepped care were previously implemented and separately judged similar effective as in specialist care. However, when both interventions were combined in a stepped care format, treatment results were not optimal. Several problems with implemented stepped care were encountered that may have contributed to the differences in effect of the intervention provided in the MHC and in the CFS/ME specialist centre. Therapists had little experience with providing CBT for CFS/ME in a stepped care context and only 1/ 3 of patients who needed further therapy actually stepped up. We assumed patients who are not sufficiently treated after the first step of treatment, may be more difficult to treat during the second step of care i.e. face-to-face therapy.

In response to the encountered problems, several suggestions were made how to optimize the results of implemented stepped care.

New CBT treatment options for CFS/ME

In recent years, the traditional face-to-face CBT for CFS/ME was adapted into other treatment formats such as a booklet with self-instructions plus email contact with a therapist or group therapy. In this thesis, the efficacy of guided self-instructions was tested in patients with less severe forms of CFS/ME. We also developed an internet-based version of CBT and its efficacy was tested in patients with CFS/ME.

CBT for idiopathic chronic fatigue (ICF)

In **chapter 5**, we described a study testing the efficacy of a minimal CBT intervention for patients with ICF, operationalized as having severe fatigue but fewer than four additional symptoms and/ or only moderate levels of overall impairment. Prevalence rates of ICF are much higher than of CFS/ ME.

Primary objective of the study was to test the efficacy of the minimal intervention for patients

with ICF on fatigue severity, and overall impairment. Secondary objective was to determine whether treatment effects were moderated by the number of additional symptoms and/ or the level of baseline overall impairment.

In total 100 patients were randomized to either a self-instruction-booklet plus e-mail contact with a therapist or to a waiting list control group. Outcome measures were assessed prior to randomization, and following treatment or wait list control group of six months.

The patients who followed the minimal intervention were less fatigued, less impaired, had less psychological distress and higher levels of physical functioning compared to the wait list group at second assessment. In the treatment group, 48% (24/ 50) of patients had fatigue scores within normal limits at second assessment, compared to 20% (10/ 50) patients in the waiting list. Patients with fewer than four, or four or more additional symptoms had similar treatment gains. Patients with high baseline overall impairment had higher overall impairment scores following treatment than those with less initial overall impairment.

The findings of this study emphasize that the large group of patients meeting criteria for ICF can effectively be treated with CBT for CFS/ME. Patients with high levels of overall impairment may better be referred to face-to-face CBT directly as they profited less from a minimal intervention.

Testing the efficacy of an internet-based CBT for CFS/ME

During recent years many traditional face-to-face CBT's were transformed into e-health-interventions. E-health or internet-based versions of therapy are then used in addition to traditional forms or as a stand-alone therapy. **Chapter 6** described a study protocol for testing the efficacy of the first internet-based CBT (iCBT) for adult CFS/ME-patients, conducted in a CFS/ ME specialist centre.

It was planned to allocate 240 patients randomly to three conditions (ratio 1:1:1). Two iCBT conditions had variation in the role of the therapist and there was a wait list control group. Within the first iCBT condition, protocol-driven feedback was provided meaning the therapist sought contact with a patient following a pre-defined schedule. In the second iCBT condition, feedback on demand, feedback was only provided when patients explicitly asked for it. The intervention took six months.

Primary outcome measure was fatigue severity, assessed at six months after baseline. Secondary outcome measures were overall impairment, physical functioning, psychological distress, and the proportion of patients with clinical significant improvement in fatigue severity. It was also determined whether iCBT with feedback on demand costed less therapist time compared to iCBT with protocol-driven feedback.

Efficacy of iCBT for CFS/ME

Chapter 7 described the results of the RCT testing the efficacy of iCBT for CFS/ME according to the protocol presented in chapter six. As planned, 240 patients were randomized over two internet

conditions and the waiting list (*n* = 80 in each condition).

ICBT for CFS/ME significantly reduced fatigue severity, overall impairment and psychological distress compared to the waiting list. Physical functioning did only significantly improve in iCBT with feedback on demand. No significant differences were found between both iCBT conditions on all outcome measures. The proportion of patients that had fatigue scores within normal limits at second assessment was significantly higher in both iCBT conditions compared to the waiting list. ICBT with *feedback on demand* required less therapist time (*M* = 4h 37 m) than iCBT with *protocol-driven feedback* (*M* = 6 h 9 m). The therapy time required for both conditions was less than for face-to-face CBT as reported in the literature.

It was concluded that both iCBT conditions were efficacious and time efficient.

General discussion

This thesis showed that CBT for CFS/ME is efficacious in a larger group of severely fatigued patients than the group of patients meeting CDC criteria of CFS/ME. CBT for fatigue seems effective in patients with severe fatigue that leads to disability.

CBT leads to a reduction of fatigue and disability immediately following treatment and at long-term follow-up. For a substantial subgroup of patients, treatment gains are not sustained at long term. Several suggestions were given that may improve treatment outcome or prevent relapse.

Therapy via internet is known to have its own challenges as the role of the therapist is reduced when compared to traditional CBT provided face-to-face. The therapist can be supported by technological innovation like video calls, automated feedback and serious gaming elements.

We hope these studies will stimulate the further development of (i)CBT for chronic fatigue.

Cognitieve Gedragstherapie voor het Chronische Vermoeidheidssyndroom: Lange Termijn Follow-up en Behandeling via Internet

Nederlandse samenvatting

Het chronische vermoeidheidssyndroom (CVS), ook wel bekend onder de naam Myalgische Encefalomyelitis (ME) is een ernstige aandoening. Slechts 5% van de patiënten herstelt spontaan. CVS/ ME kan alleen worden vastgesteld op basis van door patiënten gerapporteerde symptomen. Er zijn geen somatische markers bekend die gebruikt kunnen worden voor diagnostiek van CVS/ ME. Een veelgebruikte casusdefinitie van CVS/ ME is die van de 'Centers for Disease Control and prevention (CDC)' uit de Verenigde Staten. Volgens deze casusdefinitie (die voor het laatst werd aangepast in 2003) kan er worden gesproken van CVS/ ME indien patiënten minimaal 6 maanden ernstig vermoeid zijn. Er mag geen lichamelijke verklaring zijn voor de moeheid. De vermoeidheid moet gepaard gaan met aanzienlijke beperkingen in het dagelijks leven. Patiënten moeten naast vermoeidheid last hebben van minimaal vier bijkomende klachten, uit de volgende acht: niet uitgerust wakker worden, spierpijn, gewrichtspijn, toename van klachten na inspanning, keelpijn, hoofdpijn, gevoelige klieren en geheugenklachten en/ of concentratieproblemen.

De Nederlandse gezondheidsraad schatte in 2005 het aantal CVS/ ME patiënten op 30.000 tot 40.000. In vergelijking met internationale prevalentiecijfers is de Nederlandse schatting conservatief.

Er is een groep patiënten die ook last heeft van ernstige, lichamelijk onverklaarde en chronische vermoeidheid, maar niet voldoet aan alle criteria van CVS/ ME. Zij hebben minder dan vier bijkomende klachten of relatief milde beperkingen. Deze groep wordt door het CDC beschreven als patiënten die lijden aan 'idiopathische chronische vermoeidheid' (ICV). De prevalentie van ICV is veel hoger dan van CVS/ ME.

Het cognitief-gedragsmatige model van CVS/ ME veronderstelt dat symptomen en beperkingen in stand worden gehouden door gedrag en opvattingen. Cognitieve gedragstherapie (CGT) heeft als doel de vermoeidheid en beperkingen te verminderen door verandering van gedrag en de opvattingen die de klachten in stand houden. Uit gecontroleerde en gerandomiseerde studies blijkt dat CGT leidt tot een significante afname van vermoeidheid en beperkingen.

Het CGT-behandelprotocol voor CVS/ ME dat gebruikt werd in de studies van dit proefschrift start met het formuleren van de doelen voor de behandeling. Patiënten leren vervolgens een vast-slaap-waak ritme te hanteren. Daarna oefenen zij met het formuleren van helpende gedachten in reactie op vermoeidheid en het verleggen van de aandacht van de vermoeidheid naar andere zaken. Daarnaast leren zij op een andere manier over CVS/ ME te communiceren. Hierna volgt een systematische opbouw van lichamelijke activiteit. Als het patiënten hierbij lukt hun mogelijkheden te vergroten, starten zij met het realiseren van persoonlijke doelen, zoals werk of studie. Het doel van de behandeling is herstel. Herstel wil zeggen niet langer ernstig moe meer zijn en niet langer belemmerd worden in het functioneren door vermoeidheid.

In dit proefschrift werd het effect van CGT onderzocht bij verschillende groepen (patiënten met CVS/ ME en ICV), in verschillende behandelcentra (gespecialiseerd behandelcentrum voor vermoeidheid en binnen een algemene GGZ instelling), bij verschillende behandelvormen (begeleide zelfhulp, CGT via internet en face-to-face CGT), en op verschillende momenten (direct na therapie of op lange termijn).

Lange termijn uitkomsten van CGT voor CVS/ ME

In **hoofdstuk 2** werd de ernst van vermoeidheid en het fysiek functioneren beschreven van patiënten tot 10 jaar na het afronden van CGT. Follow-up studies zijn nodig om de lange termijn effecten van CGT voor CVS/ ME te onderzoeken. Uit de literatuur was bekend dat het behandeleffect tot 1,5 jaar na afronding van CGT over het algemeen behouden blijft. De studie beschreven in hoofdstuk 2, beantwoordde de vraag in hoeverre de positieve effecten van CGT voor CVS/ ME op lange termijn behouden blijven.

Deelnemers (*n* = 583) van vier eerder gepubliceerde studies die de effecten van CGT voor CVS/ ME onderzochten, werden gecontacteerd met het verzoek mee te doen met een follow-up meting. Van deze groep vulden 511 personen een follow-up vragenlijst in (respons van 88%). De tijd tussen eind van de therapie en de follow-up meting varieerde tussen deelnemers van 21 tot 125 maanden (*M* = 64.97, SD = 28.56). Primaire uitkomstmaat was de ernst van de vermoeidheid (Checklist Individuele Spankracht, CIS, subschaal ernst ervaren vermoeidheid) en het fysiek functioneren (Rand36, subschaal fysiek functioneren). Bij de follow-up meting had 37% van de patiënten een vermoeidheidsscore binnen normaalwaarden in vergelijking met 64% direct na afronding van de therapie. Op fysiek functioneren behaalde 70% van de patiënten een score passend bij een gezond fysiek functioneren in vergelijking met 81% direct na afronding van de therapie.

Er werd geconcludeerd dat de positieve effecten van CGT voor CVS/ ME op vermoeidheid en fysiek functioneren op langere termijn gedeeltelijk behouden blijven. Echter, een substantiële groep patiënten rapporteerde weer ernstige vermoeidheid. Verder onderzoek is nodig om te begrijpen waarom sommigen het behandelresultaat weten te behouden en anderen niet. Hopelijk biedt dat vervolgonderzoek aanknopingspunten voor optimalisatie van de behandeling en het voorkomen van terugval.

Het voorspellen van de lange termijn uitkomsten na CGT voor CVS/ ME

In **hoofdstuk 3** onderzochten we welke variabelen de lange termijn uitkomsten na CGT voor CVS/ ME kunnen voorspellen. We deden dit in een patiëntengroep (*n* = 511) die ook had deelgenomen aan de studie in hoofdstuk 2. Van demografische variabelen, cognitief-gedragsmatige variabelen die worden beschouwd als mogelijke in stand houdende factoren van vermoeidheid, en de symptomen van CVS/ ME werden nagegaan of zij de lange termijn uitkomsten van CGT konden voorspellen. Het doel van de studie was het voorspellen van de ernst van vermoeidheid op lange termijn, maar ook een vermoeidheidsscore binnen normaalwaarden en het niveau van fysiek functioneren, eveneens op lange termijn.

De uitkomsten op lange termijn werden voornamelijk voorspeld door de uitkomsten direct na afronding van de CGT. Daarnaast werd een lagere vermoeidheidsscore op lange termijn voorspeld door een kortere duur van CVS/ ME symptomen en minder ernstige vermoeidheid bij aanvang van de therapie en geringere gevoelens van frustratie in reactie op vermoeidheid direct na afronden van de CGT. Vermoeidheid binnen normaalwaarden werd voorspeld door minder ernstige vermoeidheid en minder gevoelens van frustratie in reactie op vermoeidheid, beiden gemeten direct na afronding van de CGT. Beter fysiek functioneren op lange termijn werd voorspeld door het idee controle te hebben over de vermoeidheid alsmede door een beter fysiek functioneren, beide direct na afronding van de behandeling. Ook leeftijd bleek een voorspeller. Patiënten die jonger waren hadden een beter fysiek functioneren op langere termijn.

De positieve relatie tussen lange termijn uitkomsten en scores op dezelfde uitkomstmaten direct na CGT, suggereert dat het van belang is zo lang door te behandelen tot er geen verdere verbetering meer optreedt in moeheid en beperkingen. Het nog meer versterken van de opvatting dat de patiënt invloed kan hebben op de moeheid, naast het verminderen van gevoelens van frustratie in reactie op vermoeidheid tijdens CGT, draagt mogelijk bij aan behoud van het behandelresultaat. Eerder starten met CGT, liefst direct na het diagnosticeren van CVS/ ME, kan waarschijnlijk ook de lange termijn effecten van CGT verbeteren.

Lange termijn uitkomsten van getrapte zorg voor CVS/ ME in een GGZ-instelling

Hoofdstuk 4 beschreef getrapte zorg voor CVS/ ME-patiënten, geïmplementeerd in een GGZ instelling. De getrapte zorg bestond uit een minimale interventie als eerste stap en face-to-face CGT als tweede stap indien nodig. Voor en na getrapte zorg, en bij de lange termijn follow up werd de ernst van de vermoeidheid en beperkingen gemeten.

Het belangrijkste doel van de studie was het vaststellen van de effectiviteit van getrapte zorg, gemeten direct na behandeling en op lange termijn. Daarnaast werden de resultaten van getrapte zorg in de GGZ-instelling vergeleken met de behandelresultaten van CGT in een gespecialiseerd CVS/ ME centrum.

Getrapte zorg in de GGZ-instelling (*n* = 123) resulteerde in een significante afname van vermoeidheid en een significante verbetering van het fysiek functioneren. De follow-up meting was ingevuld door 94 patiënten (78%), gemiddeld 4.31 jaar na behandeling met een spreiding van 1 tot 6 jaar. Het behandelresultaat bleek behouden bij de lange termijn follow up.

Patiënten in de GGZ-instelling die getrapte zorg hadden gevolgd verbeterde minder dan patiënten die CGT ontvingen in een gespecialiseerd CVS/ ME-centrum. Na getrapte zorg had 36% (40/ 111) van de patiënten een vermoeidheidsscore binnen normaalwaarden. Na CGT in het gespecialiseerde CVS/ ME-centrum behaalde 62% van de patiënten (337/ 543) dat resultaat. Na getrapte zorg in GGZ-instelling herstelden weliswaar minder patiënten. Echter, de patiënten die hersteld waren lieten weinig terugval zien op de lange termijn.

Beide stappen van getrapte zorg -de minimale interventie en de face-to-face CGT- zijn eerder als losstaande interventies geïmplementeerd in de GGZ en vergeleken met eenzelfde behandeling in een gespecialiseerd CVS/ ME-centrum. Geïmplementeerde zorg bleek niet minder effectief dan zorg in een gespecialiseerd CVS/ ME centrum. Het huidige onderzoek laat zien dat het gecombineerd aanbieden van beide behandelstappen in de vorm van getrapte zorg leidde tot een suboptimaal behandeleffect direct na behandeling.

Verschillende problemen hebben mogelijk een rol gespeeld bij het verschil in effect tussen getrapte zorg in een GGZ-instelling en CGT in een gespecialiseerd CVS/ ME-centrum. Ten eerste hadden therapeuten weinig ervaring met het geven van face-to-face CGT aan patiënten die nog onvoldoende hadden geprofiteerd van de eerste stap van getrapte zorg. Mogelijk dat deze patiënten moeilijker te behandelen zijn. Ten tweede stroomde maar 1/ 3 van de patiënten die verdere hulp nodig had door naar de volgende stap van zorg; de face-to-face CGT. Er werden verschillende suggesties gedaan voor het verbeteren van de effectiviteit van getrapte zorg voor CVS binnen een GGZ-instelling.

Nieuwe behandelopties voor CVS/ ME

In de afgelopen jaren is de face-to-face CGT voor CVS/ ME omgezet naar andere behandelvormen. Voorbeelden hiervan zijn begeleide zelfhulp bestaande uit een boekje met zelf-instructies gecombineerd met emailcontacten met een therapeut en groepstherapie. In dit proefschrift is de effectiviteit van begeleide zelfhulp getoetst in patiënten met een mildere vorm van CVS/ ME, Idiopathische Chronische Vermoeidheid (ICV). Daarnaast werd een internet variant van CGT voor volwassenen met CVS/ ME ontwikkeld (iCGT). De effectiviteit van iCGT werd onderzocht in een gerandomiseerde en gecontroleerde studie.

CGT voor idiopathische chronische vermoeidheid (ICV)

In **hoofdstuk 5** werd een studie beschreven waarin de effectiviteit van een minimale CGT interventie (zelf-instructies) voor ICV werd onderzocht. Er wordt van ICV gesproken als patiënten chronisch en ernstig vermoeid zijn zonder dat er een lichamelijke oorzaak bekend is, maar minder dan vier bijkomende klachten hebben en/ of minder beperkingen rapporteren dan CVS/ ME patiënten. De prevalentie van ICV in de algemene bevolking is veel hoger dan van CVS/ ME.

De studie testte de effectiviteit van de minimale interventie voor ICV-patiënten. Tevens werd onderzocht of het behandelresultaat verschillend was voor patiënten met veel bijkomende klachten en/ of met meer beperkingen. De primaire uitkomstmaten waren ernst van de vermoeidheid en de hoeveelheid beperkingen. Secundaire uitkomstmaten waren psychisch welbevinden, fysiek functioneren en het scoren binnen normaalwaarden wat betreft vermoeidheid.

Er werden 100 patiënten gerandomiseerd. De helft van deze patiënten volgde begeleide zelf-behandelinstructies en de andere helft vormde de wachtlijstgroep. De uitkomstmaten werden gemeten vóór randomisatie en direct na de behandeling of de wachtperiode.

De patiënten die de minimale interventie hadden gevolgd waren significant minder vermoeid, minder beperkt, en scoorden hoger op psychisch welbevinden en fysiek functioneren in vergelijking met de patiënten uit de wachtlijstgroep. In de behandelgroep had 48% (24/ 50) van de patiënten een vermoeidheidsscore binnen normaalwaarden na behandeling in vergelijking met 20% (10/ 50) van de patiënten van de wachtlijstgroep. Patiënten met minder dan vier bijkomende klachten hadden dezelfde behandelresultaten als patiënten met meer dan vier bijkomende klachten. Patiënten met veel beperkingen vóór behandeling hadden ook meer beperkingen na behandeling.

De resultaten van deze studie laat zien dat een grote groep patiënten met ICV effectief kan worden behandeld met CGT voor CVS/ ME. Patiënten met veel beperkingen kunnen beter direct worden doorverwezen voor face-to-face CGT omdat zij minder profiteerden van de minimale interventie.

Onderzoek naar het effect van CGT via internet voor CVS/ ME

Tot voor kort werd CGT meestal face-to-face aangeboden. In de afgelopen jaren zijn veel CGT behandelingen omgevormd tot e-health varianten. E-health of therapie via internet wordt in de praktijk gebruikt als aanvulling op bestaande vormen van therapie of als een op zichzelf staande therapie. **Hoofdstuk 6** beschreef een studieprotocol van een effectiviteitsstudie naar de eerste CGT via internet voor volwassen CVS/ ME-patiënten, uitgevoerd in een gespecialiseerd behandelcentrum.

Er zouden 240 patiënten worden gerandomiseerd naar drie condities (ratio 1:1:1). Er waren twee internet-CGT (iCGT) condities met variatie in de rol van de therapeut en er was een wachtlijstgroep. In de eerste iCGT-conditie, ‘feedback volgens protocol’, zocht een therapeut contact met een patiënt volgens een vooraf vastgesteld schema. In de tweede iCGT-conditie, ‘feedback op aanvraag’, werd feedback alleen gegeven als patiënten daar expliciet om vroegen. De interventie duurde zes maanden.

De primaire uitkomstmaat was ernst van vermoeidheid, gemeten zes maanden na de voormeting. Secundaire uitkomstmaten waren de mate van beperkingen, fysiek functioneren, psychisch welbevinden, en de proportie patiënten met vermoeidheidsscores binnen normaalwaarden. Er werd ook bepaald of iCGT met feedback op aanvraag minder tijd van therapeuten kostte in vergelijking met iCGT met feedback volgens een vooraf vastgesteld schema.

De effectiviteit van iCGT voor CVS/ ME

Hoofdstuk 7 beschreef de uitkomsten van de studie naar de effectiviteit van iCGT voor CVS/ ME. Zoals gepland werden 240 patiënten gerandomiseerd over twee internet condities en een wachtlijst groep (n = 80 in elke conditie).

Vergeleken met de wachtlijstgroep resulteerde iCGT voor CVS/ ME in een significante afname van de ernst van vermoeidheid en beperkingen en een toename aan psychisch welbevinden. Fysiek functioneren verbeterde alleen significant in de iCGT-conditie met feedback op aanvraag.

Tussen beide iCGT-condities werden verder geen significante verschillen gevonden op de hiervoor genoemde uitkomstmaten. De proportie patiënten met een vermoeidheidsscore binnen normaalwaarden was in beide internetcondities significant hoger dan in de wachtlijstgroep.

Er bleek minder therapeutentijd nodig voor iCGT met feedback op aanvraag (gemiddeld ongeveer 4,5 uur) dan voor iCGT met feedback volgens protocol (gemiddeld iets meer dan 6 uur). De benodigde therapeutentijd voor het geven van iCGT is minder dan beschreven in de literatuur voor traditionele face-to-face CGT.

Geconcludeerd werd dat beide iCGT condities effectief en tijdsefficiënt waren.

Algemene discussie

Dit proefschrift liet zien dat CGT voor CVS/ ME effectief is in een grotere groep van chronisch vermoeide patiënten dan alleen de groep van patiënten die voldoen aan de CDC criteria voor CVS/ ME. CGT voor vermoeidheid blijkt effectief voor patiënten met ernstige, lichamelijk onverklaarde vermoeidheid die leidt tot beperkingen, ook als patiënten niet voldoen aan de andere criteria van CVS/ ME.

CGT leidt tot een afname van vermoeidheid en beperkingen direct na beëindiging van therapie en op lange termijn. Een relatief groot aantal patiënten blijkt echter weer ernstig moe te worden op lange termijn. Verschillende suggesties werden gegeven die kunnen helpen het behandelresultaat te verbeteren en/ of terugval te voorkomen.

Therapie via internet kent zijn eigen uitdagingen, onder meer omdat de rol van de therapeut beperkter is dan in een traditionele face-to-face CGT. Met iCGT kan de therapeut worden ondersteund door technologische innovaties zoals beeldbellen, automatische feedback en ‘serious gaming’ elementen.

We hopen dat de studies uit dit proefschrift de verdere ontwikkeling van (i)CGT voor CVS/ ME zal stimuleren.

Contribution of authors

Chapter 2 Janse A., Nikolaus S., Wiborg J.F., Heins, M., van der Meer, J.W.M., Bleijenberg, G., Tummers, M., Twisk, J., Knoop, H. (2017). Long-term follow-up after cognitive behaviour therapy for chronic fatigue syndrome. *Journal of Psychosomatic Research.* 97:45-51. doi: 10.1016/j.jpsychores.2017.03.016.

AJ was the primary investigator together with SN. Both were responsible for data collection and analysis. JT was consulted for statistical advice. HK supervised the study. AJ and SN drafted the article, which was critically revised by JFW, MH, JWMM, GB, MT and HK. All authors have read and approved the final manuscript.

Chapter 3 Janse A, Bleijenberg G, and Knoop H. (2019) Prediction of long-term outcome after cognitive behavioral therapy for chronic fatigue syndrome. *Journal of Psychosomatic Research*. 121: p. 93-99. doi: 10.1016/j.jpsychores.2019.03.017

AJ was the primary investigator and responsible for data collection and analysis. HK supervised the study. AJ drafted the article, which was critically revised by HK and GB. All authors have read and approved the final manuscript.

Chapter 4 Janse, A., van Dam, A., Pijpers, C., Wiborg, J.F., Bleijenberg, G., Tummers, M., Twisk, J., Nikolaus, S., Knoop, H. (2019). Implementation of stepped care for patients with chronic fatigue syndrome in community-based mental health care: outcomes at post-treatment and long-term follow-up. *Behavioural and Cognitive Psychotherapy.* 47(5): p. 548-558. doi: 10.1017/S1352465819000110

AJ was primary investigator and responsible for analysis. AD, CP, JFW and MT were responsible for data collection. JT was consulted for statistical advice. HK supervised the study. AJ drafted the article, which was critically revised by AD, JFW, GB, MT, JT, SN and HK. All authors have read and approved the final manuscript.

Chapter 5 Janse, A., Wiborg, J.F., Bleijenberg, G., Tummers, M., & Knoop, H. (2016). The efficacy of guided self-instruction for patients with idiopathic chronic fatigue: A randomized controlled trial. *Journal of Consulting and Clinical Psychology, 84*(5), p. 377-388. doi:10.1037/ccp0000085

GB and HK designed the study. Together with MT, AJ was responsible for data collection. AJ was responsible for analysis and drafted the article, which was critically revised by JFW, GB, MT, and HK. JFW and HK supervised the study. All authors have read and approved the final manuscript.

Chapter 6 Janse, A., Worm-Smeitink, M., Bussel-Lagarde, J., Bleijenberg, G., Nikolaus, S., & Knoop, H. (2015). Testing the efficacy of web-based cognitive behavioural therapy for adult patients with chronic fatigue syndrome (CBIT): study protocol for a randomized controlled trial. *BioMed Central Neurology*, 15, 137. doi: 10.1186/s12883-015-0392-3

AJ was the primary investigator and responsible for data collection and analysis. AJ drafted the article, which was critically revised by MWS, JBL, GB, SN and HK. The original idea to vary the role of the therapist originates from GB and HK. The intervention was developed by AJ, JBL, GB, and HK. All authors have read and approved the final manuscript.

Chapter 7 Janse, A., Worm-Smeitink, M., Bleijenberg, G., Donders, R., Knoop, H. (2018). Efficacy of web-based cognitive-behavioural therapy for chronic fatigue syndrome: randomised controlled trial. *British Journal of Psychiatry* 212(2): p. 112-118. doi: 10.1192/bjp.2017.22

AJ was the primary investigator and responsible for data collection and analysis. HK, AJ and GB developed the intervention. HK designed and supervised the study. AJ drafted the article, which was critically revised by MWS, GB, RD and HK. All authors have read and approved the final manuscript.

PhD portfolio

Name PhD student : Antheunis Lein Janse
PhD period : September 2012 – December 2019
Name PhD supervisor : Prof. dr. Hans Knoop & Prof. dr. Gijs Bleijenberg (Radboudumc)

	Year	ECTS
Basiscursus Regelgeving Klinisch Onderzoek (BROK), NFU	2013/2017	2.5
Endnote workshop, Radboudumc	2013	0.1
Specific courses		
Academic writing	2016	1.5
Seminars, workshops and master classes	N/A	N/A
Presentations		
'*Efficacy of web-based CBT for CFS.*' PsyQ, National policy meeting, Noordwijk, (poster)	2017	0.25
Congress VGCT, Veldhoven, (laptop presentation and visitor)	2016	0.75
Efficacy of web-based CBT for CFS.' Annual Health meeting, Amsterdam, (poster)	2016	0.5
'*The role of the partner and relationship satisfaction in treatment outcome of patients with chronic fatigue syndrome.*' European Health Psychology Society (EHPS) Conference, Limassol, Cyprus, (oral)	2015	1.0
International Congress of Behavioural Medicine (ICBM), Groningen, (oral)	2014	0.5
'*CBT for CFS: new research findings and future treatment options*', Research meeting department of Clinical Psychology, Radboud University, Nijmegen, (oral)	2014	0.2
'*Guided self-instruction for idiopathic chronic fatigue. The (ir)relevance of case definitions.*' VNO-ChroVer, Nijmegen, (oral)	2014	0.5
'*Project "Grip op klachten". Recovery of CFS with the help of e-CBT.*' National annual meeting of Soma & Psyche, PsyQ, (oral)	2014	0.5
'*Guided self-instruction for idiopathic chronic fatigue.*', Congress of the European Association for Behavioural and Cognitive Therapies (EABCT), Marrakech, Morocco, (oral)	2013	0.5
'*Web-based CBT for CFS: treatment of the future?*' VNO-ChroVer, Nijmegen, (oral)	2013	0.5
'*Internet therapy for chronic fatigue syndrome patients and options to personalize healthcare.*' Science day, Nijmegen Centre for Evidence Based Practice (NCEBP), Nijmegen, (laptop presentation)	2013	0.25
'*Web-based CBT for CFS.*' Congress VGCT, Veldhoven, (oral)	2013	0.5
(Inter)national conferences		
VGCT congress, Veldhoven, (visitor)	2009-2017	2.5
Other		
Weekly research meeting	2012-2016	5

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Curriculum Vitae

Anthonie Janse werd geboren op 1 juni 1986 te Delft en groeide op in Naaldwijk. In 2004 behaalde hij zijn atheneum diploma (Interconfessionele Scholengemeenschap Westland) te Naaldwijk. Datzelfde jaar verhuisde hij naar Nijmegen voor start van de opleiding psychologie. Na afronding van de bachelor Gerontologie, koos hij voor de bachelor Klinische psychologie. Tijdens dat 'overgangsjaar' werkte hij naast zijn studie als onderzoeksassistent aan onderzoek naar trauma (binnen het Behavioural Science Institute van de Radboud Universiteit). In 2010 heeft hij een masterdiploma Klinische Psychologie behaald. Een klinische stage bij Hendriks en Roosenboom (2e lijns-zorg, Arnhem) was onderdeel van deze master. Hij schreef een masterthesis over de plek van mindfulness binnen Acceptance en Commitment Therapy in vergelijking met Mindfulness Based Cognitive Therapy.

In 2011 is Anthonie aangenomen als therapeut bij het Nederlands Kenniscentrum Chronische Vermoeidheid te Nijmegen. Vanaf dat moment startte hij met het opleidingstraject tot cognitief gedragstherapeut VGCt waarvoor hij in de jaren daarna cursus, supervisie en leertherapie volgde. Vanaf september 2012 kreeg hij ook een parttime aanstelling als promovendus. Centraal bij dit promotie onderzoek stond de ontwikkeling en het testen van een online cognitieve gedragstherapie voor patiënten met het chronische vermoeidheidssyndroom.

Momenteel werkt Anthonie bij GGNet als psycholoog binnen een vroeg interventie team psychose te Doetinchem en bij BAS basisGGZ te Zevenaar. Hij is kartrekker van de inzet van o.a. Virtual Reality en andere technologie binnen therapie. Anthonie heeft de basisregistratie voor het doen van Eye Movement Desensitisation and Reprocessing (EMDR). Ter voorbereiding op een GZ-opleidingsplaats heeft hij een traineeship voor basispsychologen gevolgd. Daarnaast heeft hij recent zijn registratie behaald als cognitief gedragstherapeut VGCt. In september 2020 start hij met de GZ-opleiding.

Anthonie leeft samen met Anky Hermans. Zij hebben een zoon (Joppe van bijna 4) en een dochter (Floor van 10 maanden).