Cognitive behaviour therapy *for* chronic fatigue syndrome

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Pars sanitatis velle sanari fuit

gezond willen worden is een deel der genezing

Lucius Annaeus Seneca

(uit: tragedie Phaedra)

aan mijn ouders

aan Peter

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Chapter 1

General introduction

General introduction

Diagnosing chronic fatigue syndrome

From 1990, the Nijmegen Fatigue Research Group of the University Medical Centre Nijmegen studied chronic fatigue syndrome (CFS). In the beginning, studies of CFS were limited by lack of proper diagnostics and different working case definitions[1,2]. The first objective of our interdisciplinary study group was to develop multidimensional assessment methods[3]. Nine dimensions were identified, measuring emotional, behavioural, cognitive and social functioning and each providing a unique contribution to the assessment of CFS. In this study the use of different methods in the multidimensional assessment was advised.

In 1994 the Nijmegen Fatigue Research Group contributed to the development of international guidelines for the clinical evaluation and study of fatigued persons[4]. In the revised and until now latest case definition, CFS is characterised by persistent or relapsing unexplained chronic fatigue, lasting for at least six months, of new or definite onset, not the result of an organic disease or ongoing exertion, not alleviated by rest, and resulting in substantial reduction in previous levels of occupational, educational, social and personal activities. Several additional criteria were specified.

Our outpatient clinic has seen large numbers of patients suffering from chronic fatigue, both in the context of outpatient care and within the framework of scientific research. In both settings guidelines and measuring instruments had been developed to help improve CFS diagnostics. In our scientific studies patients filled out questionnaires to establish whether they meet the operational and CDC *(Centers for Disease Control)* criteria for CFS. At our outpatient clinic, a chronic fatigue protocol was applied[5,6]. Nevertheless, clinicians still voiced difficulty in diagnosing CFS, because there is no known organic substrate and there is debate as to which medical examinations are needed to exclude physical causes for the fatigue symptoms. Also, the criteria on the basis of which the physician could establish the severity of the fatigue and functional impairment were a matter of discussion.

Chronic fatigue syndrome: initiating and perpetuating factors

Several somatological and psychosocial hypotheses concerning the aetiology of CFS were explored[7,8]. In clinical, microbiological and immunological studies, causes for CFS were not found[9-15]. Up to now, the nature of the initial pathology is still poorly understood[16]. Longitudinal research pointed out that most patients do not recover[17,18]. Since causal factors were absent and the prognosis of CFS turned out to be poor, the attention of our studies for perpetuating factors was further elaborated. The discrimination between precipitating and perpetuating factors opened up hypotheses with regard to somatic and psychological factors. The possibility exists that a somatic event may have triggered the symptoms. Psychological processes appeared to be involved in the perpetuation of complaints in CFS patients[19]. These processes involved ideas of patients concerning complaints (cognitions) and

behavioural factors such as persistent avoidance of activities associated with an increase in symptoms. A strong focus on bodily symptoms, low levels of physical activity and a poor sense of control contributed to an increase in the severity of the fatigue and functional impairment. Strong somatic attributions indirectly influenced fatigue, via lower levels of physical activity. Most factors in the model of perpetuating factors in CFS were found in other studies as well[20,21]. However, the model also had its limitations. The focus was on complaint-related cognitions and behaviours. Cognitions and behaviours concerning the patient's surroundings were not included, although perceived social support and the relationship with doctors may also be of importance in the perpetuation of CFS.

Cognitive behaviour therapy for chronic fatigue syndrome

Obscurity about the cause of CFS is not necessarily an obstruction for an effective treatment. In 1994 our first case study of a CFS patient treated with cognitive behaviour therapy was published[22]. Since the results in clinical practice were promising, a preliminary treatment protocol for cognitive and behavioural interventions was developed[23]. In the meantime no pharmacological treatments had proven to be effective[24,25] and the model of perpetuating factors in CFS had shown causal relations between perpetuating factors and complaints[19]. These findings were a good starting point for further elaboration of evidence-based cognitive behavioural treatment. Cognitive behaviour therapy (CBT) is a general form of psychotherapy directed at changing condition-related cognitions and behaviours. In controlled studies CBT appeared to be effective in conditions such as panic disorder, depression, obsessive-compulsive disorder (OCD) and irritable bowel syndrome (IBS)[26-30]. CBT is directed at cognitions and behaviours relevant for each specific disorder, which implies that CBT for depression is not the same as CBT for IBS or CBT for OCD. CBT for depression appeared to be not effective for CFS patients[31]. In our opinion, this finding was not surprising, since clear differences between depressed CFS patients and patients with a major depression were found[32]. In an uncontrolled study effect of CBT for CFS was found in 22 of 27 patients[33]. CBT was directed at increasing self-efficacy and performing activities that were avoided for a long time. In 80% of the treated CFS patients this effect was sustained over four years[34]. In the first randomised controlled trial (RCT), both CBT and medical treatment were combined with immunotherapy or placebo[35]. Results were disappointing. None of the groups treated had a larger effect than those receiving the standard medical treatment. In our view, CBT was too short, not stand-alone treatment and due to the combination with immunotherapy or placebo the somatic attributions were aggravated rather than reduced.

In 1995 we applied a grant proposal for a multicentre randomised controlled trial of CBT for patients with CFS. Shortly after the start of the trial in 1996 another RCT was published showing the effectiveness of CBT compared to medical care[36]. CBT consisted of 16 weekly sessions within four months. Therapy was directed at

changing cognitions and a gradual increase in activity. The controls received standard medical care, mainly consisting of reassurance that no organic disease had been diagnosed. Twelve months later, at follow-up, 73 percent of the CFS patients treated with CBT showed significant improvement in daily functioning as measured by the Karnofsky scale, a global rating of the performance status. Improvement mostly occurred during the follow-up period, which can be best explained from the relatively short treatment duration. A period of four months seems rather short to extend the building up of activity to work rehabilitation. The rating of the Karnofsky scale is largely determined by being active in work. However, since the control group did not receive any treatment, it remained unclear whether the treatment effect was to be attributed to elements of the CBT or to non-specific factors such as attention by the therapist.

One year later three other RCT's were published, in which CBT was compared to other treatments[37-39]. A controlled study of Deale and colleagues has ascertained that effects of CBT may not be attributed to non-specific treatment factors solely[37]. CBT and relaxation therapy, both consisting of an average of 13 sessions spread over six months, were compared. The CBT was educational in nature with an emphasis on behavioural changes. Not until the patient had made certain advances in his or her activity levels was cognitive restructuring started. The relaxation therapy entailed progressive muscle relaxation, visualisation and exercises inducing rapid relaxation. Sixty CFS patients were randomly assigned to CBT or relaxation therapy. Patients treated with CBT improved more on functional impairment and fatigue than patients treated with relaxation therapy. Improvements were sustained over six months of follow-up. After conclusion of the CBT the somatic attributions were unchanged and they were not found to predict a poorer outcome. Attitudes towards the avoidance of activity had changed in the CBT group, but not in the control group. This change coincided with a positive treatment outcome[40]. The condition of the immune system did not change during the treatment, nor was it predictive of improvement following CBT[41]. A major methodological limitation of this study was that one therapist performed all therapies of both kinds.

In a randomised controlled study Fulcher and White compared graded exercise therapy (GET) with a combined therapy of flexibility exercises and relaxation therapy, both consisting of weekly sessions in a period of twelve weeks[38]. Whereas the rationale for most types of CBT for CFS is fear and avoidance of activity, the experimental treatment was based on a physiological model of deconditioning. Patients weekly worked on their physical condition. Patients treated with GET reported significantly more improvement than the patients treated with relaxation and flexibility exercises. It was not possible to establish the effects of therapy at follow-up, because more than half of the patients crossed over from flexibility exercises to GET. Striking in this study was a selection-bias of the patients. Forty-one percent was treated preceding the study as a result of psychiatric co-morbidity. Wearden et al.[39] studied the effects of the anti-depressive drug fluoxetine or a placebo both with and

without GET. No placebo was offered for GET. Merely one-third of the patients completed the 6-months treatment program. More dropouts were present among those who had been prescribed GET. Nevertheless, GET showed significant improvement with regard to fatigue and functional impairments, whereas the effect of fluoxetine was not significant.
In 2000 in a review, CBT and GET were found to be the only effective treatments for CFS patients[16]. However, it was questioned whether the results could be generalised outside specialist centres where only a few highly skilled therapists, or even a single therapist[37], administered CBT.

Outline of the thesis
The studies presented in this thesis are primarily concerned with the effectiveness of cognitive behaviour therapy for CFS patients and factors influencing the outcome in CFS patients with and without treatment.
For these studies, between October 1996 and January 1998 all patients with a major complaint of fatigue referred to the outpatient clinic of general internal medicine of the University Medical Centre Nijmegen were clinically evaluated by physicians using a standardised protocol and also screened for CFS criteria by computerised assessment (MID TestOrganizer). Considering the above-mentioned problems of clinicians in diagnosing CFS, we asked the question whether the CFS diagnoses resulting from both methods were consistent. We were especially interested in the extent to which there is agreement on the diagnosis of CFS between physicians using the chronic fatigue protocol and researchers evaluating the computerised questionnaires. This study is presented in *Chapter 2*.
Studying CBT for CFS, we first asked the question whether the treatment protocol for CFS patients was successful in systematic evaluation of several case studies. Multidimensional assessments of outcome measures and process variables at baseline, after treatment and during follow-up were made to compare the results to the data of healthy controls and to shed light on the criteria for clinical significant improvement. In one of these case studies the treatment protocol developed by our research group, which has many in commons with the treatments by Sharpe[36] and Deale[37] is extensively described. This study is presented in *Chapter 3*.
Our next investigations dealt with the effectiveness of CBT for CFS in a randomised-controlled trial. In a multicentre study, we questioned the effectiveness of CBT, administered by 13 behaviour therapists of three different disciplines in three different settings, compared to guided support groups and natural course. None of the therapists was familiar with CBT for CFS at the start of the trial. The treatment protocol was further refined and consisted of 16 sessions. In the initial sessions impeding cognitions are dealt with. Subsequently, recognising and respecting limits is practised, and finally, increasing the activity levels becomes the central component. Main goal of the treatment was full recovery, supplementary objective being return to the workplace. The multicentre randomised controlled trial is described in *Chapter 4*.

In the RCT the role of perpetuating factors in treatment outcome was also studied. We addressed the question if the perpetuating factor physical activity could be defined by means of intra-individual physical activity patterns. In clinical practice we observed that part of the CFS patients was characterised by profound physical inactivity. Other patients were far more active but nevertheless judged themselves as rather inactive. We tested whether patients' self-reported long-term inactivity after exertion as well as large day-to-day fluctuations in activity and pervasive inactivity could be substantiated by a behavioural measure of activity. This study is presented in *Chapter 5*.

We addressed the questions which other factors of interest for the persistence of CFS complaints in patients with and without treatment could be identified. CFS frequently has been associated with psychiatric disorders. Obstacles in clarifying the role of psychiatric disorders in CFS arise from overlap between symptoms of CFS and psychiatric disorders like depression. Over- or underdiagnosis of psychiatric disorders may be the result. As predictors of outcome in the prognosis of CFS patients psychiatric disorders have shown conflicting results. These issues raise questions about the impact of psychiatric disorders on the effectiveness of CBT for CFS. The prevalence of lifetime or current psychiatric disorders among CFS patients and the role of psychiatric co-morbidity in treatment outcome are described in a study presented in *Chapter 6*.

Another factor possibly influencing treatment outcome was financial benefit. In the Deale et al. RCT[37] poor outcome was associated with making a new claim for disability-related benefit during CBT. In clinical practice we noticed that progress during CBT was slow and recovery often absent in patients engaged in legal procedures for financial benefits. Consequently, the treatment outcome of CFS patients with claims for disease-related financial benefits was studied. These results are presented in *Chapter 7*.

In former studies of the Nijmegen Fatigue Research Group, the social environment of CFS patients received little attention. Although we pay attention to environmental reactions in the treatment protocol of CBT for CFS, we are not familiar with the role of social support in the persistence of CFS. The research questions were the comparison of social support in CFS patients with other patient groups, the course of social support in patients with and without treatment and the role of social support as a predictor of CFS complaints. This study is presented in *Chapter 8*

The general practitioner is part of the social environment too. The role of the general practitioner seems especially important, because often the general practitioner is the first professional confronted with the complaints of chronic fatigue. How this first consultation passes off may determine the future course of the CFS patient considerably. We were interested in the use of the diagnosis CFS by general practitioners, their reactions to self-diagnosis and their opinion about the communication with CFS patients, as well as the patients' opinions about general practitioners. This study is presented in *Chapter 9*.

If the effectiveness of CBT for CFS patients is proven, transfer of the treatment from CFS research clinics to mental health institutes is essential to increase accessibility of CBT for more CFS patients in the future. One of the questions was if the treatment protocol of CBT for CFS could be transferred to therapists outside university medical settings. This was studied by checking if therapists had stuck to the standardised treatment and by questionnaires to reveal the therapists' opinion of the treatment. This study is presented in *Chapter 10*.
Implementation of CBT for CFS not only depends on transferability of the treatment to other therapists, but also on the economic evaluation of the intervention. Before CBT for CFS can be implemented in day to day health care practice, information about cost-effectiveness is desirable. A cost-effectiveness analysis was an integral part of the effectiveness study. This study is presented in *Chapter 11*.
The results of the presented studies, practical implications and directions for future research will be discussed in *Chapter 12*.

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Chapter 2

Diagnosing chronic fatigue syndrome: comparison of a protocol and computerised questionnaires

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Diagnosing chronic fatigue syndrome: comparison of a protocol and computerised questionnaires

Abstract

Background In the context of outpatient care and within the framework of scientific research, guidelines and measuring instruments have been developed to help improve CFS diagnostics. The purpose of this study was to measure the agreement between the evaluations of chronically fatigued patients by physicians using a CFS protocol and by researchers using computerised questionnaires.

Methods The sample consisted of 516 patients referred to an internal medicine outpatient clinic with complaints of chronic fatigue. Retrospectively the medical records and the computerised questionnaires were checked separately and compared to see whether the criteria for diagnosis of CFS had been met. In addition, the reasons for not diagnosing CFS were evaluated.

Results Agreement between the physicians' and the researchers' evaluations was 84%. Disagreement mostly concerned severity of fatigue and functional impairment, or premorbid exclusion criteria. A physical cause for the chronic fatigue was only found in 3% of the cases.

Conclusions For physicians questionnaire assessment may be complementary to the CFS protocol in optimising the process of diagnosing CFS.

Introduction

In recent years we have seen a rise in the diagnosis of chronic fatigue syndrome (CFS). A comparison of studies investigating the prevalence of CFS has revealed that general practitioners diagnose CFS more often than a decade ago. In 1993 27% of GPs never diagnosed CFS[1]. In a similar study in 1999 this percentage had dropped to 13%. However, despite this increase in diagnosing CFS, many clinicians still have difficulty in making this diagnosis, among other reasons because there is no known organic substrate. The international criteria that have facilitated scientific research[2] have not been validated for individual patients and are thus less appropriate for use in clinical practice. There is a debate among medical professionals, for instance, as to which medical investigations are needed to exclude physical causes of the symptoms of fatigue. Also, the criteria on the basis of which the physician can establish the severity of the fatigue and functional impairment are a matter of discussion.

During the last decade our outpatient clinic has seen large numbers of patients suffering from chronic fatigue, both in the context of outpatient care and within the framework of scientific research. In both settings guidelines and measuring instruments have been developed to help improve CFS diagnostics[3,4]. At our outpatient clinic a chronic fatigue protocol is applied[5]. In our scientific studies patients fill in several computerised questionnaires to establish whether they meet the operational and Centers for Disease Control (CDC) criteria for CFS[6].

In this paper we report a retrospective study aimed at establishing the extent to which there is agreement on the diagnosis of CFS between physicians using the chronic fatigue protocol and researchers evaluating the computerised questionnaires.

Methods

Patients and procedure

The sample consisted of all patients referred to the general internal medicine outpatient clinic of the University Medical Centre St Radboud in Nijmegen with complaints of chronic fatigue between October 1996 and January 1998. These patients were screened according to the CFS protocol. The protocol included an extensive anamnesis administered by the attending physician, frequently a resident in internal medicine, followed by a medical examination and a restricted number of laboratory tests. This consultation lasted approximately one hour. Subsequently, after a trained nurse had instructed the patient on how to operate the computer, the patient was requested to fill in the questionnaires on a computer in a separate consulting room, which took about 30 minutes. The nurse remained available throughout the procedure for any questions. After four weeks the patient was called in for a second consultation during which the physician explained the findings of the clinical examination. The diagnosis of CFS was based solely on the physician's judgment of these clinical findings. The outcome of the questionnaire assessment was used later to select CFS patients eligible for a randomised controlled trial[6] and was not taken into account in the clinical judgment.

CFS protocol

To streamline and facilitate CFS diagnostics in patients referred with complaints of chronic fatigue, a CFS protocol for outpatients was developed containing guidelines for both the anamnesis and physical examinations as well as supplementary diagnostics.

CFS is defined as a self-reported fatigue that has lasted more than six months, is irrespective of physical exertion, leads to severe functional impairment, and where there is no medical explanation for the symptoms. For a diagnosis of CFS to be made, the physician needs to answer the following questions: Can a somatic explanation for the symptoms be excluded? Is this a case of severe fatigue associated with serious limitations in the patient's professional, social and/or personal functioning? Have the symptoms and impairments been present for at least six months? Do any of the exclusion criteria as formulated by the CDC concerning depression, psychosis, eating disorders or alcohol abuse apply?

Anamnesis

The first step in the symptom-specific anamnesis is to try and gain insight into the patient's expectations and objectives with respect to this consultation and this doctor? Frequently, CFS patients attribute their symptoms to a variety of factors, which cause them to have high expectations for the diagnostics. Also, there may be a hidden agenda involving insurance issues and invalidity benefit claims. It is essential

to identify these issues and expectations at an early stage to make communication more transparent and to prevent both sides from digging in[7]. When it has been established what the patient may or may not expect from his or her visit to the clinic, the severity and extent of the functional impairment is investigated. A suitable technique is to have the patient describe what a normal, average day looks like, for instance the day before. Important details that should be discussed are: At what time does the patient get up? Does he or she take a shower, have breakfast, get dressed? Also issues such as who does the shopping, or the cooking, whether he/she goes to work, plays sports, etc. should be addressed. It is recommended to literally go through the patient's day, hour by hour[8]. Subsequently, the duration and the course of the symptoms are discussed. It is essential to try and establish whether the patient has been fatigued his/her entire life or whether the onset of the complaints can be more or less clearly defined. This is assessed both from the physician's and the patient's perspective.

Next, any concomitant complaints are investigated, which are often abundant. It is important to determine whether fatigue is indeed the principal complaint. In principle, the interview continues with a full internal anamnesis, use of medication (including alternative medication) and stimulants, and the patient's case history, specifically with respect to psychiatric complaints and eating disorders. Finally, any previous diagnoses and treatment(s) are discussed.

Physical examination

The patient is given a full physical examination during which specific attention is paid to the detection of so-called stigmata indicating possible endocrine causes for the fatigue symptoms, such as orthostatic hypotension, pigmentations, pattern of body hair, etc.

Supplementary diagnostics

Laboratory tests are restricted to erythrocyte sedimentation rate (ESR), haematological parameters, minerals, liver and renal functions, protein spectrum, thyroid stimulating hormone (TSH), ferritin and creatine phosphokinase (CPK). In rare cases this range of tests may be extended on the basis of the findings of the anamnesis and/or physical examination.

Computerised questionnaires

A total of four questionnaires was administered to verify whether patients fulfilled the international criteria for CFS as used in scientific research[2]. The fundamental criterion, i.e. exclusion of physical causes, could not be included in this part of the study since a medical practitioner can only evaluate this aspect. The remaining criteria were all assessed by means of the various questionnaires, which were administered on a personal computer. Patients completed the following five questionnaires: 1) a general questionnaire on the patient's personal data, and the nature, duration and onset of the complaints, 2) the validated fatigue inventory Checklist Individual Strength (CIS)[3,9], 3) a functional impairment questionnaire consisting of eight subscales of the Sickness Impact Profile (SIP-8): sleep/rest,

housekeeping, mobility, social interaction, walking, alertness/intellectual functioning, work, recreational and leisure activities[10], 4) a questionnaire scoring premorbid functioning and finally 5) a questionnaire assessing additional CFS-related physical complaints. For the diagnosis of CFS as commonly applied in research the following, criteria needed to be met:

- Fatigue is the principal complaint
- The fatigue symptoms have been present for at least six months, excluding lifelong incidence
- A score of 35 or higher on the CIS subscale fatigue severity
- A score of 800 or higher on the eight subscales of the SIP
- Absence of premorbid eating disorders, alcohol-related problems in the two years prior to the assessment, premorbid depressive disorders or psychotic episodes.

The concomitant physical complaints were not included in the diagnosis since it has already been established that these are not contributing factors[4].

Analysis

A researcher from the department of general internal medicine (HK) retrospectively evaluated the medical files of all the patients examined in the above-mentioned period. A researcher from the department of medical psychology (JP) evaluated the computerised questionnaire data. Both evaluations were aimed at establishing whether a diagnosis of CFS had been made. In the absence of a CFS diagnosis, the rationale behind the judgment was determined. Next, the two datasets were linked and compared to determine statistically the agreement with respect to the CFS diagnosis for each patient. Concordance between the physician's diagnosis and the researcher's evaluation of the computerised questionnaires was evaluated by Cohen's kappa, which is a measure of concordance between two dichotomous variables corrected for chance. A value of Cohen's kappa of 0.40 or lower is considered moderate, between 0.40 and 0.70 satisfactory, and above 0.70 good.

Results

Patient characteristics

In the period investigated, 567 patients were referred to our outpatient clinic because of complaints of chronic fatigue. Fifty patients were not included in the study. Their symptoms could be explained on the basis of existing data and a consultation was not expected to reveal any additional information. Of the remaining 517 patients, 212 were referred by their GPs, 46 by a medical specialist and 259 patients had contacted the clinic of their own accord. Nearly 75% of the patients attended the outpatient clinic in the expectation that they would be diagnosed with CFS, 16% mentioned participating in scientific research as their main reason for requesting the consultation, and 10% reported both these motives. In one patient a full assessment proved to be impossible. Thus, the data of 516 patients could be analysed and compared. Of the patients included in the analyses 78% were female, 22% male, and their mean age was 36 years and 9 months (range 14-69 years).

CFS protocol

Figure 1 shows the results of the physical assessment of all 516 patients. Based on the protocol, the clinicians diagnosed 409 patients (79%) as suffering from CFS. In the remaining 107 patients CFS was not diagnosed on various grounds. In half of these patients (n=54) the fatigue-related symptoms or functional impairment were not judged sufficiently severe to justify a diagnosis of CFS. In 40 patients comorbidity, possibly explaining the fatigue, was diagnosed. The comorbidity included somatic illnesses (n=17), psychosocial problems (n=9), alcohol-related problems or eating disorders (n=4), and other principal complaints (n=10). Thirteen patients met the exclusion criteria for CFS relating to the premorbid condition, viz. eating disorders, depression or lifelong fatigue.

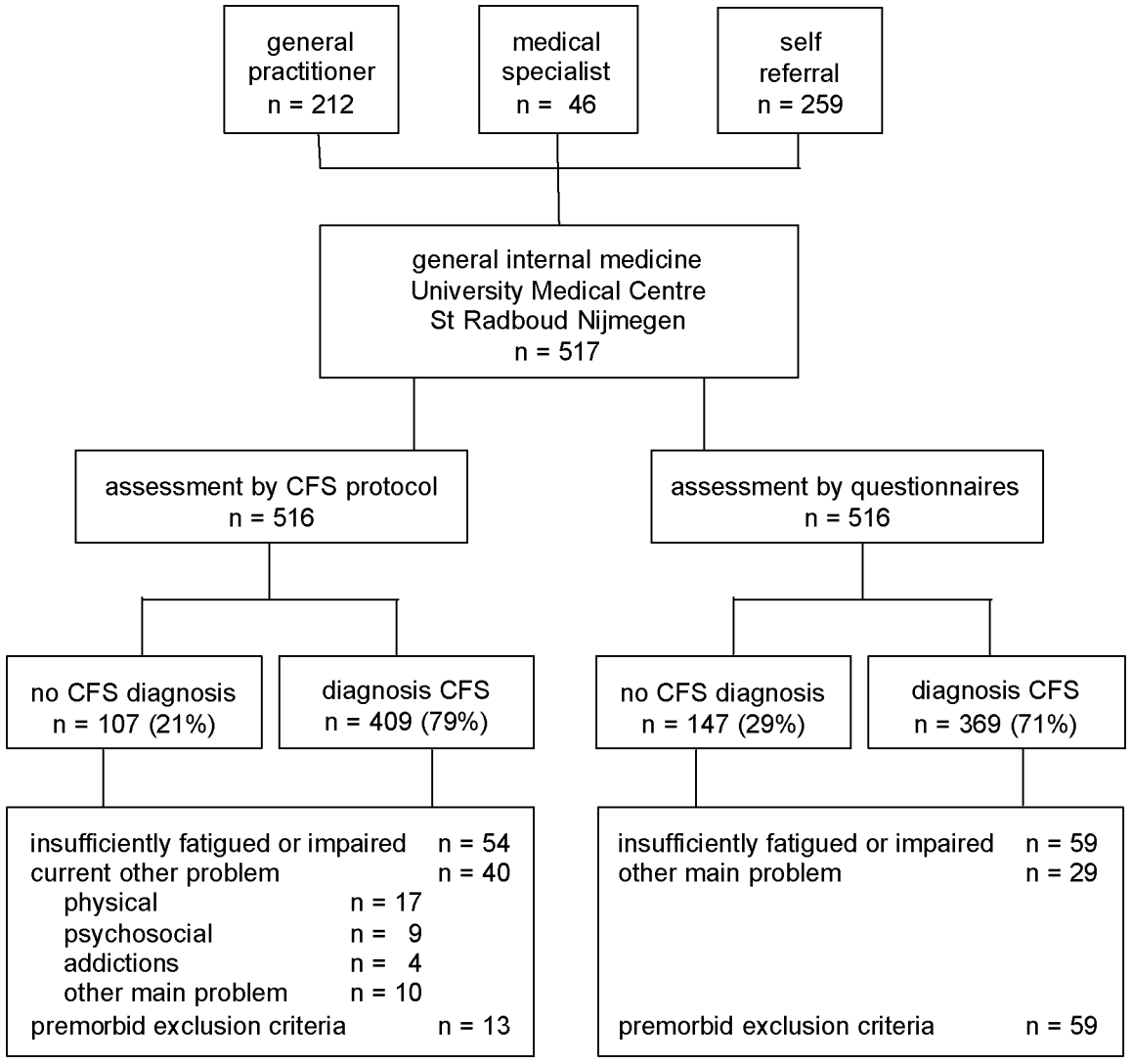

Figure 1. Number of patients referred for fatigue-related symptoms and the results of the protocol-based physicians' and questionnaire-based computerised assessments

Computerised questionnaires

The results of the questionnaire-based assessment of all 516 patients referred are also listed in figure 1. According to the outcome of the questionnaires, 369 patients (71%) met the CFS criteria investigated. The reasons why the remaining 147 patients were not diagnosed as suffering from CFS included insufficient scores on the CIS and/or SIP-8 (n=59), fatigue proved not to be the principal complaint (n=29) and the presence of premorbid eating disorders or alcohol-related problems, depression, psychoses or lifelong fatigue (n=59).

Comparison of the two assessments

Table 1 indicates that in 84% of the cases there was agreement between the clinicians' assessments and the researchers' evaluations of the questionnaires as regards the presence or absence of a CFS diagnosis. The degree of agreement was analysed using Cohen's Kappa and was 0.58 (se 0.04), a correspondence that is common in scientific research in a clinical setting[11] and is generally regarded as satisfactory[12].

Of all 516 patients examined, 21 (4%) were diagnosed as suffering from CFS on the basis of the computerised questionnaires whereas the internist excluded CFS. In these 21 patients a different diagnosis was made in six of them: either somatic (n=3) or psychiatric (n=3). In the remaining 15 patients the physician found insufficient complaints and/or impairments for a diagnosis.

Table 1. Numbers and percentages of patients evaluated for the diagnosis of CFS by physician's use of CFS protocol and researcher's evaluation of computerised questionnaires

		QUESTIONNAIRES		
		CFS	no CFS	
CFS PROTOCOL	CFS	348 (67%)	61 (12%)	409 (79%)
	no CFS	21 (4%)	86 (17%)	107 (21%)
		369 (71%)	147 (29%)	516

In 61 (12%) of the patients the inclusion criteria for CFS were not met according to the questionnaire-based assessment, whereas the specialist did diagnose CFS. The scores on the CIS or SIP were found to be too low in 40% of the patients concerned, while the physician judged the complaints and impairments as sufficiently severe. In the computer assessment 29% of the patients had not indicated fatigue as their main complaint and 31% had reported premorbid eating disorders or alcohol-related problems, depression or lifelong fatigue, aspects that had not come to light during the physician's consultation.

Shortened Fatigue Questionnaire (SFQ)
University Medical Center Nijmegen, The Netherlands
Dept. of Medical Psychology

Name: ..... Gender : male/female
Date of birth: .....
Today's date: .....

On this page you will find four statements indicating how you have been feeling the past two weeks.

You can answer each question by placing a mark in one of the seven boxes. The position of the marking indicates to what extent you feel the statement applies to you.

For example: if you think the statement is completely true, you should place a cross in the left box, like this:

yes, that is true | X | | | | | | | no, that is not true

If you think the answer is not 'yes, that is true' but also not 'no, that is not true', you should mark the box that best corresponds with your feeling, for example like this:

yes, that is true | | | | | X | | | no, that is not true

Please answer all the statements and place only one cross for each statement.

1. I feel tired	yes, that is true							no, that is not true
2. I tire very quickly	yes, that is true							no, that is not true
3. I feel fit	yes, that is true							no, that is not true
4. Physically I feel exhausted	yes, that is true							no, that is not true

Figure 2[a]**.** Shortened fatigue questionnaire (SFQ)

Discussion

It goes without saying that the diagnosis of CFS can and should never be solely based on an assessment using computerised questionnaires. First and foremost, any physical cause for the complaints should be excluded, a criterion that always requires the judgment of a physician. In this study, a physical cause for the fatigue symptoms could only be found in a few cases. Apparently, prior to their referral, the majority of patients had been screened in such a way that further diagnostics did not yield any additional information. We concluded that referral of CFS patients to our internal medicine outpatient clinic seldom lead to new medical insights. Therefore, referrals

Score form SFQ
University Hospital Nijmegen
Department of Medical Psychology

Name: ..... Gender : male/female
Date of birth: .....
Today's date: .....

Chief complaint: .....
Date of origin: .....(month).....(year)

Diagnosis:.....

Groups	Average age	low	< average	= average	> average	high
Healthy groups:						
healthy adults	37	4	4	5-8	9-14	≥15
students normal circumstances	22	4	5-7	8-14	15-21	≥22
students demanding circumst.	21	≤5	6-9	10-17	18-23	≥24
servicemen at rest (normal)	21	4	5-6	7-14	15-22	≥23
servicemen in field exercise	21	≤5	6-11	12-18	19-24	≥25
Patient groups:						
cancer	61	4	5-12	13-21	22-27	28
functional bowel disease	41	≤ 6	7-12	13-21	22-27	28
multiple sclerosis	36	≤12	13-19	20-26	27	28
chronic fatigue syndrome	38	≤22	23-25	26-27	28	28

1. I feel tired	yes, that is true	7	6	5	4	3	2	1	no, that is not true
2. I tire very quickly	yes, that is true	7	6	5	4	3	2	1	no, that is not true
3. I feel fit	yes, that is true	1	2	3	4	5	6	7	no, that is not true
4. Physically I feel exhausted	yes, that is true	7	6	5	4	3	2	1	no, that is not true

Total score SFQ: .....

Figure 2[b]**.** Score form Shortened fatigue questionnaire

could be limited to those patients for whom the expertise of a specialist is required to exclude any physical causes, for instance in case of suspected adverse effects of medication, slightly deviating laboratory test results or somatic comorbidity. According to a recent unpublished survey among general practitioners, currently 78% of fatigued patients are still being referred to a medical specialist. It is our view that administration of the presented protocol for chronic fatigue complaints by GPs not only would lead to substantial reductions in public spending, but would also prevent undue expectations in patients about new or additional medical diagnoses.
Retrospectively comparing the diagnoses based on the CFS protocol with the

diagnoses on the basis of the computerised questionnaires, agreement between both assessments was found in the majority of the cases. In 16% of the cases the clinicians' and the researchers' conclusions were contradictory. In quite a few instances, there was ambiguity about the severity of the fatigue and functional impairment. When a physician is having doubts about symptom severity, questionnaire assessment might be considered. Supplementary to the protocol the Shortened Version of the Fatigue Questionnaire[13,14] could be administered to assess fatigue severity (figure 2) or the physical functioning subscale of the SF-36 questionnaire (MOS-Short Form-36)[15-17] to measure functional impairment (figure 3).

MOS-Short Form-36 questionnaire (SF-36)
subscale physical functioning
Ware J, Sherbourne C, 1992

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
Moderate activities, such as moving a table pushing a vacuum cleaner, bowling or playing golf	1	2	3
Lifting or carrying groceries	1	2	3
Climbing **several** flights of stairs	1	2	3
Climbing **one** flight of stairs	1	2	3
Bending, kneeling, or stooping	1	2	3
Walking **more than a mile**	1	2	3
Walking **several blocks**	1	2	3
Walking **one block**	1	2	3
Bathing or dressing your self	1	2	3

Score range 10-30
Score < 25 indicative of severe impairment in physical functioning

Figure 3. MOS-Short Form-36 questionnaire (SF-36), subscale physical functioning

Physicians using the CFS protocol more often diagnosed CFS than researchers evaluating the computerised questionnaires (79% and 71% respectively). Premorbid exclusion criteria for the diagnosis CFS, such as alcohol dependency, eating disorders or depressive disorders, were found more in the computerised questionnaires than in the physician's consultation. Obviously, it is difficult to establish the patient's case history or current situation with respect to psychological

problems or psychiatric disorders. Questionnaire assessment might lead to additional information.
At our outpatient clinic, after consulting the internist patients with chronic fatigue routinely fill in computerised questionnaires to establish whether they meet the operational criteria for CFS. The physician is able to consider the questionnaire data concerning fatigue severity, functional impairment and actual and premorbid functioning before the second consultation. In this way the questionnaire assessment is complementary to the CFS protocol and the process of diagnosing CFS is optimised.

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Chapter 3

Cognitive behavior therapy for chronic fatigue syndrome: a case study

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Cognitive behaviour therapy for chronic fatigue syndrome: a case study

Abstract

The case of a 26-year old woman with Chronic Fatigue Syndrome (CFS) is presented. Multidimensional assessment showing severe debilitating fatigue and considerable psychological, social and occupational impairment confirmed the diagnosis. Cognitive behaviour therapy (CBT) was based on a tested causal model of CFS and individual behavioural analyses. Key elements in CBT were process variables from the CFS model, like sense of control, causal attributions, physical activity and focusing on bodily functions. Goals were recovery of fatigue, returning to work and relapse prevention. The course of therapy is described in detail to illustrate difficulties in treating CFS. Assessments were made five times, at baseline and at 8, 14, 21 and 33 months. Comparison of the pre-test, post-test and follow-up scores of the outcome variables, fatigue and functional impairment and of the process variables showed clinically significant improvement from the range of CFS patients to the range of healthy controls.

Introduction

Chronic fatigue syndrome (CFS) is characterised by persistent or relapsing unexplained chronic fatigue of new or definite onset and lasting for at least six months. Fatigue is not the result of an organic disease or ongoing exertion, it is not alleviated by rest and it results in substantial reduction in previous levels of occupational, educational, social and personal activities[1]. In clinical, microbiological and immunological research, causes for CFS have not been found[2]. Longitudinal research pointed out that most patients do not recover[3,4]. No pharmacological treatments have proven to be effective[5,6].

Cognitive behaviour therapy (CBT) seems to be the most promising treatment of CFS[7]. Obscurity about the cause of physical complaints is not necessarily an obstruction for an effective treatment. The effect of CBT was also proved in other somatic complaints without a known course, like irritable bowel syndrome[8,9]. However, several of the studies on CBT for CFS suffer from methodological shortcomings. One of the difficulties is the definition of the outcome variables. Most studies report effects of CBT on functional impairment, health status or self-reported improvement, but hardly on fatigue, the main complaint of patients with CFS. In an uncontrolled study Butler and colleagues[10] showed effect of CBT in 22 of 27 CFS patients. CBT was directed at increasing self-efficacy and performing activities that were avoided for a long time. In 80% of the treated patients this effect was sustained over four years[11]. In a randomised controlled trial of Sharpe and colleagues[12] CBT was compared to medical care. CBT consisted of 16 sessions within four months. Therapy was directed at changing cognitions and gradually building up activities. Twelve months later, at follow-up, 73% of the CFS patients treated with CBT showed

significant improvement in daily functioning as measured by the Karnofsky scale, a global rating of the performance status. Perhaps the short duration of CBT may explain the absence of a post-test effect. A period of four months seems rather short to extend the building up of activity to work rehabilitation. The rating of the Karnofsky scale is largely determined by being active in work. A controlled study of Deale and colleagues[13] has ascertained that effects of CBT may not be solely attributed to non-specific treatment factors. CBT and relaxation therapy, both consisting of 13 sessions within six months, were compared. Patients treated with CBT improved more on functional impairment and fatigue than those treated with relaxation therapy. Improvements were sustained over six months of follow-up. A major methodological limitation of this study was that one therapist performed all therapies of both kinds. In a randomised controlled study Fulcher and White[14] found a specific effect in the treatment of CFS patients. They compared graded exercise with flexibility exercises and relaxation therapy, both consisting of weekly sessions in a period of 12 weeks. Patients treated with graded exercise showed significantly more self-reported improvement than the patients treated otherwise. However, striking in this study was a selection-bias of the patients. Forty-one percent was treated preceding the study as a result of psychiatric co-morbidity. Further, it was not possible to establish the effects of therapy at follow-up, because more than half of the patients crossed over from flexibility exercises to graded exercise. CBT in a format of six sessions is less effective for CFS patients when it is combined with immunologic therapy or placebo[15]. CBT developed for depression is also not effective for CFS patients[16]. This latter finding is not surprising. Although it has been suggested that depression plays a pathogenic role in CFS and even that CFS is a form of depression[17], Powell and colleagues[18] have shown clear differences between depressed CFS patients and patients with a major depression. Furthermore, pharmacological anti-depressant therapy has proven not to be effective for depressed and non-depressed CFS patients[6]. From the above facts it has been made clear that CBT is indeed an effective treatment for CFS. However, only little is known about the processes contributing to improvement.

The Dutch Fatigue Research Group has developed CBT for CFS[19] based on a model of maintaining factors in chronic fatigue syndrome[20]. The model is shown in Fig. 1.

In this model factors playing a role in perpetuating fatigue were tested with structural equation modelling. Attributing complaints to a somatic cause produced low levels of physical activity, which in turn had a causal effect on fatigue severity. Sense of control and focusing on bodily symptoms each had a direct causal effect on fatigue. Depression had to be deleted from the model. The model showed an excellent fit for CFS patients, but was rejected for fatigued patients with multiple sclerosis. The newly developed CBT is directed at the mechanisms underlying CFS. Sense of control and physical activity will be increased and somatic attributions and focusing on bodily symptoms will be reduced. Goals of the therapy are recovery from fatigue and functional impairment, work rehabilitation and relapse prevention.

The primary goal of this case study was to evaluate the model-based form of CBT. Additional goals were to give insight in both the mechanisms underlying CFS and the cognitive and behavioural techniques used in therapy, and to illustrate pitfalls in cognitive behaviour therapy for patients with CFS.

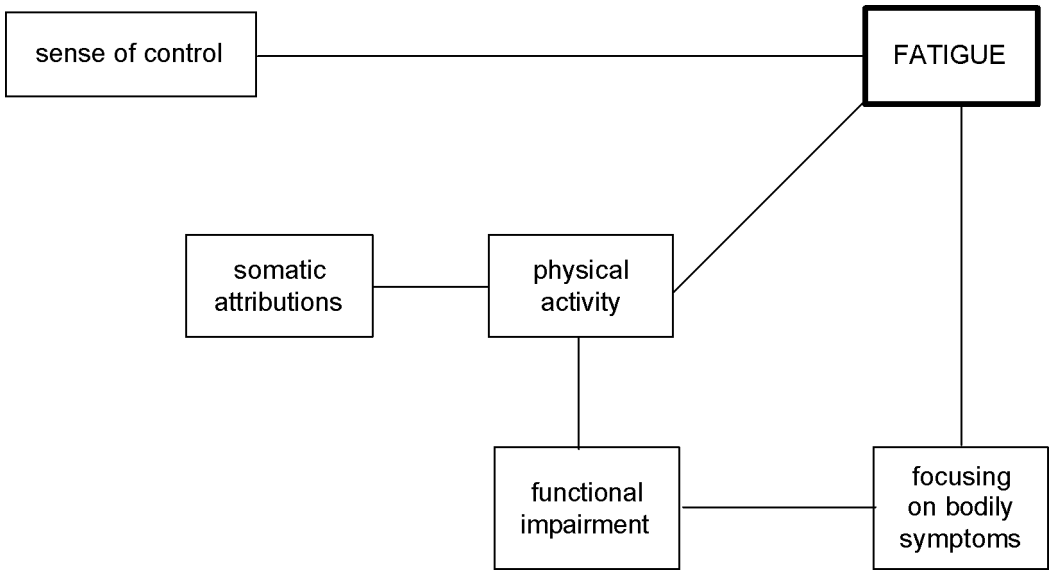

Figure 1. Model of CFS, developed and tested with LISREL (Vercoulen et al. 1998)

Case description

Mrs.B, aged 26 years, was referred to the department of Medical Psychology at the University Hospital Nijmegen by the general practitioner because of chronic fatigue complaints and severe myalgia. First of all a consultation was requested with the internist, who did not detect any physical defects and who diagnosed CFS. Additional assessment at Medical Psychology involving an interview and measurements of the complaints, confirmed the diagnosis. During interviews Mrs.B told the clinical psychologist that she had come from East Germany, where she had met her present Dutch husband seven years ago when she was studying information science. Her intention of marrying him and moving to the Netherlands caused resistance with her parents, because they would hardly be able to keep in touch with her from the then GDR (German Democratic Republic). In spite of periods of doubt and active opposition from the 'Staatssicherheitsdienst', Mrs.B was able to leave the country two years later, a month before the Berlin wall came down and permission was not required anymore. Meanwhile, her education had been completed. Half a year after the marriage took place, Mrs.B's father passed away. This message reached her three days late, because of an over-occupied telephone network in her native

country. Feelings of guilt and presumed, but non-existent reproaches from her mother because she had been absent when her father had been ill, played tricks on her. At the same time, living in the Netherlands meant a big change for her. She mastered the Dutch language quickly, resulting in a full-time position as a systems analyst. Her spare time was filled up with obligatory courses, sports and various hobbies.
After the last exam, Mrs.B became extremely fatigued. A few weeks later the feeling of too much strain disappeared, but she remained tired and listless, had muscular pains, slept a lot and often felt as if she was coming down with something. The general practitioner did not find any defects after physical and laboratory examinations. Mrs.B herself supposed that she had taken on too much. Back at work, she often had headaches and she dreamt a lot about her last period in East Germany. The general practitioner suspected that there was a relation between her fatigue and her problems in dealing with her emigration and her father's death. Therefore he referred her to a social worker. An important aim was coming to terms with the pain of losing her father. Interventions were among others conversations with her mother about her feelings of guilt and the supposed criticism on the way that she acted. The effect of the treatment was a decrease in stress, but the fatigue remained. Still, she went back to work part-time and at great cost managed to work half days for a period of almost six months. Eight months later when referred to our institute, Mrs.B underwent a provisional examination in connection with the Disablement Insurance Act and was been found completely unfit for work. At home, too, extreme exhaustion, muscular pains and problems in focusing, seriously weakened her. Even light household chores were often too much for her. Activities in the field of sports, spare time and social contacts hardly ever took place anymore.

Behavioral assessment

Holistic theory

In the past years Mrs.B was faced with great mental and physical efforts. Thanks to discipline and efficiency she succeeded in passing examinations and in receiving permission to leave the country. In the Netherlands new goals were adapting to the regimen of the Dutch community, learning to command the new language like a native speaker and getting a job. Because of her strong motivation and high intelligence her plans worked out. However, once her goals had been attained she became extremely fatigued. She realised that her fatigue was the result of being overloaded in the previous months and she reposed for several weeks. Despite her husband's advice to take a longer period of rest after years of exertion, she insufficiently seized the opportunity to recover and took up the thread of daily life. However, she did not succeed in resuming her work like before and lost her balance. Periods of high activity caused by the pressure of work alternated periods of exhaustion while being at leisure. Regularity was absent in daily life. Mrs.B was disappointed and angry for not being capable of continuing her former lifestyle.

These feelings were mitigated by her final assumption that a physical abnormality must be causing the complaints and that she was not responsible for this situation herself.

Behavioural analyses

Two patterns of the perpetuation of fatigue were revealed. The first behavioural analysis starts with an increase of fatigue or myalgia. Despite of night's rest and lack of exertion Mrs.B is suffering of extreme fatigue and muscular pains. Her first reaction is based on thoughts like 'it is awful being fatigued again and not being capable of normal daily activities'. Consequently, she feels depressed. She avoids activities as much as possible. Short-term, avoidance is followed by diminished fatigue. However, this short-term decrease of fatigue is not beneficial and antecedent to the second behavioural analysis. Long-term avoidance leads to decline in physical fitness. The patient's body is not used anymore to exertion and reacts with fatigue and pain. Thus, inconsiderable effort causes physical overburden.

The second behavioural analysis starts with a decrease of fatigue or myalgia. The most prominent thought of Mrs.B is to profit by her good form and to make up arrears. She feels restless and tense, and strives to get going quickly before fatigue or pain hit her again. Compared to other days she is rather active. Short-term, she feels relieved and satisfied with the tasks finished. However, later that day fatigue increases because she engaged in more activities than her body could cope with.

Mrs.B has tried a lot to recover. She was bedridden for a while, at other times she forced herself to activity, but she did not find a way to cope with fatigue. On the contrary, complaints increased due to the described ways of reacting to fatigue and pain. Peaks of activity and inactivity interchange. The level of activity is mainly based on thoughts considering her present situation and is no longer in accordance with physical sensations. Both behavioural analyses result in an increase of fatigue. In the long run the second behavioural analysis occurs less frequently. Mrs.B seldom feels less fatigued and her level of activity has declined more and more.

According to these analyses an important goal of therapy must be increasing the level of activity. However, this goal cannot be reached until Mrs.B has learned to react to fatigue in a different way. Irrational cognitions considering fatigue prevent improvement of the level of activity. Therefore, at first therapy will be directed at changing these irrational cognitions.

Measures

Prior to the initiation of treatment (T1), Mrs.B was administered multidimensional assessment for patients with CFS[21]. These measures were administered again during treatment at 8 months (T2), post-treatment at 14 months (T3), and both at 21 months (T4) and at 33 months as follow-up (T5). The outcome variables such as fatigue and functional impairment, the process variables sense of control, physical activity, somatic attributions and focusing on bodily functions, and the CFS related

dimensions pain, concentration and attention, and psychological well-being were assessed. The following measures were used.

Checklist Individual Strength: A 20-item self-report instrument of fatigue referring to the previous two weeks. Each item is scored on a 7-point Likert scale. From factor analysis four factors emerged. In this case study the factors subjective experience of fatigue (CIS-fat) and concentration (CIS-con) are used. The checklist has good reliability (Cronbach's alpha's varying from 0.83 to 0.92) and discriminative validity[21].

Self-observation list daily functioning: During 12 days patients rate fatigue and pain on a prescheduled diary four times daily on a scale of 0 (not at all) to 4 (very much). The daily observed fatigue (DOF) score and the daily observed pain (DOP) score vary from 0 to 16. Daily registration of hours being at work is registered as well (WORK). The psychometric qualities are good[22].

Sickness Impact Profile: Impairment in daily functioning is assessed using eight out of 12 subscales: home management, mobility, alertness behavior, sleep/rest, ambulation, social interactions, work, recreation and pastimes. A total score (SIP) is calculated[23,24].

Causal Attribution List: This list presents 10 possible causes of the complaints patients have, and distinguishes physical and psychosocial causes. A mean score of causal somatic attributions (SOM-att) is calculated[22].

Actometer: A matchbox sized motion-sensing device used to provide a measure of actual levels of physical activity. The actometer is attached to the ankle of the patient and worn for a period of two weeks, day and night. It provides activity scores every 5 minutes. The data are read by a computer program which calculates the average activity over the two week period (ACTO) and produces a visual display of the activity[25].

Modified Pain Cognition List: A subscale of the MPCL was used to assess catastrophic thoughts concerning fatigue (MPCL-ca)[22,26].

Sense of control scale: Consisting of one specific question and four selected items of the modified Pain Cognition List in which the word pain is replaced by fatigue. Responses are scored on a 5-point Likert scale and the total score is calculated by adding all items (SE). The reliability is reasonable (Cronbach's alpha coefficients of 0.75)[22].

Symptom Checklist (SCL-90): The Symptom Checklist is a 90-item indicator of psychopathology and screens for anxiety, agoraphobia, depression, somatization, cognitive difficulties, interpersonal sensitivity, hostility and sleep disturbances. Scores on each item range from 1 to 5. The total score ranges from 90 to 450 (SCL-tot). The subscale somatization (SCL-som) was used to assess the process variable focusing on bodily functions[27].

Beck Depression Inventory: A standardised self-report questionnaire, consisting of 21 items, to measure depression (BDI). Scores on each item range from 0 to 3. The maximum total score is 63. Four diagnostic categories are based on the total score: 0-9 non-depressed, 10-15 mildly depressed, 16-23 moderately depressed, 24 or

more severely depressed. A score of 16 or more is indicative of a clinical depression[28,29].

Complex Reaction Time Task: Composed of three succeeding tasks, each providing a reaction time (RT) and movement time (MT). RT reflects speed of information processing and MT reflects motor speed[30].

Treatment

CBT consisted of 22 sessions within 14 months. Three follow-up sessions followed in the next 7 months. Treatment goals were recovery of fatigue and accompanying symptoms, returning to work and relapse prevention. CBT was directed at the process variables in the model of CFS[20]: to increase sense of control and physical activity and to decrease somatic attributions and focusing on bodily symptoms. CBT consisted of four phases, partially overlapping in time. The course of Mrs.B's therapy will be described in order to illustrate different treatment methods.

Phase 1: Cognitive restructuring session 1-8

Conditions to treatment

First of all, the therapist checked with Mrs.B whether she found herself sufficiently tested for physical abnormalities. This seemed to be the case. Then the therapist explained in detail the difference between factors causing fatigue in the past and factors perpetuating the complaints in the present. In Mrs.B's case no somatic defects were found that could explain the present complaints. The therapist clarified that it would not be advantageous and may even be devastating to further speculate about the cause of CFS. The central question should rather be: 'How can I recover?' Mrs.B agreed with this view. Next, two important conditions of CBT were discussed. Firstly, agreement upon no further examinations or treatments for CFS was asked for. Secondly, Mrs.B was asked to express her willingness to active participation during therapy. She agreed with both conditions.

Discussing behavioural analyses and goals

By means of the behavioural analyses it was explained to Mrs.B how her cognitive and behavioural reactions might aggravate her complaints. Different thoughts and behaviour could stop the complaints from worsening. Mrs.B's goal 'recovering quickly' was redefined as 'learning to cope with fatigue in order to recover and to resume important activities, like work'.

Changing impeding cognitions into cognitions reflecting acceptance of fatigue

The next step in therapy was drawing up an inventory of cognitive reactions to fatigue. Impeding cognitions and accompanying feelings were shown to aggravate fatigue. To avoid this aggravating effect a different cognitive reaction should contain elements of acceptance of the complaints. Goal of this intervention was to make Mrs.B familiar with thoughts like 'I will stop resisting to my complaints and looking back for possible causes. Instead I will find out what I can do about it'. Next, Mrs.B was asked to imagine a situation in which fatigue had aggravated. She learned how to evoke more accepting thoughts. She went on to apply this technique at home. She

realized that she was able to prevent fatigue from quickly aggravating.

Recognizing and respecting limits

Registration of fatigue and daily activities taught Mrs.B to see that she goes on with activities for a long time, thus causing increased fatigue. She learned to detect early symptoms of fatigue, being a signal of reaching her current limit. If she was able to stop in time, she could notice that fatigue did not increase and after some time some reduction of fatigue occurred. She was instructed to stop with daily activities as soon as fatigue comes up or increases. This exercise was hard for Mrs.B, whose discipline and opinions about work prevented her from suddenly stopping activities. Impeding cognitions resulting from this attitude were changed in cognitions helping her to come to a stop when necessary. In her view stopping meant not completing. However, stopping may also mean interrupt temporarily or take rest in-between. In the first phase of treatment Mrs.B realised that she could exercise influence on her complaints, a sign of increased sense of control. Focusing on bodily symptoms was decreased because of the agreement upon no further examinations and because of altered cognitions about fatigue and accompanying symptoms. Somatic attributions were diminished because she had stopped speculating about the causes of her complaints. At the end of this phase Mrs.B was not continuously extremely fatigued anymore. Therefore, she could start with building up physical activity.

Phase 2: Building up activity, session 6 - 15

Next, physical activity was built up gradually and systematically. Mrs.B was asked to select a physical activity that she could perform every day, that could easily be registered and that enabled her to build up gradually. Mrs.B chose cycling as a lot of other patients do. Some patients prefer walking. The level to start with building up activity is defined by the period that the patient is able to perform the selected activity, without getting fatigued. Mrs.B. had a secure start at 5 minutes each day. Every week this period was increased with 1 or 2 minutes. She cycled every day, in the beginning building up systematically, but later taking pains to fulfil the daily cycling. She reported being afraid of a relapse when building up further. Her fear was reinforced by a visit to a meeting of the ME-association, at that time frequented by mainly non-believers of CBT. Their reaction compelled her to visit a colour-therapist, who diagnosed a lot of viruses and advised his special treatment for her complaints. The act of visiting another therapist for her complaints was conflicting with the agreement at the beginning of therapy. The therapist confronted her to choose between CBT and colour-therapy. Because of the progress she had already made with CBT, she decided not to engage in the other treatment. This incident gave rise to a renewed start of building up activities. It was suggested to Mrs.B to cycle twice a day, thus accelerating the building up of activities. From that point on she actively engaged in the therapy again. In time mental and social activities were added too. Vigilance to respect her limits was harder during these latter activities, but she took more pleasure in those activities than in cycling. Gradually, Mrs.B performed more

and more activities in daily life without getting fatigued. The return of regularity in daily activities was considered a good preparation of returning to work.
In the second phase of treatment Mrs.B achieved a huge improvement in the level of activity. She also felt less frequently fatigued and depressed. She was still suffering from myalgia, although she reported a different kind of myalgia. The therapist labelled this pain as a possible consequence of building up activities.

Phase 3: Returning to work, session 12-22
Before the building up of activities was fully achieved, it was suggested to Mrs.B to draw up a plan for returning to work. She reacted frightened, judging herself not sufficiently recovered to even consider returning to work at that time. However, it was possible to motivate her to evaluate the reactions of the company doctor and the general manager to a plan of reintegration. In case of Mrs.B the company doctor was positive about her plan to return to work for several hours a day as an extension of therapy. He advised her to discuss this plan herself with her employer. Together with the therapist Mrs.B drew up a specific plan, containing the date she liked to resume work, the number of hours she was able to work each day and a program of building up the hours being at work every three or four weeks. Despite the preparation, the first meeting with the employer was very disappointing. In his opinion she could not come back in her former capacity as systems analyst. This profession was considered too stressful for her. Furthermore, the employer was of the opinion that he was not legally obliged to co-operate with the reintegration plan of resuming work therapeutically. With the aid of an occupational expert of the office executing the Disablement Insurance Act Mrs.B eventually succeeded in convincing the employer of the advantages of her plan. The first month she worked two hours each day. The second month the number of hours being at work was built up to four hours daily.
In the third phase of treatment Mrs.B was able to maintain the achieved improvements, despite of the hard negotiations with her employer and the number of hours being at work each day.

Phase 4: Relapse prevention, session 19-22
<u>Discussing changed lifestyle</u>
Mrs.B's expectations of recovery were explored. She was no longer afraid of relapse. She hoped that she could function again like she did before she became ill. It was discussed that resuming the premorbid lifestyle might increase the risk of relapse. During therapy Mrs.B made herself familiar with a new lifestyle. The changed lifestyle will be of help in problematic situations. Mrs.B's perfectionism is less prominent and she has learned to say no. She was able to stop if a situation was extremely fatiguing and she displayed several cognitive alternatives in her repertoire to support these behavioural changes.
<u>Stop labelling oneself as a patient</u>
The term 'patient' literally means someone being ill or suffering. Mrs.B no longer

suffers from extreme fatigue. She considers herself cured. Continuing to name herself 'CFS patient' will influence her cognitions and behaviour and those of others. Undoubtedly, Mrs.B will enter situations in which she exceeds her limits and becomes very fatigued. This will be no problem, because she has learned what she can do about it.
In the last phase of therapy cognitive restructuring of the premorbid lifestyle consolidated improvement. The former lifestyle was no longer an ideal for Mrs.B.

Results

Based on the model of CFS, fatigue and functional impairment were chosen as variables to assess therapy outcome. Variables to assess the therapy process were sense of control, physical activity, somatic attributions and focusing on bodily functions. Based on the behavioural analyses the therapy effects on complaints of pain, psychological wellbeing and concentration were analysed as well. Individual scores on these variables were compared to scores of CFS patients and healthy controls [22,30].

Table 1. Outcome variables fatigue (CIS-fat, DOF) and functional impairment (SIP, WORK-hours) at five times (T1, T2, T3, T4, T5) compared to mean scores of CFS patients and healthy controls

	T1	T2	T3	T4	T5	CFS		Healthy	
						m	sd	m	sd
CIS-fat	56	39	33	36	21	48.2	7.9	17.3	10.1
DOF	10	5.8	3	2.8	3	8.6	2.6	1.7	1.6
SIP	1554	1307	623	523	130	1741	698	-[a]	-
WORK-hours	0	0	3.9	6.8	4.8	0.9	1.6	6.1	2.2

[a] Data not available; test not suitable for healthy controls.

Outcome variables: fatigue and functional impairment

Table 1 shows the scores of the outcome variables at five times. At baseline the scores on fatigue and functional impairment are within the range of the scores of CFS patients. During treatment (T1–T3) fatigue and functional impairment decrease and this change is further continued during follow-up (T4). At the final follow-up the scores are within the range of healthy controls.

Process variables: sense of control, physical activity, somatic attributions and focusing on bodily functions

The results of the process variables are shown in Table 2. During treatment an increase of sense of control to almost maximal is found as well as an increase in physical activity to the level of healthy controls. This result is maintained during follow-up. Scores reflecting focusing on bodily functions and catastrophic thoughts decreased to the range of healthy controls and remained stable during follow-up. Causal somatic attributions did not change during treatment and follow-up.

Other dimensions of CFS: pain, psychological wellbeing, concentration and attention
Table 3 shows that the CFS-related complaints reported by Mrs.B at baseline have changed too from the range of CFS patients to the range of healthy controls.

Table 2. Process variables sense of control (SE), catastrophic thoughts (MPCL-ca), somatic attributions (SOM-att), physical activity (ACTO) and focusing on bodily symptoms (SCL-som) at five times (T1,T2, T3, T4, T5) compared to mean scores of CFS patients and healthy controls

	T1	T2	T3	T4	T5	CFS		Healthy	
						m	sd	m	sd
SE	16	22	22	21	23	14.8	3.2	- [a]	-
MPCL-ca	54	38	29	37	33	42.2	9.0	32.3	14.2
SOM-att	3.3	3.8	3.5	2.5	3.3	3.7	0.8	- [a]	-
ACTO	53	69	90	93	86	65	28	88	25
SCL-som	32	23	19	18	17	30.1	8.0	14.5	3.5

[a] Data not available; test not suitable for healthy controls.

Table 3. Variables concerning pain (DOP), psychological well-being (BDI, SCL-tot) and concentration and reaction time (CIS-con, RT) at five times (T1, T2, T3, T4, T5) compared to mean scores of CFS patients and healthy controls

	T1	T2	T3	T4	T5	CFS		Healthy	
						m	sd	m	sd
DOP	7.3	2.2	1.3	1.3	1	6.5	3.4	0.1	1.5
BDI	15	10	7	9	3	10.8	4.7	2.7	3.7
SCL-tot	162	129	113	108	100	156.1	28.1	108.6	21.4
CIS-con	29	21	10	11	8	26.2	7.2	9.5	5.0
RT	0.649	0.326	0.350	0.317	0.321	0.502	0.236	0.373	0.05

Discussion

In this case study cognitive behaviour therapy for chronic fatigue syndrome was highly successful. At baseline the diagnosis CFS was confirmed by multidimensional assessment. Compared to other CFS patients the symptoms of Mrs.B were severe. During treatment practically all process variables improved to the level of healthy controls. The outcome variables consequently improved too, reaching the level of healthy controls during follow-up. It is concluded that clinically significant change was realised, defined by Jacobson and Truax[31] as the extent to which therapy moves someone outside the range of the dysfunctional population or within the range of the functional population.

Cognitive behaviour therapy was based on both an empirically developed model of CFS and individual behavioural analyses of Mrs.B's complaints. Probably, the strength of this therapy lies in the combination of empirically derived and individual

aspects. The model points out psychological factors crucial for recovery. Individual behavioural analyses reveal the relative importance of each of these factors in treatment.

Despite the successful results some side-notes should be discussed. In this case study experimental analyses of behaviour were absent. This leaves open the possibility that other factors, like repeated contacts with the therapist, may have contributed to the favourable changes. In our opinion therapist attention is ruled out as a contributing factor. Before the start of cognitive behaviour therapy, Mrs.B had a therapeutic relationship with a social worker, which she described as warm and empathic. However, the attention of this therapist was not sufficient in remedying the severe somatic complaints of Mrs.B. As to the contents of the therapy some critical remarks can be made too. Preparation of work rehabilitation was initiated too late in therapy and took a great deal of time. Mrs.B had lost sight of the important goal of work rehabilitation. Therefore, a gap was caused between building up of physical activity and returning to work. Further, the duration of therapy could have been diminished in case of more rapid building up of physical activity. Probably, more moments in the physical activity program each day should have speeded up therapy and should have avoided disappointment in the rate of improvement. In this phase of therapy the therapist was less active too and followed a wait-and-see policy. Looking back, it is not surprising that in this period two incidents came up. Mrs.B decided to visit a meeting of members of the ME-association again. No one of the patients she met was as optimistic as Mrs.B about cognitive behavior therapy, which caused a severe fear of relapse. In this period she chose to undergo color-therapy, thus not standing by the agreement made at the start of cognitive behavior therapy. These incidents urged on the therapist to breathe new life into therapy. The motivation of Mrs.B was restored and the therapy passed off smoothly.

Although part of the model of CFS, causal somatic attributions did not change during cognitive behavior therapy. This may be a result of therapy. At first Mrs.B was taught to make a distinction between initiating and perpetuating factors in CFS. After that, CBT was directed at the perpetuating factors, like gradually building up physical activity. The therapist has thus disconnected causal attributions and physical activity.

Cognitive behavior therapy based on both the model of CFS and individual behavioral analyses seems a promising treatment. At the moment the Dutch Fatigue Research Group is conducting a multicenter randomized controlled trial to test the efficacy of an 8-month treatment protocol of this newly developed cognitive behavior therapy.

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Chapter 4

Cognitive behaviour therapy for chronic fatigue syndrome: A multicentre randomised controlled trial

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Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial

Abstract

Background Cognitive behaviour therapy (CBT) seems a promising treatment for chronic fatigue syndrome (CFS), but the applicability of this treatment outside specialised settings has been questioned. We compared CBT with guided support groups and the natural course in a randomised trial as three centres.

Methods Of 476 patients diagnosed with CFS, 278 were eligible and willing to take part. 93 were randomly assigned CBT (administered by 13 therapists recently trained in this technique for CFS), 94 were assigned the support-group approach, and 91 the control natural course. Multidimensional assessments were done at baseline, 8 months, and 14 months. The primary outcome variables were fatigue severity (on the checklist individual strength) and functional impairment (on the sickness impact profile) at 8 and 14 months. Data were analysed by intention to treat.

Findings 241 patients had complete data (83 CBT, 80 support groups, 78 natural course) at 8 months. At 14 months CBT was significantly more effective than both control conditions for fatigue severity (CBT vs support groups 5.8 [2.2-9.4]; CBT vs natural course 5.6 [2.1-9.0]) and for functional impairment (CBT vs support groups 263 [38-488]; CBT vs natural course 222 [3-441]. Support groups were not more affective for CFS patients than the natural course. Among the CBT group, clinically significant improvement was seen in fatigue severity for 20 of 58 (35%), in Karnofsky performance status for 28 of 57 (49%), and self-rated improvement for 29 of 58 (50%). Prognostic factors for outcome after CBT were higher sense of control predicting more improvement, and a passive activity pattern and focusing on bodily symptoms predicting less improvement.

Interpretation CBT was more effective than guided support groups and the natural course in a multicentre trial with many therapists. Our study showed a lower proportion of patients with improvement than CBT trials with a few highly skilled therapists.

Introduction

Chronic fatigue syndrome (CFS) is characterised by persistent or relapsing unexplained fatigue, of new or definite onset and lasting for at least six months. Fatigue is not the result of an organic disease or ongoing exertion, rest does not alleviate it, and there is substantial limitation of occupational, educational, social and personal activities[1]. No cause of CFS has been found, and most patients do not recover. No somatic or pharmacological treatments have proven to be effective[2]. Cognitive behaviour therapy (CBT) seems to be a promising treatment of CFS[3-5]. Two randomised controlled trials reported positive results[6,7]. A recent review questioned whether these results can be generalised outside specialist centres were only a few highly skilled therapists, or even a single therapist administered CBT.

Furthermore, in both studies the primary outcome variable was functional impairment and not fatigue, the main complaint of CFS patients. In our study, criticisms of both previous randomised trials were addressed.

The effectiveness of CBT was tested in a multicentre randomised trial. CBT was compared with a treatment condition, guided support groups, and a control condition, the natural course. CBT was administered in three different centres rather than one specialist centre. Experts taught the treatment protocol to many therapists with no previous experience in CBT for CFS. Guided support groups should control for the absence of specific cognitive-behavioural interventions and the presence of therapist attention and treatment expectations. We assumed that support groups, as in other chronic diseases[8,9], might contribute to a feeling of mutual understanding, acceptance and support and thereby have a healing effect.

In this study, the outcome variables were fatigue severity and functional impairment, with the same instruments for inclusion and outcome. Moreover, CBT for CFS was based on a statistically tested model of perpetuating factors in CFS[10,11] rather than on hypothesised factors in CFS or on treatments of other medically unexplained syndromes. The model of CFS is shown in figure 1. Focusing on bodily symptoms, low levels of physical activity and sense of control contribute to increasing severity of fatigue and functional impairment. CBT is directed at these perpetuating factors.

The main aim of our multicenter trial was to show the effectiveness of CBT for patients with CFS. Our hypothesis that fatigue severity and functional impairment should decrease significantly more in the group of patients assigned CBT than in patients in the control groups.

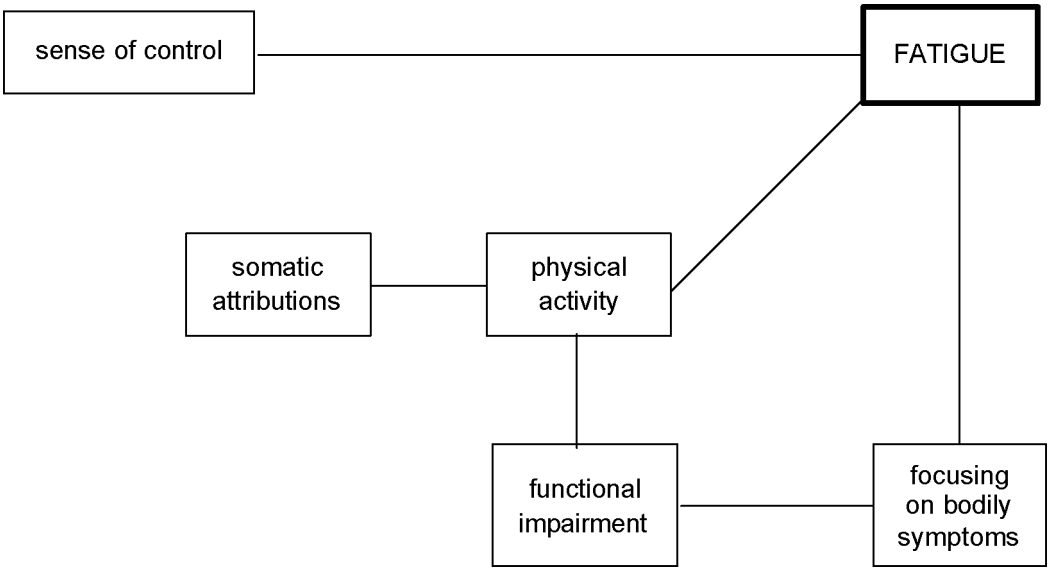

Figure 1. Model of CFS, developed and tested with LISREL (Vercoulen et al. 1998)

Patients and methods

Patients

All patients with a major complaint of fatigue referred to the outpatient clinic of the departments of internal medicine of the University Medical Centre Nijmegen and the University Hospital Maastricht between October, 1996, and January, 1998, were assessed by means of detailed history, physical examination, and computer assessment of questionnaires. Patients were eligible for the study if they met the US Centers for Disease Control and Prevention criteria for CFS[1], with the exception of the criterion requiring four of eight additional symptoms to be present. Severe fatigue and severe functional impairment were defined by cut-off scores- a score of 40 or more on the subscale fatigue severity of the Checklist Individual Strength and a score of 800 or more on the Sickness Impact Profile. Additional inclusion criteria for this study were age between 18 and 60 years, and residence within 1-5 h travelling time of one of the study centres. Additional exclusion criteria were previous or current participation in CFS research, pregnancy, and current treatment to achieve pregnancy.

A sample size of 80 patients per group was estimated assuming significance of 5%, power of 90%, a dropout rate of 20%, and a medium effect size on the actometer, the measure of our multidimensional approach in need of most individuals to show improvement. Multidimensional assessment has been recommended for studies assessing the effect of therapeutic interventions for CFS, to measure change in different dimensions of the patients' functioning[12]. During the trial the dropout rate was higher than that estimated in the calculation of sample size. Therefore, the target sample size for inclusion was set at 90 patients per study group.

Design and procedures

The study was an open multicentre randomised controlled trial in which individual CBT was compared to participation in guided support groups and with the natural course, a control condition in which no treatment was offered. The ethics committees of the three participating centres gave approval for the study. Treatment effects were expected in the primary outcome variables fatigue severity and functional impairment and were explored in the secondary outcome variables: Karnofsky performance status, psychological well-being, quality of life, and work. The predictive role of perpetuating factors in the model of CFS was tested exploratively also.

Patients who met the trial criteria and were willing to take part in the trial had to give informed written consent. To ensure adequate generation and adequate concealment in the allocation process, patients were allocated sequentially to one of three conditions, by blockwise randomisation (block size six), separately for each centre. The allocation was concealed in series of envelopes for each centre and assigned by (assistant) researchers before baseline in the presence of the patient, in order of enrolment in the trial. CBT and support groups took place in three different settings, the Department of Medical Psychology of the University Medical Centre Nijmegen,

the Department of Psychiatry of the Leiden University Medical Centre, and the Department of Psychotherapy of the Maastricht Mental Health Institute. CBT and support groups were administered by different therapists and on different days to prevent contamination. CBT consisted of 16 sessions of 1 h over 8 months. Patients in this group had to meet the requirements of no further medical examinations or other treatments for CFS during the trial. These conditions were essential in reducing focusing on bodily symptoms and somatic attributions. A preliminary version of CBT has been extensively described. An essential part of CBT is self-control: this means that the CFS patient is acquiring control over symptoms instead of dependence on physicians prescribing treatments or medications. In this study, CBT was outlined in a treatment protocol. First, the model of perpetuating factors was explained, and the therapist attempted to motivate the patient for CBT. Next, fatigue-related cognitions were challenged to diminish somatic attributions, to improve sense of control over symptoms, and to facilitate behaviour change. Patients were encouraged to attain and maintain a base level of physical activity needed to prevent bursts of activity and resultant extreme fatique. Subsequently, a structured activity programme was started. After a gradual increase of physical activity, a plan for work rehabilitation was outlined and carried out. For patients without a job, rehabilitation in other personal activities was achieved. The final sessions dealt with relapse prevention and further improvement of self-control.

Thirteen behaviour therapists of three different disciplines (psychologist, psychiatrists, and health scientists) took part. Therapists varied in previous CBT (non-CFS-related) experience, because the study was done with the therapists available within the three centres. However, none of the therapists was familiar with CBT for CFS at the start of the trial. Two experts in CBT for CFS (GB, EB) trained the therapists in using the treatment protocol in a workshop, consisting of two blocks of 2 days each, separated by a month, in which the therapists started the treatment of two CFS patients in a pilot study. Therapists were supervised once every 2 weeks throughout the trial. Patients were allocated to therapists in a fixed sequence by the researcher in order of patients' random allocation to CBT in each centre separately. An integrity check of a random sample of 5% of all audiotaped CBT sessions was done. An independent judge used a checklist to rate the degree and the amount of time spent on the basic elements of CBT (restructuring of fatigue-related cognitions, attaining a base level of daily activity, gradual increase of physical activity, and returning to work or personal activities) in each session. The analyses showed that 91.5% of the time spent in therapy was relevant for CBT and that 87% of the sessions were adequate or good overall.

The guided support groups were similar to CBT in terms of time spent and treatment schedule. Each group, consisting of about eight patients, had 11 meetings of 1-5 h over 8 months. One social worker was available for all 11 groups in the three centres. The treatment orientation was non-directive and client-centred. The social worker was supervised once every 2 weeks by a psychotherapist, who had no links with

CBT or CFS. The goal of the support groups was to offer mutual understanding and recognition by means of exchanging experiences with one central theme during each meeting. In this study group, patients were free to have other examinations or treatments. All support-group sessions were videotaped, and the tapes were randomly checked to make sure that the social worker was not using CBT-like strategies. In the control condition natural course, no interventions were offered, and no further requirements were made. Patients were free to have other examinations or treatments.

Assessment

Multidimensional assessments were made at baseline, at 8 months, and a follow-up (14 months). The baseline assessment included the screening assessment before randomisation (fatigue, functional impairment, criteria of the Centers for Disease Control and Prevention) and those made immediately after randomisation.

Fatigue severity was assessed by a subscale of the Checklist Individual Strength[14]. In this questionnaire, the patient is asked about fatigue in the two weeks preceding the assessment. The subscale consists of 8 items, each scored on a 7-point Likert scale (range 8-56). The questionnaire has good reliability (Cronbach's alpha varying from 0.83 to 0.92) and discriminative validity[12,14,15].

Functional impairment was measured by the Sickness Impact Profile[16,17]. This widely used measure has good reliability and content validity[18]. As in our previous studies, a total score was calculated by addition the weights of items (range 0-5799) in eight subscales: home management, mobility, alertness behaviour, sleep/rest, ambulation, social interactions, work, and recreation and pastimes. Comparison data for CFS patients were available[12].

The Karnofsky performance status scale is a descriptive, ordinal scale. An independent clinical psychologist rated the patient's functional status in 10-point intervals from 0 to 100. The validity and reliability of this scale have been shown in several populations[19,20]. Comparison data for CFS patients were available[6].

The Symptom Check List 90[21] measured psychological well-being. The scale consists of 90 items scored on a 5-point Likert scale. The total score ranges from 90 to 450. A low total score reflects high psychological well-being. This scale is widely used and the reliability and discriminating validity are good.

The visual analogue scale of the EuroQol[22] measured quality of life. The scale ranges from 0 (worst health status) to 100 (best health status). The EuroQol has been validated in normal populations, patients and in CFS patients[23].

Hours working in a job were recorded on a 24 h timetable of the 12-day self-observation list[24].

Self-rated improvement was measured at 8 months and at follow-up by one specific question: patients indicated whether they had completely recovered, felt much better, had the same complaints or had become worse compared with the previous measurement. This measure has been validated in several of patients populations

and was used in this study as one of the measures for clinically significant improvement[24-26].

The Self-Efficacy Scale, consisting of five questions, measured sense of control in relation to CFS complaints. Four items were scored on a 5-point Likert scale and one item on a 4-point Likert scale. The total score ranges from 5 to 24, a higher score reflecting more sense of control. Cronbach's alpha reliability coefficients range from 0.70 to 0.77 [10,12,25].

Somatic attributions with respect to CFS were measured by the causal attribution list consisting of five questions scored on a 4-point Likert scale. The total score ranges from 5 to 20, a higher score indicating stronger somatic attributions. Cronbach's alpha reliability coefficients range from 0.71 in previous studies[12,25] to 0.74 in this study.

Physical activity was measured by the actometer, a motion-sensing device attached to the ankle and worn continuously for 12 days. Such devices are reliable and valid measures of physical activity[27]. The activity pattern of each patient was typified by comparison of daily activity scores with the reference score of CFS patients. Three categories were defined: pervasively passive (90% or more beneath the reference score); moderately active; pervasively active (90% or more above the reference score)[28].

Focusing on bodily symptoms was measured by the subscale somatisation of the symptom checklist 90[21], as in previous studies in which CFS patients were compared with healthy individuals and patients with multiple sclerosis[10,29]. The subscale consists of 12 items scored on a 5-point Likert scale. The score ranges from 0 to 60.

Analysis

A general linear model for repeated measurements (by the method of mixed linear models) was used to analyse the effects of CBT on the two primary variables (fatigue severity and functional impairment and the secondary variables Karnofsky performance status, symptom checklist 90, Euroqol, and hours working in a job. Differences at 8 months and 14 months from baseline were used as repeated measurements, with treatment (3 levels), centre (3), time (2 levels) and their first-order interactions as fixed factors. The covariance matrix was specified as unstructured (implying a general structure), estimation method used was restricted maximum likelihood, and Satterthwaite's method was used to estimate denominator degrees of freedom. First, we tested, for the primary variables, whether the œntre terms could be regarded as redundant (likelihood ratio test comparing the 2 models). If this was the case for both variables, reduced models with treatment and time factors and their interaction were used in all subsequent analyses. All treatment effects, as well as differences between treatments were estimated within these models; 95% CI were computed from these estimates and their standard errors. We used the procedure MIXED from the SAS package (version 6.12). Although the methods of analysis for the primary and secondary variables are the same, results for

the latter should be regarded as exploratory.

To define clinically significant improvement in fatigue severity, we first calculated for each patient a reliable change index to decide whether statistically significant improvement had occurred (reliable change > 1.64, $p<0.05$). Second, a cut-off score of 36 or lower was calculated to decide whether a patient's score had moved from the range of CFS patients to the range of healthy individuals[30]. A patient was classified as showing clinically significant improvement if both criteria were met.

Improvement in the Karnofsky performance status was explored also, so that we could compare the results with those of Sharpe and colleaques[6]. Clinically significant improvement was defined as an improvement of 10 points or more and a score of 80 or more.

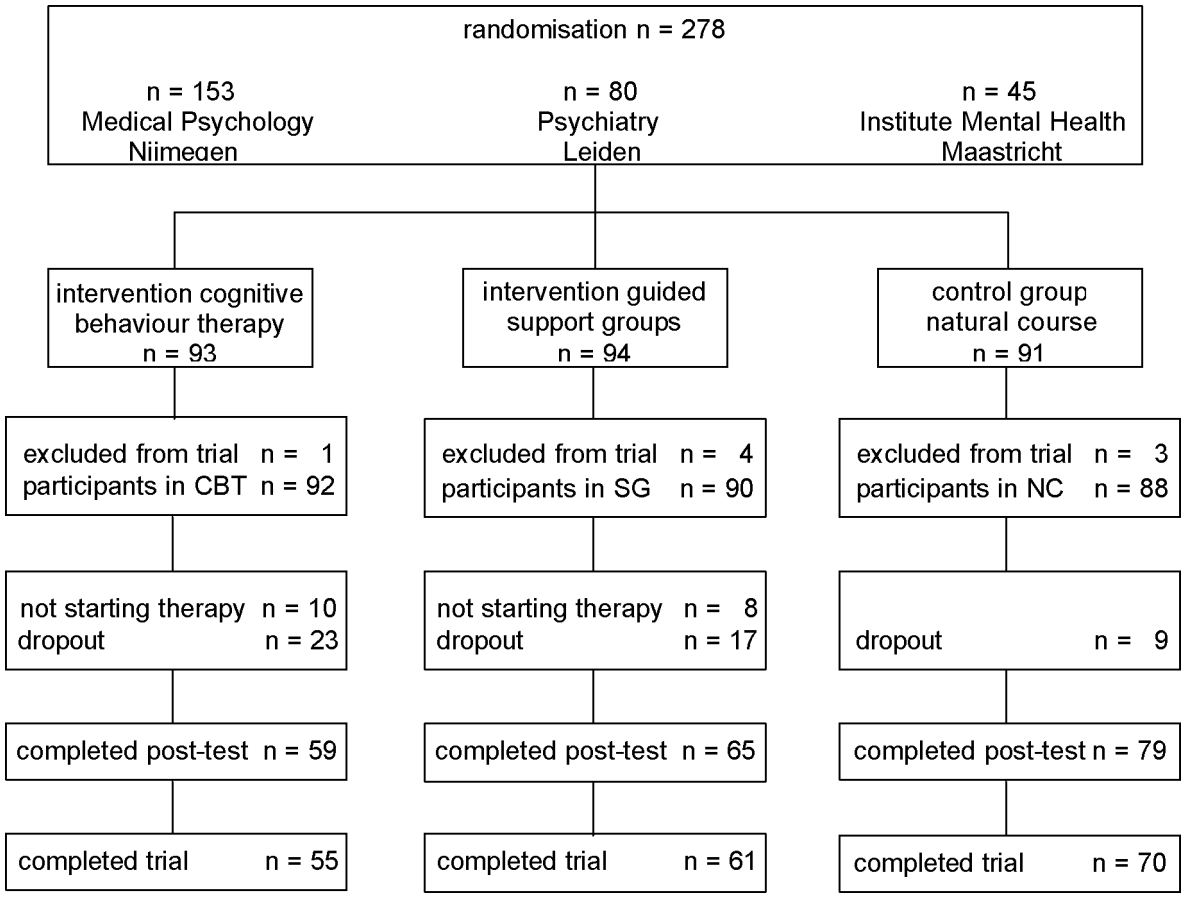

Figure 2. Trial profile

Self-rated improvement was defined as a patient's indication that he or she was completely recovered or felt much better. The categorical variables which were calculated by the procedures applied on the original variables checklist individual strength, Karnofsky performance status and Self-rated improvement, were compared between treatments by Fisher's exact test at 8 months and 14 months.

Analyses of possible predictors were done with multiple linear regressions. The

predictors were included and excluded with the stepwise method. Independent variables were treatment, baseline value of the dependent variable, age, sex, duration of complaints, education, and the baseline values of the perpetuating factors: sense of control, activity pattern, focusing on bodily symptoms, and somatic attributions, and all first-order interactions between treatment and other factors. The main interest was the relation between predictors and the direct treatment effect. Therefore, only the outcomes at 8 months were analysed. Results from these analyses should be regarded as exploratory.

Results

518 patients were referred to the University Medical Centre Nijmegen with a major complaint of fatigue; CFS was diagnosed in 410. Another 66 patients were diagnosed with CFS at the University Hospital Maastricht. Of these 476 patients, 99 did not meet the eligibility criteria and 99 refused to take part. The remaining 278 patients were randomly to the study groups at the centres of Nijmegen, Leiden and Maastricht (figure 2). In total, 93 patients entered the CBT group, 94 the support groups, and 91 the control natural course group. Six patients were excluded: five developed other diseases during the trial and one was pregnant at baseline. After randomisation, two patients were found not to meet the criteria for CFS because they had premorbid anorexia nervosa. Thus, the trial consisted of 270 patients (92 CBT, 90 support groups, 88 control groups), of whom 203 (75%) completed 8 months and 186 (69%) 14 months in the trial. 18 patients did not start treatment. 49 withdrew during the test phase and 17 withdrew during follow-up. Withdrawal was defined differently for the three groups. In the natural course group, only patients not attending the assessments were classified as withdrawing, whereas in the two intervention groups those who stopped treatment were also counted. Moreover, in contrast to CBT, frequent non-attendance in the guided support groups had no consequences for further treatment, unless a patient declared the intention to withdraw. This difference was reflected in the significant difference in mean hours of attending treatment between CBT group and the guided support group (15,6 vs 13.2; $p< 0.0001$). Table 1 shows the baseline characteristics of the three groups.

At 8 months, 241 patients (89%) had complete data (83 CBT, 80 support groups, 78 natural course). At 14 months, 196 patients (73%) had complete data (58 CBT, 62 support groups, 76 natural course). The data of these patients were included in the analyses. Only 9% of the patients had missing data at one or both posttreatment assessments.

For both primary outcome variables, a reduced model without any centre term could be used ($p= 0.437$ for checklist individual strength, fatigue; $p=0.202$ for sickness impact profile, likelihood ratio test with 8 df). Consequently, all subsequent analyses were done with such models.

Table 1. Baseline characteristics of study participants

	CBT (n= 92)		Guided support groups (n= 90)		Natural course (n= 88)	
Demography						
age (yrs)	36.2	9.4	37.1	10.6	36.7	10.3
duration of complaints (yrs)	4.9	4.8	6.6	6.4	5.3	5.4
education (1=low to 7=high)	3.9	1.6	4.3	1.4	4.4	1.6
M/F *	22/70		19/71		17/71	
Dependent variables						
CIS fatigue	52.2	3.9	52.3	4.0	51.9	4.1
SIP total	1755	613	1842	560	1859	671
Karnofsky	71.5	8.5	71.2	7.5	70.8	7.9
SCL-90	170	38.5	169	41.5	166	36.0
EuroQol	46	17	43	16	40	14
work (hours in 12 days)	16.3	21.1	12.8	19.1	13.5	18.6
Indepedent variables						
sense of control	14.8	3.5	14.6	3.1	14.6	3.6
somatic attributions	13.9	2.8	14.1	2.5	13.5	2.4
focusing on bodily symptoms	30.7	6.9	30.0	7.6	29.8	7.2
Activity pattern[#]						
generally passive*	21 (23%)		16 (19%)		24 (29%)	
moderately active*	56 (62%)		53 (62%)		50 (59%)	
generally active*	13 (15%)		16 (19%)		10 (12%)	

Data are mean (sd) or *numbers of participants. [#]11 cases had incomplete actometer data and are not included

Table 2. Estimated effect of CBT compared with support groups and natural course on fatigue severity (CIS) and functional impairment (SIP)

		CBT vs support groups		CBT vs natural course	
		Treatment effect (95%CI)	p	Treatment effect (95%CI)	p
CIS	8 months	6.0 (3.1-9.0)	0.0001	6.0 (3.1-9.0)	0.0001
	14 months	5.8 (2.2-9.4)	0.0015	5.6 (2.1-9.0)	0.0016
SIP	8 months	217 (26-408)	0.0261	213 (22-403)	0.0287
	14 months	263 (38-488)	0.0223	222 (3-441)	0.0470

CBT= Cognitive Behaviour Therapy

In the primary outcome variables, significant differences between the treatment effects of CBT support groups, and natural course were found (figure 3). Estimated differences are shown in table 2.

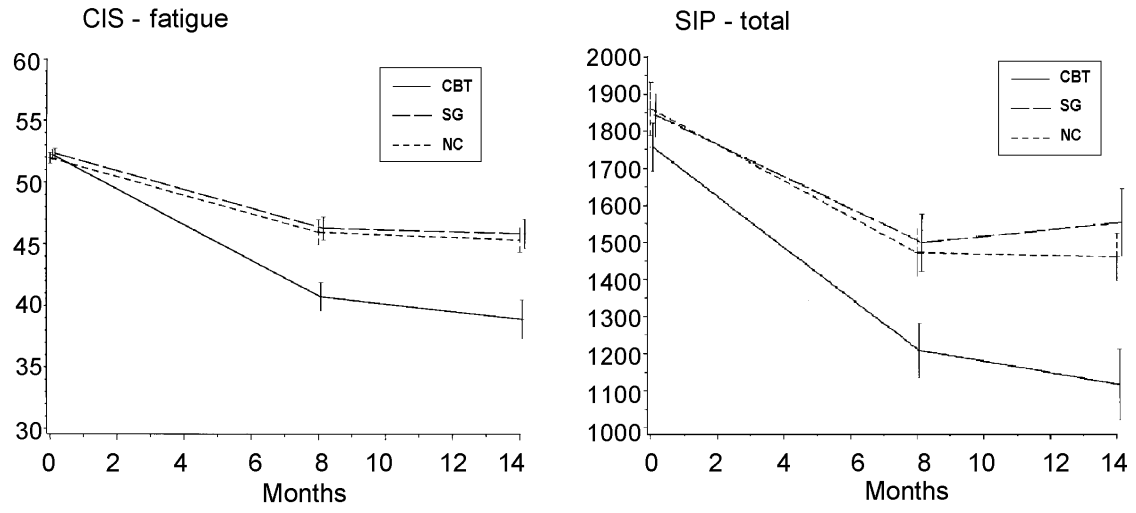

Figure 3. Effect of three study conditions on the two primary outcome variables, fatigue severity (CIS) and functional impairment (SIP)

Table 3 gives the estimated differences between the study groups in secondary outcome variables. At 8 months, improvement in Karnofsky performance status, psychological well-being and quality of life was statistically significantly greater in the CBT group than in either of the other groups. Differences in the time spent working in a job did not reach the 5% level of significance. Statistically significant treatment effects between CBT and support groups were found in all secondary outcome variables at 14 months. Treatment effects of CBT and natural course showed statistically significant differences for the Karnofsky performance status at both 8 and 14 months and for psychological well-being at 8 months.

Table 3. Estimated effect of CBT compared with support groups and natural course on secondary endpoints

		CBT vs support groups		CBT vs natural course	
		Treatment effect (95% CI)	p	Treatment effect (95% CI)	p
Karnofsky	8 months	- 5.7 (-8.4 to -3.1)	0.0001	- 5.2 (-7.8 to -2.6)	0.0001
	14 months	- 6.3 (-9.6 to -3.0)	0.0002	- 5.4 (-8.6 to -2.2)	0.0009
SCL-90	8 months	13.9 (4.3 to 23.5)	0.0048	13.4 (4.0 to 22.7)	0.0053
	14 months	11.2 (1.1 to 21.3)	0.0304	6.7 (-3.0 to 16.5)	0.1767
EuroQol	8 months	- 7.8 (-14.0 to -1.8)	0.0114	- 4.0 (-10.0 to 2.0)	0.1878
	14 months	- 9.2 (-15.6 to -2.8)	0.0049	- 2.3 (-8.4 to 3.8)	0.4619
Work	8 months	- 5.6 (-11.7 to 0.4)	0.0681	- 2.9 (-8.8 to 3.0)	0.3362
	14 months	- 9.6 (-17.1 to -2.0)	0.0132	- 5.9 (-13.2 to 1.4)	0.1134

CBT= Cognitive Behaviour Therapy

Table 4. Clinically significant improvement in the treatment groups for fatigue severity, Karnofsky performance status, and self-rated improvement

		Number of patients with improvement / total						p*	
		CBT		Support Groups (SG)		Natural Course (NC)		CBT vs SG	CBT vs NC
8 months	CIS fatigue	27/83	33%	10/80	13%	10/78	13%	0.003	0.005
	Karnofsky	29/71	41%	11/69	16%	9/75	12%	0.001	<0.001
	Self-rated improvement	42/74	57%	12/71	17%	23/78	30%	<0.001	0.001
14 months	CIS fatigue	20/58	35%	8/62	13%	13/76	17%	0.009	0.026
	Karnofsky	28/57	49%	12/62	19%	17/75	23%	0.001	0.001
	Self-rated improvement	29/58	50%	9/62	15%	24/76	32%	<0.001	0.034

CBT= Cognitive Behaviour Therapy. CIS=checklist individual strength. * Fisher's exact test

Table 5. Parameter estimates, SE and partial R^2 of all factors related to the outcome measure fatigue severity or functional impairment (baseline minus 8 months) at p<0.05 in order of entrance to the models

Factor	Coefficient	SE	Partial R^2
Fatigue severity (CIS)			
CBT x sense of control	0.5088	0.0883	0.0856
baseline CIS fatigue severity	0.7010	0.1469	0.0515
focusing on bodily symptoms	-0.2611	0.0838	0.0368
CBT x activity pattern 1	-8.902	2.545	0.0208
activity pattern 2	-3.439	1.229	0.0229
sense of control	0.3535	0.1723	0.0147
sex (female)	2.761	1.386	0.0133
Functional impairment (SIP)			
baseline SIP	0.4767	0.0604	0.1788
CBT	1005	281.9	0.0321
CBT x focusing on bodily symptoms	-25.06	8.838	0.0266

CIS=checklist individual strength; SIP=sickness impact profile.

Table 4 shows the proportions of patients with clinically significant improvements in fatigue severity, Karnofsky performance status, and self-rated improvement. For these three variables, the proportion with clinically significant improvement was statistically significantly higher in CBT than in the control conditions.

All factors in the stepwise regression related to the outcome measures fatigue severity and functional impairment at p<0.05 are presented in order of entrance in the model in table 5. The improvement in fatigue severity at 8 months was predicted by interactions of CBT with sense of control and by a passive activity pattern, rather than by CBT alone. In the CBT study groups, patients with a greater sense of control at baseline had a larger decrease in fatigue severity at 8 months, immediately after

CBT, than patients with lower sense of control. The reverse was true for patients with a passive activity pattern; they improved less than patients with other activity patterns.
Improvement in functional impairment at 8 months was predicted by CBT alone and by interaction of CBT and focusing on bodily symptoms. Patients assigned CBT improved more than patients in both control groups. However, patients in CBT with a high level of focusing on bodily symptoms were improved less than patients with lower scores on this factor

Discussion

In this study, CBT was more effective for CFS patients than guided support groups or the natural course. Intention-to-treat analyses showed clinically significant improvement in fatigue severity, Karnofsky performance status, and self-rated improvement in substantial proportions of patients treated with CBT.
An unexpected finding was that support groups were no more effective than the natural course (figure 3). This finding contrasts with other chronic diseases in which support groups are beneficial. However, 80% or more of the patients experienced mutual understanding in the support group, and rated the contact with the therapist and the atmosphere in the group as good. These findings suggest that clinical improvement and patients' satisfaction are not correlated and may be independent.
There was a large withdrawal rate in the trial, especially in the CBT and support groups. Many CFS patients eagerly expect a medical solution for their complaints and are quite sceptical about psychological treatments. Others expected more benefit from medical examinations or alternative treatments. These patients may have withdrawn prematurely. The physical burden of travelling to the centre for therapy was another reason for patients to withdraw. However, many patients who withdrew during treatment were willing to attend for assessment of the primary outcome variables. At 8 months, there was a withdrawal rate of 25%, but only 11% of the patients had missing data.
Results of the analyses depend among other assumptions on that of "missingness at random" which means that missingness is possibly related to the observed data, but, conditional on these data, not to the (unknown) value of the variable itself. Although we cannot prove the assumption, we can partially check in as follows[31]: comparison of characteristics of completers and non-completers (age, sex, duration of complaints, centre, and all baseline measures) showed no differences. Furthermore, the results of the intention-to-treat analyses and those of the analyses of the completers, were mostly qualitatively similar.
Supporting evidence of the effectiveness of CBT was found in the significant improvement in Karnofsky performance status rated by an independent clinical psychologist in the group of patients treated with CBT compared with the control groups. A significant treatment effect on quality of life, psychological wellbeing, and work rehabilitation was only found in the comparisons of CBT with support groups

and not between CBT and natural course. We were especially interested in work rehabilitation, a new element in the tested treatment protocol. The final goal of CBT for CFS included work rehabilitation for patients who used to be active in a job and resumption of other personal activities for patients without a job. We good not conclude the extent to which this goal was reached, because only hours working in a job were measured. However, in our sample of 270 patients only 33% had a job at baseline, whereas 76% had been employed before the onset of CFS. For the unemployed patients, securing employment within the limited period of treatment and follow-up would be difficult, although most of these patients did resume personal activities. The development of adequate measures of rehabilitation should have high priority in future research on CBT for CFS.

The proportions of patients with clinically significant improvement in this study were lower than in other CBT trials. We suggest several explanations for this discrepancy. First, therapists in this study had no clinical experience with CFS patients at the start of the trial. Afterwards, 82% of the therapists agreed with the statement that CFS patients are more difficult to treat than patients with psychiatric diagnoses, and 54% agreed that CFS patients are more difficult to treat than patients with other functional somatic syndromes. Second, criteria for statistical and clinical significance in this study were more stringent than in the previous trials. The cut-off score for clinically significant improvement was based on normative comparisons of CFS patients and healthy individuals and was perhaps overly stringent. In a recent evaluation of the concept of clinically significant improvement[32], Kendall and colleagues questioned whether patients should be compared with a non-representative "supernormal" sample of healthy people, from which all individuals with any psychological or physical disorders are excluded. Third, the treatment protocol seemed not to be suitable for a group of CFS patients who showed passive activity patterns. Analyses of prognostic factors showed that patients with this activity pattern and patients with a strong tendency to focus on bodily symptoms improved less than did patients not characterised by one of these factors. In our clinical practice, the treatment protocol already has now been adjusted to both aspects. In the new treatment protocol, the emphasis is now on impeding cognitions and behaviour rather than on symptoms. Furthermore, a different treatment protocol has been developed for patients with a passive activity pattern. The early emphasis in CBT on a base level of daily activity, so important for moderately active CFS patients, seems to increase the fear of physical activity in passive CFS patients and impedes the subsequent gradual increase of physical activity. Therefore, CBT for patients with passive activity patterns starts with building up physical activity, whereas more active patients still start with attaining and maintaining a base level of daily activity.

The results of this trial suggest that CBT can be transferred from CFS research clinics to therapists with no previous experience in CBT. This transfer is essential to detach the treatment from medical research settings, in which only a limited number of CFS patients can be treated. To increase accessibility of this treatment for all CFS

patients in future, CBT will have to be implemented outside university medical settings. This idea accords with Wessely and colleagues' suggestion of transferring the diagnosis and treatment of functional somatic syndromes from medical subspecialists to more broadly based general physicians aided by psychiatrists or psychologists[33]. Ideally, general practitioners should diagnose CFS and refer patients to psychotherapists for CBT, without detours to medical specialists, as in other functional somatic syndromes[33]. Before this goal can be reached, expertise needs to be generalised from specialist centres to general practitioners and behaviour therapists in general (mental) health settings.

Contributors

Judith Prins co-ordinated data collection, and analysis and drafted the report. Gijs Bleijenberg developed the original idea, was responsible for the study design, study co-ordination, training of therapists, and development of treatment protocol, and contributed to writing of the paper. Ellen Bazelmans contributed to study design, training of therapists, and treatment protocol, supervised the therapists, and contributed to editing of the paper. Lammy Elving was responsible for the development of the diagnostic protocol and selection of patients and contributed to data collection and editing of the paper. Theo de Boo was responsible for data analysis and statistics and contributed to the writing of the paper. Johan Severens contributed to study design and editing of the paper. Gert-Jan van der Wilt contributed to the study design and data analysis. Philip Spinhoven contributed to study co-ordination, data collection and editing of the paper. Jos W.M. van der Meer developed the original idea and contributed to study design, study coordination, and writing.

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Chapter 5

Identifying physical activity patterns in chronic fatigue syndrome using actigraphic assessment

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Identifying physical activity patterns in chronic fatigue syndrome using actigraphic assessment

Abstract

Objective: Changes in physical activity are thought to play an important role in maintaining symptoms in chronic fatigue syndrome (CFS). The aim of this study was to describe intra-individual physical activity patterns in more detail and to identify pervasively passive patients.

Methods: With help of a movement-sensing device, physical activity levels were registered continuously over a 12-day period in 277 CFS patients. Within this registration period, the ten largest activity peaks were computed. The intensity and duration of these activity peaks and their subsequent rest periods were described and compared to those of 47 healthy controls. In addition, the patients' 12 daily activity scores were used to identify patients who were characterised by low levels of physical activity throughout the registration period.

Results: The CFS sample had less intense and shorter activity peaks, while the average rest periods that followed these peaks lasted longer. Approximately one fourth of the CFS sample differed distinctly from the control group and was labelled as pervasively passive.

Conclusion: The measurements and classification of actual physical activity levels were found to reduce heterogeneity in the CFS population and therefore could provide the opportunity to optimise behavioural intervention protocols for CFS.

Introduction

Patients with chronic fatigue syndrome (CFS) often describe themselves as being profoundly less physically active, and unable to reach similar physical activity levels as compared to before the onset of their illness. Many CFS patients report that even minor physical exertion results in a significant increase in fatigue and CFS related symptoms. There is evidence that many CFS patients cope with their illness by resting or avoiding physical activity[1-3]. In cognitive behaviour models of CFS it has been hypothesised that pervasive avoidance of physical activity decreases the tolerance for physical exertion, and as such can perpetuate the CFS-related symptoms[4].

Clinical observations and especially patients' self reports suggest, that the lifestyles of some other CFS patients are characterised by very active periods, followed by abnormally long periods of inactivity. Some authors have suggested that in CFS the periods of rest are interrupted by short periods of marked activity during which patients perform at "normal" levels[5]. These short periods of high physical activity may have detrimental effects and cause fatigue in patients with a low overall physical activity level. However, until now no empirical data are available to test this assumption.

Since changes in physical activity patterns are supposed to play an important role in

maintaining symptoms and subsequently many therapeutic interventions have emphasised on activity regulation, it is crucial to identify abnormal activity patterns in a valid and reliable way. In earlier studies of our research group, actual motor-activity has been recorded with an ankle-worn motion sensing device (actometer) in conjunction with self-report measures of physical activity[6,7]. The data of these studies suggest that self-report measures of activity reflect the patients' view about their physical activity and may have been biased by cognitions concerning illness and disability.

In clinical practice it has been observed that part of the CFS patients are characterised by profound physical inactivity, while other patients are far more active but nevertheless judge themselves as rather inactive. Both, research results and clinical impressions, indicate that it is important to test whether patients' self-report concerning long term inactivity after exertion, large day-to-day fluctuations in activity, and pervasive inactivity, can be substantiated by a behavioural measure of activity.

In this study, physical activity was measured with an actometer over 12 consecutive days in both healthy controls and CFS patients. The general activity scores that were used in previous studies provided little information about intra-individual differences and might have obscured large fluctuations in daily activity scores. Therefore, parameters were developed to describe changes in physical activity in more detail. Specific attention was paid to periods of high activity and subsequent rest periods. Furthermore, it was tested whether the CFS sample was characterised by many large day-to-day fluctuations in physical activity. The actometer measurements were also used to subtype activity patterns in CFS in order to identify pervasively passive patients.

Previous studies found that part of the CFS patients had elevated depression scores. Since physical inactivity could be a symptom of depression, one might hypothesise that in particular pervasively passive patients would be characterised by increased levels of psychological distress. Therefore, it was tested whether levels of fatigue, psychological distress and functional impairment were elevated in pervasively passive CFS patients, as compared to more physically active CFS patients.

Method

Subjects

All patients with a major complaint of fatigue, referred to the outpatient clinics of internal medicine of the University Medical Centre Nijmegen and the University Hospital Maastricht between October 1996 and January 1998 were assessed by means of detailed history, physical examination and questionnaires. Patients had to fulfil the CDC criteria for CFS[8]. Additional criteria were age between 18 and 60 years, no previous or current engagement in CFS research, not pregnant or engaged in pregnancy-stimulating techniques and living within one-and-a-half hour travelling time of the participating centres. Ninety-nine of the 476 patients who fulfilled the criteria of CFS did not meet the additional operational criteria. The remaining patients were

asked whether they wanted to participate in a randomised controlled study to assess the effects of cognitive behavioural therapy upon fatigue and functional disability. Ninety-nine patients refused participation and one patient was excluded because of pregnancy at pre-test. The baseline data of the remaining 277 CFS patients were analysed in this study.
Furthermore, actometer and self-report data of 47 healthy subjects were collected. Most of these subjects were asked by fatigued patients as neighbourhood controls in other chronic fatigue studies.

Instruments
The actometer (©Actilog V3.0) that was used is a motion sensing device that can register and quantify human physical activity[6]. The actometer is small (55*25*15mm) and light (26gr) and has to be worn at the ankle. The small size makes the actometer suitable for long term continuous registrations. The actometer has a piezo-electric sensor that is sensitive in three directions. Accelerations of the sensor larger than a pre-defined threshold are considered as activity and are stored into an internal memory. Each second the counter of the actometer is read and reset by the micro controller. The integration counter is set at five minutes providing every 5 minutes an activity score that is stored in the internal memory of the actometer. At the end of the registration period data are fed into an external computer.
In this study the actometer was worn day and night during at least a 14-day period. In order to retain twelve complete registration days, the first and last registration days were omitted for the analyses. Subjects were asked to remove the actometer only in certain situations (swimming, bathing) and to write in a daily complaint diary whether there were any other lengthy periods that they removed the actometer. When the actometer had failed more than two days, patients were asked to carry the actometer for an additional two weeks. In the final statistical analyses, maximally one invalid registration day was allowed. This missing value was replaced by the mean value of the remaining 11 registrations days.
Specialised software was used to calculate several parameters. This software also graphically visualised the levels of activity (figure 1). The software distinguished rest (night) and wake (day) periods, resulting in a day length score. All other parameters that were developed pertain to these daily active (wake) periods.

Definition of general physical activity
For the total registration period 12 daily physical activity scores were calculated. Subjects who were missing more than one valid registration day were omitted from further analyses. In case of one missing day, that day was substituted with the mean value of the remaining 11 registration days. A general physical activity score reflected the average physical activity level over the total 12-day time period and was expressed in the average number of accelerations per five minute period.

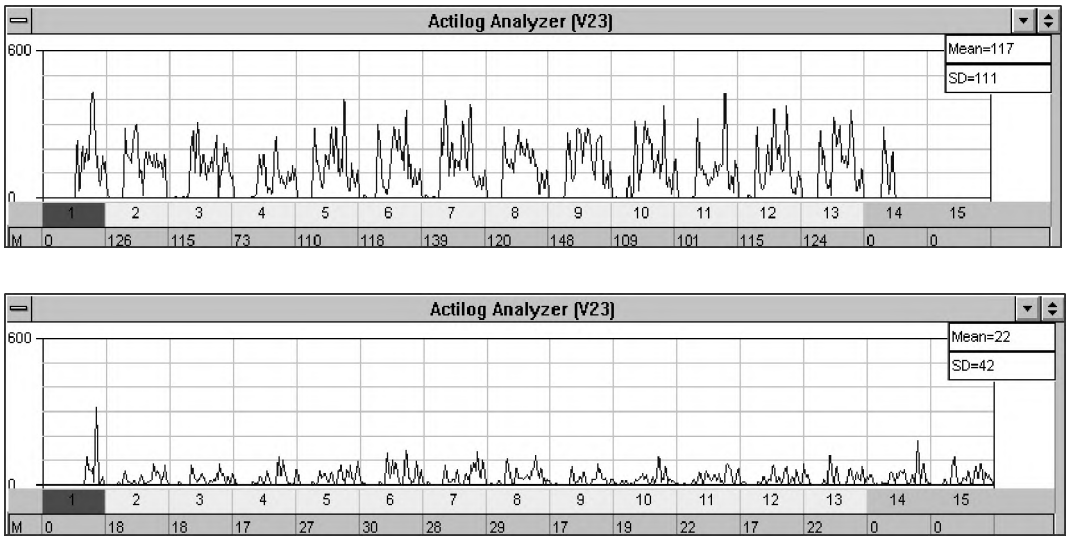

Figure 1. Twelve day actigraphs of a pervasively active and pervasively passive patient

Definition of parameters of high activity and subsequent rest periods

In order to distinguish between relatively high (peak) and low (valley) activity periods the average general physical activity score of the control group (table 2, mean score =91) was designated as cut-off. The succeeding (5-minute) time periods above this cut-off were labelled as peaks and the succeeding 5-minute time periods below this cut-off as valleys. The program identified the ten largest activity peaks by calculating the total energy of each peak (duration peak * Δ number of accelerations in each succeeding 5 minute period). Subsequently, both the average peak duration and average peak amplitude of these ten largest peaks were calculated.

Specific attention was paid to what happened after each of these ten activity peaks. Rest periods were defined as the amount of time (after a large peak) that the actometer score stayed below the pre-set value of 91. The average duration of these ten rest periods was calculated for each subject (rest duration after peak).

Both, peak and rest duration were expressed in minutes by multiplying the number of succeeding registration intervals by 5. The number of accelerations occurring in a 5-minute interval expressed the intensity of activity (peak amplitude).

Furthermore, the average intensity of activity during the one-hour period following each peak was computed. Theoretically, another peak could occur during this time period. Subsequently, the average peak amplitude during the 10 largest peaks was compared with the average actometer amplitude during the one-hour periods following these peaks. This comparison made it possible to calculate the relative decrease in activity after peak performance, which could be expressed as a percentage of reduction in activity: % activity reduction after peak.

Definition of large day-to-day fluctuations

Both absolute and relative fluctuation scores were computed to detect fluctuations in activity over subsequent days. A major day-to-day fluctuation was counted as the individuals' daily physical activity score showed a 22-point difference with the subsequent day. The absolute difference of 22 points that was used equals the standard deviation of the mean general physical activity score of the total CFS sample (table 1). The number of absolute large day-to-day fluctuations in a 12-day period could range from 0 to 11. Relative large fluctuations were defined as day-to-day differences of more than 33%; the total score was the number of relative large day-to-day fluctuations and could also range from 0-11 points.

Definition of pervasively passive CFS patients

The individuals' activity patterns were based on the 12 individual daily physical activity scores. Since our purpose was to make a classification within the CFS sample, the mean general physical activity score of the total CFS sample served as reference value (mean=66). For each subject the 12 daily physical activity scores were compared to this reference value. When a daily physical activity score fell below this value, that day was labelled as relatively inactive. A daily physical activity score equal or above this value was labelled as relatively active.

Taking in account the possibility of unforeseen external circumstances affecting activity levels, it was decided that pervasively passive patients had to be less active compared to other CFS patients for at least 90% of the total observation period. Subsequently, pervasively passive patients were defined as those subjects whose average daily physical activity scores stayed below the reference score in at least eleven of the twelve assessment days. Patients scoring at least eleven days above the pre-set value were defined as pervasively active, while the remaining patients were labelled as moderately active. For comparison, activity profiles of healthy controls were calculated by using the same procedure and the same CFS reference value.

Self-reported fatigue, activity, depressive symptoms and functional disability

Patients and controls were asked to rate their fatigue and activity levels four times a day on a five point (0-4) scale. These daily ratings were averaged into experienced daily fatigue and reported daily activity scores (range 0-16). Depressive symptoms were rated with the Beck Depression Inventory (BDI-tot)[9]. Seven subscales of the Sickness Impact Profile (SIP) were used to assess functional disability in the following areas: home management, mobility, alertness behaviour, sleep/rest, ambulation, social interactions and recreation and pastimes[10]. These seven subscale-scores were added to provide a total score of general disability.

Statistical analyses

Testing differences between CFS and controls on nominal variables was done by the Chi^2 test, and continuity correction was applied. T-tests or analyses of variance were

used to make group comparisons between other variables. To control for the gender differences in both samples, gender was introduced as fixed factor in the analysis. We tested two-sided and the alpha was set at 0.05.
For the behavioural measures a multivariate analysis of variance was carried out with general physical activity, peak duration, peak amplitude, rest duration after peak and % activity reduction after peak, as dependent variables and group and gender as factors. Similar multivariate analyses were carried out for the relative and absolute large day-to-day fluctuation scores, and for the experienced daily fatigue and reported daily activity score.
Four one-way Anova's were used to assess whether pervasively passive, moderately active, and pervasively active CFS patients differed with respect to their experienced daily fatigue, reported daily activity, depressive symptoms and general disability scores. In case of an overall significance, the Bonferoni correction was applied to compare the three individual groups.

Results

The group characteristics of the CFS patients and healthy controls are displayed in table 1. The CFS sample had significantly more females but the groups were comparable concerning their average age. Tables 2 and 3 show that the general physical activity was significantly higher for the controls and that in both groups men had higher general activity scores compared to women.

Table 1. Group demographics

	CFS total (n= 277)	Controls (n= 47)	
Gender			
F/M	218/59	23/24	Chi^2 =14.2, p=0.00[a]
% females	79%	49%	
Age			
yrs	37.5	40.1	t=1.5, p=0.14[b]
range	(18-60)	(19-63)	

[a] Chi^2 test, [b] t-test

Peaks and subsequent rest periods

Tables 2 and 3 illustrate that the average peak amplitude of healthy controls was higher, and men (across groups) had higher peaks compared to women. The peak duration was also longer for healthy controls, while in both the control and CFS group men had longer peaks than females. The rest duration after peak was longer for CFS patients and no gender differences were found. The % activity reduction after a peak was larger for CFS patients, no gender differences were found.

Table 2. Means, standard deviations and proportions of activity parameters and the types of activity patterns

	CFS ♂ (n=218)	CFS ♀ (n=59)	CFS Total	Control ♂ (n =23)	Control ♀ (n=24)	Control Total
General physical activity[1]	65 ± 22	70 ± 22	66 ± 22	84 ± 16	97 ± 30	91 ± 25
Peak amplitude[1]	177 ± 27	182 ± 30	178 ± 28	179 ± 20	198 ± 27	189 ± 25
Peak duration in minutes[2]	102 ± 40	124 ± 55	107 ± 44	141 ± 40	157 ± 51	150 ± 46
Duration rest period after peak[2]	92 ± 51	87 ± 43	91 ± 50	53 ± 22	70 ± 58	62 ± 45
% activity reduction after peak	59 ± 15	57 ± 15	59 ± 15	44 ± 16	47 ± 19	46 ± 17
Nr. of relative large day-to-day fluctuations	4.0 ± 2.2	3.6 ± 2.1	3.9 ± 2.2	3.3 ± 1.8	3.3 ± 1.9	3.3 ± 1.8
Nr. of absolute large day-to-day fluctuations	3.4 ± 2.0	3.7 ± 2.1	3.5 ± 2.0	3.8 ± 1.6	4.1 ± 2.0	3.9 ± 1.8
Experienced daily fatigue	8.1 ± 2.2	7.7 ± 2.0	8.0 ± 2.1	2.4 ± 1.8	1.0 ± 0.8	1.7 ± 1.6
Reported daily activity	4.7 ± 1.7	4.4 ± 1.5	4.6 ± 1.7	6.0 ± 2.5	6.2 ± 2.4	6.1 ± 2.4
% pervasively passive	26%	17%	24%	0%	0%	0%
% moderately active	58%	69%	60%	56%	58%	59%
% pervasively active	16%	14%	15%	44%	42%	41%

[1] activity levels expressed in number of accelerations per 5 minute period
[2] peak and rest durations expressed in minutes

Large day-to-day fluctuations

There were no significant group, gender or interaction effects for the number of absolute large or relatively large day-to-day fluctuations (tables 2 and 3).

Pervasively passive CFS patients

In total 64 CFS patients (24%) were subtyped as pervasively passive. None of the healthy controls met this qualification. (0% controls vs. 24% CFS, Chi^2 =14.2, p=0.000) In both the control and CFS group the majority of subjects was classified as moderately active (58% controls vs. 60% CFS, Chi^2=0.07, p=0.870), while proportionally more controls got the qualification pervasively active (42% controls vs. 15% CFS, Chi^2 =18.1, p=0.000).

Experienced daily fatigue and reported daily activity

Multivariate analysis showed significant group and gender effects, but no interaction effect. CFS patients reported more experienced daily fatigue and less reported daily activity compared to controls. Overall, men reported less experienced daily fatigue compared to women (tables 2 and 3).

Table 3. Results of the statistical analyses

Dependent measures	F	df	p	Dependent measures	F	df	p
General physical activity				Number of relative large day-to-day fluctuations			
group*	39.7	3,320	0.00	group	2.0	3,308	0.16
gender	6.1	3,320	0.01	gender	0.1	3,308	0.70
group x gender	0.9	3,320	0.35	group x gender	0.3	3,308	0.56
Peak Amplitude				Number of absolute large day-to-day fluctuations			
group	3.9	3,320	0.05	group	1.3	1,308	0.25
gender	7.3	3,320	0.01	gender	0.7	1,308	0.39
group x gender	2.4	3,320	0.13	group x gender	0.1	1,308	0.94
Peak duration				Experienced daily fatigue			
group	25.8	3,320	0.00	group	346.1	1,311	0.00
gender	7.3	3,320	0.01	gender	6.8	1,311	0.01
group x gender	0.2	3,320	0.68	group x gender	2.6	1,311	0.11
Duration rest period after peak				Reported daily activity			
group	12.2	3,320	0.00	group	24.8	1,308	0.00
gender	0.7	3,320	0.42	gender	1.8	1,308	0.68
group x gender	2.0	3,320	0.16	group x gender	0.1	1,308	0.84
% Activity reduction after peak							
group	25.3	3,320	0.00				
gender	0.1	3,320	0.72				
group x gender	1.0	3,320	0.32				

*group: CFS/Controls

Activity patterns and the relation with experienced daily fatigue, reported daily activity, depressive symptoms, and general disability

One-way analyses of variance revealed a significant effect for reported daily activity (table 4). Post-hoc testing revealed that pervasively passive CFS patients reported less daily activity compared to moderately active and pervasively active CFS patients. Moderately active patients had significantly lower reported daily activity scores compared to the pervasively active patients.

Pervasively passive CFS patients had higher general disability scores compared to moderately active and pervasively active CFS patients. Levels of daily experienced fatigue and psychological distress were equal for the three types of activity patterns (table 4).

Table 4. The relation between activity patterns and self-report measures

	Pervasively passive	Moderately active	Pervasively active	F-value	p-value
Experienced daily Fatigue	8.3 ± 2.3	7.9 ± 2.1	7.8 ± 1.8	F(2,261)= 1.0	p=0.372
Reported daily Activity	4.0 ± 1.4	4.7 ± 1.6	5.6 ± 1.7	F(2,236)=11.3	p=0.00
Psychological Symptoms (BDI-tot)	13.4 ± 6.3	13.2 ± 6.4	12.9 ± 5.7	F(2,266)= 0.1	p=0.93
General Disability (SIP7-total)	1967 ± 630	1743 ± 580	1793 ± 690	F(2,266)= 3.2	p=0.04

One-way analyses of variance with type of activity patterns as independent factor

Discussion

Previous studies showed that CFS patients were as a group less physically active compared to healthy controls. Nevertheless, quite large variations in actometer scores suggested considerable individual differences. Earlier studies also indicated that self-report measures of physical activity and actual measurement of activity were not highly correlated. Furthermore, our clinical observations strengthened our belief that by merely comparing overall levels of physical activity important information about the individual's physical activity patterns would be lost.

To our knowledge this study is the first attempt to distinguish and describe physical activity patterns in a large CFS sample by means of prolonged measurement of actual physical activity. The mean general physical activity score indicated that over a prolonged period of time, CFS patients not only reported to be less active but also were physically less active compared to healthy controls. Overall, men were more physically active compared to females. However, inspection of the average scores indicated that this was especially true for the control group. The relatively small control group could have reduced the statistical power to detect a significant interaction effect (group x gender).

The average peak amplitude of the ten largest peaks was lower for the CFS group and the average duration of these intense activity periods were significantly shorter for CFS patients. It is possible that the intensity of peaks reflects to a larger extent physical or motor capacity, while the length of the peaks reflects the endurance capacity for physical exertion and is as such more closely related to fatigue. In future research one could test this assumption by comparing physical condition data of endurance tests with the actometer parameters.

Since CFS patients often indicate that they need lengthy and excessive rest periods after physical exertion, the periods after peak activity were inspected. The results showed that CFS patients indeed had longer rest periods following their activity peaks and patients were characterised by a larger drop in activity during the hour after a peak. These overall (group) findings seem to fit the general statements patients give about changes in their activity. Compared to healthy controls, no

indication was found that the CFS patients as a group were characterised by a high number of large day-to-day fluctuations in activity. However, this finding does not exclude that there are individuals who have such a pattern. The fluctuation measures used were limited to day-to-day changes and did not control whether some patients were active for some days, and then inactive for a prolonged period of time. The day-to-day fluctuation measures were based on somewhat arbitrary criteria (one standard deviation and 33% activity change). However, when we post-hoc tested alternative criteria (50 or 66% activity change) again no significant group differences between controls and CFS patients emerged. One could argue that large day-to-day differences are rare in a group of patients that is overall inactive. Additional testing revealed that when the pervasively passive patients were omitted from the analyses again no differences on day-to-day fluctuations occurred between the remaining more active CFS patients and controls. Previous research of our group has shown that self-report measures of activity and behavioural data often correlate poorly[6]. One reason for these low correlations could be that self-report of complaints and behaviour may be biased by illness and disability related cognitions.

In earlier studies we observed that CFS patients differed considerably in their physical activity levels, but that a subgroup of CFS patients seemed to be physically inactive all the time. However, with self-ratings of activity it was rather difficult to isolate this group, since the majority of CFS patients reported to be rather inactive. With a simple procedure we tried to identify these patients. The validity of this procedure was backed up by the fact that none of the healthy controls fell into the category of pervasively passive and by the fact that pervasively passive had significantly lower daily reported activity scores. In the current sample ambulant patients who volunteered and were able to participate in an intervention study were studied. Therefore, it is possible that the obtained results underestimate the prevalence of pervasively passive CFS patients in the total population of CFS patients.

The results of this study showed no relation between type of activity pattern and levels of depressive symptoms. As such, psychological distress or levels of experienced fatigue were unlikely to be the major determinants of differences in physical activity levels. One possible explanation could be that pervasively passive patients are more inclined to avoid physical exertion in order to prevent fatigue, or that those pervasively passive patients are characterised by more physical dysfunctioning. Higher incidence of physical dysfunctioning could be in line with the fact that pervasively passive patients reported more disability. In future studies it would be worthwhile to compare physiological and psychological parameters of patients according to their physical activity patterns.

Attempts have been made to associate levels of physical activity with other behavioural and psychological measures. A recent study reported a relation between neuropsychological impairment and functional disability in patients with CFS[11]. Patients who failed a higher number of neuropsychological tests reported significantly

more days of general inactivity. The authors suggested that this association was not merely a result of psychiatric factors but perhaps indicated a failure in a common physiological mechanism. However, these findings could have been biased by the fact that physical activity, in contrast to neuropsychological functioning, was measured by self-report.

The obtained results confirmed that the CFS patients were as a group less active and took more rest after physical exertion, and that it was possible to identify pervasively passive patients. However, the results also showed that a proportion of CFS patients had activity patterns and parameters comparable to those of controls. One can hypothesise that pervasively passive CFS patients do need quite a different approach compared to relatively active CFS patients. Perhaps that passive patients benefit more from increasing physical activity, while activity regulation is more important for the more active CFS group. Preliminary findings of our research group indeed indicated that subtyping physical activity patterns at baseline could significantly improve the prediction of success of cognitive behaviour therapy. Although the current findings need further exploration, they offer several perspectives for individualising treatment protocols according to the type of activity pattern, and a further refining of CFS classification.

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Chapter 6

Psychiatric disorders among patients with chronic fatigue syndrome in a randomised controlled trial for the effectiveness of cognitive behaviour therapy

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Psychiatric disorders among patients with chronic fatigue syndrome in a randomised controlled trial for the effectiveness of cognitive behaviour therapy

Abstract

Background Lifetime and current psychiatric disorders have been associated with poor outcome in the prognosis of patients with chronic fatigue syndrome. The impact of psychiatric disorders on treatment withdrawal and outcome of cognitive behaviour therapy, an effective treatment for chronic fatigue syndrome patients, is not known.

Subjects and methods Lifetime and current psychiatric diagnoses were assessed at baseline with a structured psychiatric interview in a multicentre randomised controlled trial of 270 patients allocated to cognitive behaviour therapy, support groups or natural course during 14 months. The proportions of psychiatric diagnoses in chronic fatigue syndrome patients were compared to data of a general population study. Proportions of patients with and without psychiatric diagnoses were compared concerning treatment withdrawal and clinical improvement. Outcomes of patients with and without current psychiatric diagnoses were examined in general linear models.

Results Lifetime and current psychiatric disorders were found in 50% and 32% of the chronic fatigue syndrome patients. The proportions of mood disorders were higher than in the general population. No significant differences were found between patients with and without current or lifetime psychiatric diagnoses in treatment adherence or clinical improvement in each of the conditions. In cognitive behaviour therapy, support groups and natural course patients with a current psychiatric diagnosis had outcomes of fatigue severity and functional impairment identical to patients without a current psychiatric diagnosis.

Conclusions Chronic fatigue syndrome patients with psychiatric co-morbidity have not a higher withdrawal rate or worse outcome than patients without, when treated with cognitive behaviour therapy.

Introduction

Chronic fatigue syndrome is characterised by persistent or relapsing unexplained chronic fatigue, of new or definite onset and lasting for at least six months. Fatigue is not the result of an organic disease or ongoing exertion, rest does not alleviate it, and it results in substantial reduction in previous levels of occupational, educational, social and personal activities. Causes for CFS have not been found and most patients do not recover. In the past decade chronic fatigue syndrome (CFS) frequently has been associated with psychiatric disorders. Discussions about the prevalence of psychiatric disorders in CFS have been obscured by different criteria for CFS, different instruments for psychiatric disorders and different settings in which patients were seen. Another obstacle in clarifying the role of psychiatric disorders in CFS arises from the overlap between symptoms of CFS and psychiatric disorders like depression. Over- or underdiagnosis of psychiatric disorders may be the result.

Despite these methodological and definition problems, Wessely and colleagues[1] compared a large number of studies and concluded that the evidence for some association between psychiatric disorders, most common depressive disorders, and CFS is convincing. Several explanations for the association found were considered, like misdiagnosis of CFS as a psychiatric disorder or the reverse, co-morbidity in the onset of both diagnoses or psychological symptoms as a normal reaction to physical illness. As predictors of outcome in the prognosis of patients with CFS psychiatric disorders have shown conflicting results. In two studies lifetime dysthymia has been associated with poorer outcome[2,3], whereas in another study no association with premorbid psychiatric diagnoses was found[4]. In the latter study a worse outcome was found for patients with a primary psychiatric diagnosis assessed at follow-up[4]. The complex issue of psychiatric disorders in CFS raises questions about the impact of psychiatric co-morbidity on treatment of CFS. Cognitive behaviour therapy (CBT) and graded exercise therapy were found to be the only effective therapies for CFS patients[5,6]. In two randomised controlled trials of CBT for CFS psychiatric diagnoses were assessed, but effects on treatment outcome were not reported in one study[7] and no significant differences in the presence of psychiatric diagnoses at baseline were found between improved and unimproved patients in the other study[8]. However, the latter finding may have been due to small sample size. In an uncontrolled trial CFS patients with a poor outcome four years after CBT were likely to have had a previous psychiatric history[9]. Considering the limited results available, the impact of psychiatric disorders on treatment outcome in CBT remains unclear.

In our trial CBT was more effective for CFS patients than guided support groups or the natural course[10]. However, the proportions of patients with clinically significant improvement were lower than in previous CBT trials. Several factors were suggested to explain these results. Therapists in this study had no clinical experience with CFS and afterwards many of them agreed that CFS patients are more difficult to treat than patients with psychiatric diagnoses. Also, criteria for clinical significant improvement were very stringent. Further, the treatment protocol seemed not to be suitable for patients with a passive activity pattern and patients with a strong tendency to focus on bodily symptoms[10], and patients who were engaged in a legal procedure concerning financial benefits had a worse outcome[11]. Besides lower improvement rates the trial suffered from a large withdrawal rate, especially in the treatment groups. Withdrawal was defined differently for the three groups in the trial. In the natural course group, only patients not attending the assessments were classified as withdrawing, whereas in the two intervention groups those who did not start or who stopped treatment were also counted. The explanations we suggested for the large withdrawal rate were scepticism about psychological treatments and the physical burden of travelling for treatment. Psychiatric co-morbidity might offer another explanation for the larger withdrawal rate and the smaller improvement rate in our multicentre randomised controlled trial of CBT for CFS.

In this article we will address the impact of psychiatric co-morbidity on the prognosis

of CFS in our trial. First, the proportions of lifetime and current psychiatric diagnoses occurring in association with CFS will be studied. Next, lifetime and current mood and anxiety disorders will be compared to the published results of a prospective study in a large sample of the general population in the Netherlands with the same age range during the same period also using a structured clinical interview[12]. Finally, the role of psychiatric diagnoses in treatment outcome, treatment withdrawal and the natural course of CFS will be evaluated.

Subjects and methods

Study design and sample

Psychiatric disorders were studied in 270 CFS patients, who entered a multicentre randomised controlled trial of cognitive behaviour therapy between October 1996 and January 1998. For full details of this study see Prins et al.[10] All patients had a major complaint of fatigue and were referred to the outpatient clinic of the departments of internal medicine of two university medical centres in the Netherlands. Patients aged between 18 and 60 years were assessed by means of detailed history, physical examination and computer assessment of questionnaires and had to fulfil the CDC-1994 criteria for CFS or idiopathic chronic fatigue[13]. Severe fatigue was assessed with a score of 40 or more on the subscale fatigue severity of the Checklist Individual Strength[14] and severe impairment with a score of 800 or more on the Sickness Impact Profile[15-17].

Measures

Assessments of fatigue and functional impairment, being the primary outcome measures in the RCT, and of the secondary outcome variables depression and psychological distress were made at baseline, 8 months and 14 months. Psychiatric disorders were assessed at baseline.

The Dutch translation of the Structured Clinical Interview for DSM-III-R patient version (SCID-I/P)[18] was used to assess anxiety disorders, mood disorders, somatoform disorders, and posttraumatic stress disorder. A psychologist (EKR) administered the SCID during one session of approximately one and a half-hours. The reliability and validity of the SCID were tested in many international studies.

A subscale of the Checklist Individual Strength (CIS)[14] assessed fatigue severity. In this questionnaire, the patient is asked about fatigue in the two weeks preceding the assessment. The subscale consists of eight items, each scored on a 7-point Likert scale (range 8-56). The CIS has good reliability and validity[10,14].

Functional impairment was measured by the Sickness Impact Profile (SIP)[15-17]. A total score was calculated by addition of the weight of items in eight subscales: home management, mobility, alertness behaviour, sleep/rest, ambulation, social interactions, work, and recreation and pastimes. This measure has good reliability and validity[17].

The Symptom Checklist (SCL-90)[19] consists of 90 items and screens for anxiety,

agoraphobia, depression, somatisation, cognitive difficulties, interpersonal sensitivity, hostility and sleep disturbances. The total score can be considered as a general measure of psychological distress.
The Beck Depression Inventory (BDI)[20,21] is a standardised self-report questionnaire used to measure depression.

Analyses
Proportions were calculated for each of the separate disorders in the SCID. Lifetime prevalence was the proportion of patients who reported having experienced a given disorder at some time in their lives and current prevalence refers to those that had the disorder at the time of the study. To control for overlap between symptoms of depression and CFS, mood disorders were calculated both with and without fatigue and/or poor concentration as criteria for the diagnosis. The proportions of psychiatric disorders in CFS patients were compared to the proportions in the general population by calculating z-scores.
Clinical improvement in fatigue severity was defined as a reliable change index >1.64 and a score $\leq$ 36 indicating that the patient had moved to the range of healthy individuals[10]. Treatment withdrawal was found in different stages of the trial and subdivided in patients who did not start treatment, patients who withdrew during the test phase, patients who withdrew during follow-up and patients who completed the trial. The proportion of patients with and without lifetime or current psychiatric disorders in treatment withdrawals and improved patients in each of the three groups were compared with Fischer's exact test.
Main and interaction effects of psychiatric diagnoses on the primary outcome variables fatigue severity and functional impairment in each condition were analysed with a general linear model for repeated measurements. Outcome variables at 8 and 14 months were used as repeated measurements, with condition (three levels), current psychiatric diagnosis (two levels) and their first-order interactions as independent variables. Treatment effects of the secondary outcome variables psychological distress and depression were analysed using the same model.

Results
The data of 264 patients (90 CBT, 87 support groups, 87 control group) were analysed, since the SCID data of 6 patients were missing.
The presence of at least one lifetime psychiatric disorder was found in 50% of the CFS patients. One lifetime psychiatric diagnosis was assessed in 28% of all CFS patients, two or more diagnoses in 22%. A current psychiatric disorder was reported by 32.2% of the CFS patients. One current psychiatric diagnosis was found in 21.2% of all CFS patients, two or more diagnoses in 11%. The proportions of lifetime and current mood and anxiety disorders are shown in table 1. Lifetime mood disorders were found in 98 patients (37.1%), 50 patients (18.9%) had a current mood disorder. Dysthymia and depression were assessed most, while cyclothymia and bipolar

disorder hardly occurred. Lifetime anxiety disorders were found in 52 patients (19.7%); 35 patients (13.3%) had a current anxiety disorder. Each of the separate anxiety disorders was assessed in 3 to 10 patients (1.1 to 3.8%) with the exception of simple phobia, which was found more frequently. Of the 21 patients (8%) with simple phobia 13 patients also had another psychiatric diagnosis. Only 2 patients (0.9%) had a past post-traumatic stress disorder in remission and 13 patients (4.9%) a lifetime somatisation disorder. Current other somatoform disorders were assessed in 22 patients (8.3%).

Table 1. Proportions of DSM-III-R diagnoses in a sample of CFS patients compared to the published data of a sample of the Dutch general population (de Bijl et al. , 1998)

	CFS patients n = 264 18-60 yr SCID				general population n = 7076 18-64 yr CIDI	
DSM-III-R	Lifetime		Current		Lifetime	1-month
	n	%	n	%	%	%
Mood disorders	98	37.1	50	18.9	19.0	3.9
depression	74	28.0	16	6.1	15.4	2.7
dysthymic			30	11.3	6.3	1.6
bipolar	5	1.9	1	0.0	1.8	0.6
cyclothymic	-		6	2.3		
Anxiety disorders	52	19.7	35	13.3	19.3	9.7
panic disorder	29	11.0	10	3.8	3.8	1.5
agoraphobia	8	3.0	7	2.7	3.4	1.0
simple phobia	-	-	21	8.0	10.1	5.5
social phobia	4	1.5	4	1.5	7.8	3.7
generalised anxiety disorder		-	6	2.3	2.3	0.8
obsessive compulsive disorder	4	1.5	3	1.1	0.9	0.3

When controlling for the CFS symptoms fatigue and poor concentration at least one lifetime psychiatric disorder was found in 113 patients (42.8%), one disorder in 23.5% and two or more in 19.3%, and at least one current disorder in 75 patients (28.4%), one disorder in 18.6% and two or more in 9.8%. With fatigue and poor concentration excluded 70 patients (26.5%) had a lifetime mood disorder and 37 patients (14%) had a current mood disorder.

As is shown in table 2, patients with lifetime or current psychiatric disorders were not significantly different from patients without these disorders in age, duration of complaints, education, fatigue and functional impairment. Significantly more female than male patients had a lifetime psychiatric diagnosis (53.9% vs. 36.2%, $p<0.05$). No gender differences were found in percentages of current psychiatric disorders (33% and 29%).

Table 2. Patient characteristics of CFS patients with and without lifetime and current psychiatric disorders

	Lifetime				Current			
	yes n=132		no n=132		yes n=85		no n=179	
	mean	(s.d.)	mean	(s.d.)	mean	(s.d.)	mean	(s.d.)
Age (yr)	36.5	(10.2)	36.8	(10.1)	36.5	(9.9)	36.8	(10.2)
Duration of complaints (yr)	6.1	(6.4)	5.0	(4.8)	5.8	(5.7)	5.5	(5.6)
Education (1=low to 7=high)	4.3	(1.6)	4.2	(1.5)	4.1	(1.7)	4.3	(1.5)
CIS-fatigue	52.3	(3.8)	51.9	(4.2)	52.1	(4.1)	52.1	(4.0)
SIP8-functional impairment	1848	(591)	1797	(641)	1904	(647)	1784	(603)
Male / female (%)	36.2	(53.9) [a]			29.3	(33.0)		

[a] $p<0.05$

Table 3. Number of withdrawals, completers and improved patients with and without lifetime and current psychiatric diagnoses in the conditions cognitive behaviour therapy, support groups and control group at 8 and 14 months

	Psychiatric diagnoses in 264 CFS patients						
		Lifetime			Current		
Randomisation	total	yes	no	p	yes	no	p
Cognitive behaviour therapy	90	49	41		34	56	
not start	8	5	3	n.s.	3	5	n.s.
withdrew 8 months	23	11	12	n.s.	10	13	n.s.
withdrew 14 months	4	2	2	n.s.	2	2	n.s.
completed trial	55	31	24	n.s.	19	36	n.s.
improved 8 months	27/82	14	13	n.s.	10	17	n.s.
improved 14 months	20/58	9	11	n.s.	7	13	n.s.
Guided support groups	87	40	47		23	64	
not start	7	2	5	n.s.	0	7	n.s.
withdrew 8 months	16	9	7	n.s.	5	11	n.s.
withdrew 14 months	4	2	2	n.s.	2	2	n.s.
completed trial	60	27	33	n.s.	16	44	n.s.
improved 8 months	10/79	3	7	n.s.	1	9	n.s.
improved 14months	8/61	4	4	n.s.	1	7	n.s.
Control group	87	43	44		28	59	
not start	0	0	0	n.s.	0	0	n.s.
withdrew 8 months	8	4	4	n.s.	4	4	n.s.
withdrew 14 months	9	5	4	n.s.	5	4	n.s.
completed trial	70	34	36	n.s.	19	51	n.s.
improved 8 months	10/77	6	4	n.s.	1	9	n.s.
improved 14 months	13/76	6	7	n.s.	3	10	n.s.

The proportions of current and lifetime mood and anxiety disorders in our CFS sample were compared to the proportions in a sample of the Dutch general population in the NEMESIS study[12] (table 1). The proportion lifetime mood disorders in CFS patients is significantly higher than the proportion in the general population (37,1% vs. 19,1%; z=7.2, p<0.0001). The same is true for current mood disorders (18,9% vs 3,9%; z=12.5, p<0.0001). No significant differences were found between the proportions lifetime anxiety disorders in both samples (19,7% vs. 19,3%; z=0.16, p=0.87). Also no significant difference between both samples in current anxiety disorders was found (13,3% vs. 9,7%; z=1.89, p=0.058).

In table 3 the number of patients who did not start treatment, who withdrew during the test phase or follow-up, who completed and who improved during the trial are shown in the categories with and without lifetime and current psychiatric diagnoses. Analysing separately the different withdrawal groups and the completers we did not find any significant differences between patients with and without lifetime or current psychiatric diagnoses, neither in the whole trial nor in each of the conditions. Also, no significant differences were found between patients with and without lifetime or current psychiatric diagnoses in the groups of improved and not improved patients in each of the conditions.

In the primary outcome variables fatigue severity and functional impairment general linear model testing showed neither main effects of current psychiatric diagnosis (F=0.333, df=1, p=0.564; F=1.58, df=1, p=0.209) nor interactions effects of condition and current psychiatric diagnosis (F=0.065, df=2, p=0.937; F=0.848, df=2, p=0.430). The treatment effects are shown in figure 1.

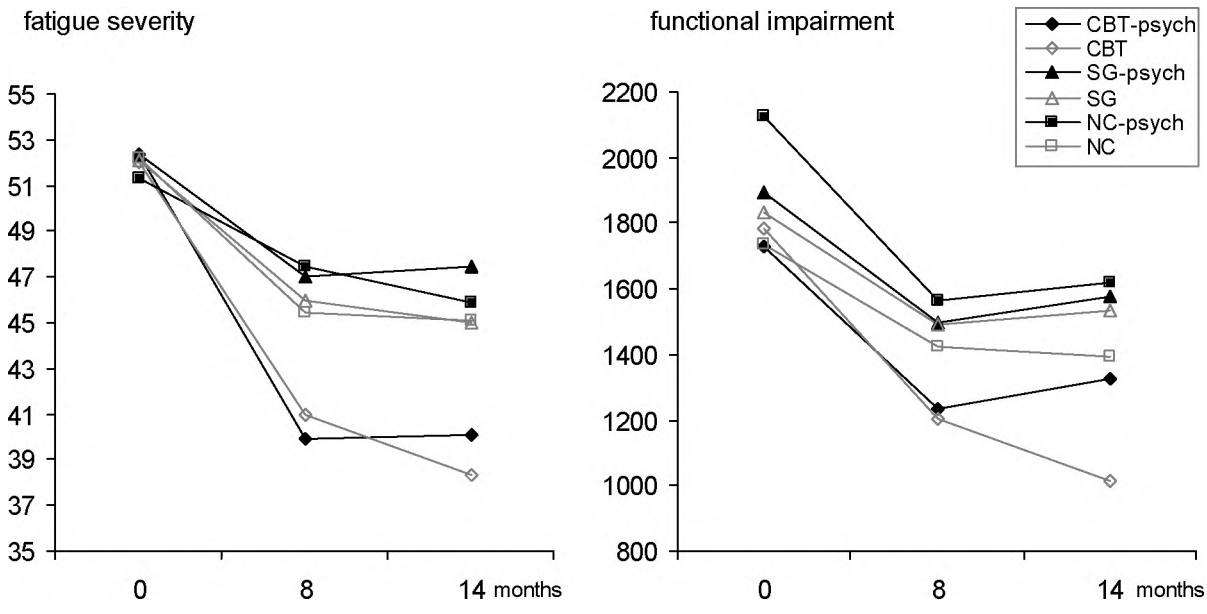

Figure 1. Effect of study conditions and current psychiatric diagnoses on the two primary outcome variables fatigue severity (CIS) and functional impairment (SIP)

In the conditions cognitive behaviour therapy, support groups and natural course CFS patients with a current psychiatric diagnosis had outcomes almost identical to patients without a current psychiatric diagnosis. In the secondary outcome variables depression and psychological distress, main effects of current psychiatric diagnosis ($F=25.4$, $df=1$, $p<0.001$; $F=20.2$, $df=1$, $p<0.001$) were found and no interaction effects of condition and psychiatric diagnosis ($F=0.067$, $df=2$, $p=0.935$; $F=0.306$, $df=2$, $p=0.737$). The treatment effects are shown in figure 2. In the conditions cognitive behaviour therapy, support groups and natural course CFS patients with a current psychiatric diagnosis had higher BDI and SCL-scores at each measurement compared to patients without a current psychiatric diagnosis. However, patients with current psychiatric diagnoses had similar difference scores from baseline to post-test and follow-up as patients without current psychiatric diagnoses.

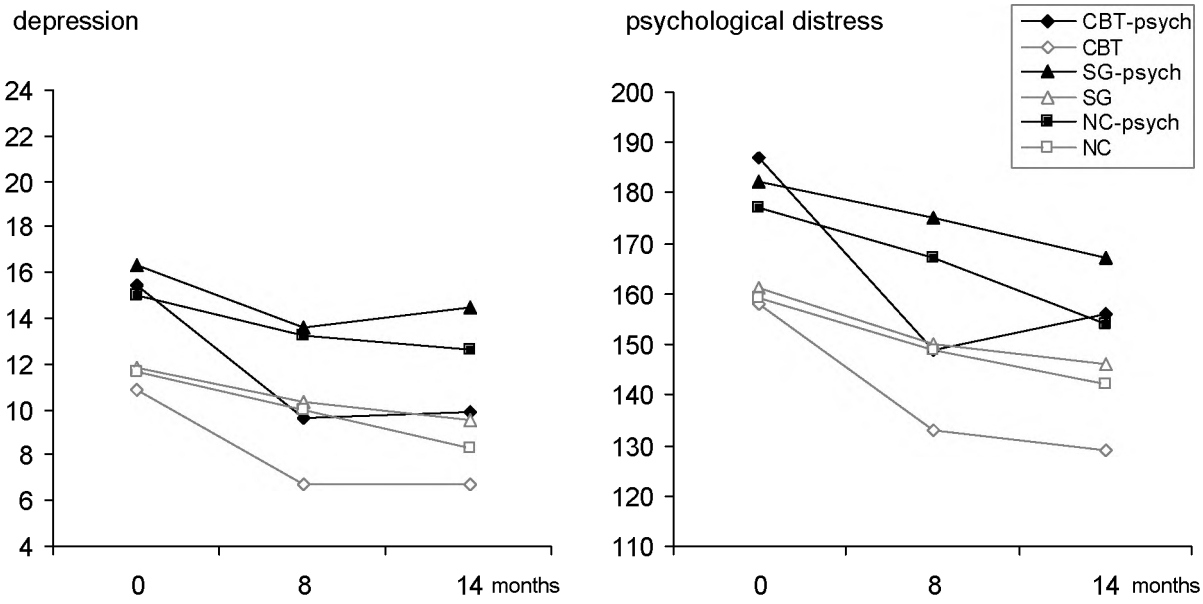

Figure 2. Effects of study conditions and current psychiatric diagnoses on the secondary outcome variables depression (BDI) and psychological distress (SCL-90)

Comment

Lifetime and current psychiatric diagnoses in respectively one half and one third of CFS patients in our sample seem low to moderate compared to proportions of DSM-III-R diagnoses found in other studies of CFS patients in hospital settings[1]. Detailed comparisons with other studies are difficult due to the use of different instruments and different CFS criteria. In our study lifetime mood disorders, anxiety disorders, PTSD and somatoform disorders were present in 50% of CFS patients. Since lifetime diagnoses are referring to both the premorbid situation and the period since the onset of CFS, interpretation of the lifetime data in our study requires some caution. With an

average duration of complaints of 5.6 years in our sample, no conclusions can be drawn about the premorbid psychiatric state of the CFS patients nor about after onset psychiatric diagnoses. Most prominent among the lifetime psychiatric disorders were major depression (28%) and panic disorder (11%). Corrected for the CFS symptoms fatigue and poor concentration, the lifetime proportion was 43%. This proportion differs from the one in a recent study in the United Kingdom in which a lower lifetime rate of 34% was found, when fatigue was excluded as a criterion[22]. An explanation might be the difference in the female:male ratio in both studies. In the UK study 63% of the patients was female compared to 78,5% in our study, in which female patients were found to have higher proportions of lifetime psychiatric diagnoses than male patients.

Current psychiatric disorders were found in 32% of CFS patients. Dysthymia was diagnosed most frequently (11%). Two other studies in which CFS patients were assessed with the same instrument showed higher rates of current psychiatric diagnoses. In a prevalence study of CFS in an Australian population 43% current psychiatric diagnoses were found with a comparable proportion of anxiety disorders and 10% more cases of depression[23]. In a Belgian study a high current prevalence rate of 77% was found in a similar setting as our study. Especially high proportions of generalised anxiety disorder were reported, which we hardly found[24]. In our study less than 5% of the CFS patients were screened positive for somatisation disorder, a rather low percentage compared to most studies in which between 10% and 20% fulfil criteria for somatisation disorder[1]. PTSD was rare, like in other studies[24,25].

We had the opportunity to compare our data to a large representative sample of the general population with the same age range in the Netherlands. Although slightly different structured clinical interviews were used in both studies, the same diagnostic categories of DSM-III-R mood and anxiety disorders were obtained during the same period. We found no differences in anxiety disorders. Significantly higher percentages current and lifetime mood disorders were found in CFS patients than in the general population. These results might be explained by a gender effect, since almost 80% of the CFS patients in our sample were female. In the general population study women were found to have higher prevalence rates of mood and anxiety disorders than men. Total proportions of lifetime or current psychiatric disorders could not be compared, because PTSD and somatoform disorders were not assessed in the general population study and substance use disorders and schizophrenia were not assessed in our study.

Considering overlap between symptoms of depression and CFS the question arises if overdiagnosis might have occurred in our study. Lower proportions of mood disorders were found when we controlled for the CFS symptoms of fatigue and poor concentration, resulting in respectively 9% and 5% less lifetime and current mood disorders.

One third of the CFS patients with current psychiatric co-morbidity had two or more psychiatric disorders. This finding stresses the importance of the role of current

psychiatric disorders in outcome during the natural course of CFS and in treatment outcome or withdrawal in CBT. In contrast to what we expected, the outcomes of CBT and support groups as well as the natural course of CFS were not influenced by current psychiatric disorders. In view of the significantly better treatment effects of CBT compared to the control conditions[10], the equal treatment effects of CBT for patients with and without current psychiatric disorders are especially interesting. After CBT, patients with and without psychiatric co-morbidity improved not only in fatigue severity and functional impairment, but also in depression and psychological distress. This is remarkable since CBT patients were not allowed other treatments, like antidepressants. Apparently, co-morbid psychiatric diagnoses also benefit from CBT specially tailored for CFS. These results accord with findings that targeted CBT for anxiety disorders is highly effective for treating a single anxiety disorder and at the same time lessens co-morbid psychopathology[26]. Clinical experience with CFS has shown that the reverse is not true. Treating psychiatric co-morbidity may relieve psychiatric symptoms or psychological distress, but does not alter somatic symptoms.

The findings in this study have practical consequences. Psychiatric screening of mood and anxiety disorders is no longer relevant for CFS patients referred for CBT, since treatment outcome and withdrawal are not affected by the presence of these disorders. Now that we found that depressive symptoms considerably benefit from CBT, we will continue our routine to refuse CBT to CFS patients not willing to stop antidepressant therapy. Antidepressants were not found effective in either treating the symptoms of depression of CFS patients or any other outcomes[6,27]. In our opinion antidepressant therapy interferes with the main goal of CBT acquiring control over symptoms instead of dependence on medication.

Another remarkable finding concerned the natural course of CFS during 14 months, which was not adversely affected by current psychiatric co-morbidity. This finding confirms the results of our previous studies, in which current depression was not a significant factor in the persistence of CFS[28,29].

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Chapter 7

Cognitive behaviour therapy for chronic fatigue syndrome: predictors of treatment outcome

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Cognitive behaviour therapy for chronic fatigue syndrome: predictors of treatment outcome

Abstract

Although cognitive behaviour therapy (CBT) for chronic fatigue syndrome (CFS) is effective in several randomised controlled trials (RCT), little is known about predictors of treatment outcome. With the data of our RCT, where CBT for CFS was significantly more effective in improving fatigue severity and functional impairment than guided support groups and natural course, the predictive value of activity pattern, disability claims and psychiatric co-morbidity was tested for outcome of CBT. Patients with a passive activity pattern and patients who were engaged in a legal procedure concerning financial benefits had a worse outcome. Psychiatric co-morbidity was not a predictor. For patients with a passive activity pattern another type of CBT has to be offered. CBT should not be offered to patients during their engagement in legal procedures of disability claims.

Introduction

Most patients with chronic fatigue syndrome (CFS) do not recover. No medical treatments have proven to be effective. The effectiveness of cognitive behaviour therapy (CBT) and graded exercise for CFS patients has been shown in six out of seven randomised controlled trials (RCT). In our opinion, both treatments are comparable, since there is no CBT without graded exercise and no graded exercise without cognitive therapy.

The conclusion of two reviews was that CBT is effective for CFS patients[1,2]. Also, the first results concerning lasting benefits of CBT after 5 years are promising[3]. Although many CFS patients achieve improved functioning, some patients do not respond at all.

However, minimal attention was directed at factors that might influence the treatment results. Only in two RCT's predictors of treatment outcome were identified. Poor outcome was associated with making a new claim for a disability-related benefit during CBT[4]. In our RCT perpetuating factors in the natural course of CFS[5] were assessed at baseline and analysed in regression analyses. Predictors for outcome after CBT were a higher sense of control predicting more improvement, and a passive activity pattern and focusing on bodily symptoms predicting less improvement[6]. For the utility of CBT in routine practice, identification of prognostic factors is of major importance.

In our study CBT for CFS was offered in three different centres by 13 newly trained therapists[6]. CFS patients were allocated to CBT, guided support groups or natural course. CBT was significantly more effective in improving fatigue severity and functional impairment than both control conditions. In this brief report, we will test the predictive value of activity pattern, disability claims and psychiatric co-morbidity for clinical outcome of all participating CFS patients in our RCT and for outcome of CBT.

Method

Design, setting, patients, interventions and outcomes

Multicentre randomised controlled trial with 8- and 14-month follow-up in three mental health settings in the Netherlands (two based in university medical centres and one in a mental health institute). 270 patients between 18 and 60 years of age (mean age 37 years, 79% women) fulfilling the CDC criteria for CFS or idiopathic chronic fatigue, and a score of $\geq$ 40 on the subscale fatigue severity of the checklist individual strength (CIS) and a score of $\geq$ 800 on the sickness impact profile (SIP). Exclusion criteria included previous or current participation in CFS research, and pregnancy. 92 patients were allocated to CBT (16 one-hour sessions over 8 months), 90 to guided support (eleven 1.5-hour meetings over 8 months), and 88 to the control group (no intervention). The primary outcomes were fatigue severity and functional impairment. Clinical improvement in fatigue severity was defined as a reliable change index > 1.64 and a score $\leq$ 36 indicating that the patient had moved to the range of a healthy individual[6,7].

Measurement of prognostic factors

Activity pattern.

At baseline, physical activity was measured by the actometer, a motion-sensing device attached to the ankle and worn day and night during 12 days. Accelerometers like the actometer are reliable and valid measures of physical activity[8]. The activity pattern of each patient was typified by comparing daily activity scores to the reference score of CFS patients. Three categories were defined: pervasively passive (90% or more beneath the reference score); moderately active; pervasively active (90% or more above the reference score)[9].

Claims for disability-related financial benefits.

At 8 months, patients received a post-intervention questionnaire. One of the questions was if the patient was engaged in a legal procedure concerning disability-related financial benefits during the preceding 8 months.

Psychiatric co-morbidity.

The Dutch translation of the Structured Clinical Interview for DSM-III-R patient version (SCID-P)[10] was used to assess psychiatric disorder (anxiety disorders, mood disorders, eating disorders, posttraumatic stress disorder). A clinical psychologist administered the SCID during one session of approximately one and a half-hours. The lifetime prevalence was the proportion of patients who reported having experienced a given disorder at some time in their lives, and current prevalence refers to those that had the disorder at the time of the study.

Results

Activity pattern

In the sample of 270 CFS patients 24% was pervasively passive, 61% was moderately active and 15% pervasively active[9]. Fatigue severity at 8 months was predicted by interaction of CBT with a pervasively passive activity pattern[6].

Therefore, the percentages of improved and unimproved CFS patients who completed CBT were explored. Figure 1 shows that at 8 months none of the patients in CBT with a pervasively passive activity pattern was clinically improved compared to 40% and 58% of the moderately active and pervasively active CFS patients. At follow-up, the improvement rates were respectively 21%, 32% and 60% in the three groups.

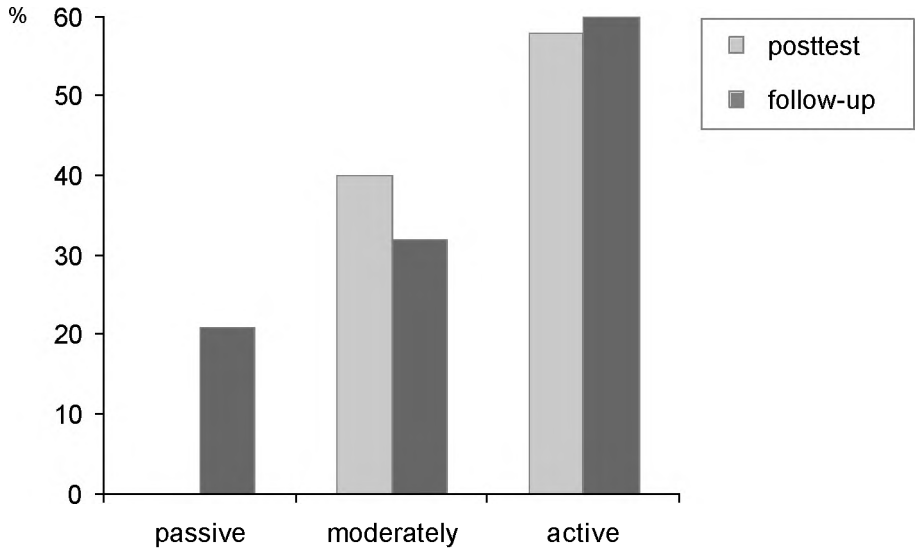

Figure 1. Percentages clinically improved CFS patients by CBT in three categories of activity pattern

Claims for disability-related financial benefits

Thirty-one percent of the patients in the trial appeared to be engaged in a legal procedure concerning financial benefits of the Disablement Insurance Act in the period between baseline and 8 months. In the total sample, the percentage of recovered patients was significantly lower in the group of patients engaged in a legal procedure compared to the group of patients not engaged in such a procedure (Chi^2=7.44, p=0.006).

The same effect was found in the group of patients treated with CBT. The percentage of clinically improved CFS patients was significantly higher in the group not engaged in a legal procedure than in the group claiming financial benefits (49% vs. 19%, Chi^2=4.37, p=0.034).

Psychiatric co-morbidity

A lifetime prevalence of at least one psychiatric disorder was found in 50% of the CFS patients. Most prominent were major depression (28%) and panic disorder (11%). At the time of the interview one or more psychiatric disorders were reported by 32% of the CFS patients. Current psychiatric disorders were mainly mood

disorders (19%) and anxiety disorders (13%), and to a lesser extent other somatoform disorders (8%). No current somatisation disorders were diagnosed.
For the patients who received CBT, no significant differences in treatment outcomes fatigue severity and functional impairment were found between patients with lifetime and/or current psychiatric disorders and patients without.

Discussion and conclusion

In CFS patients, cognitive behaviour treatment outcome is negatively affected by a passive activity pattern and by engagement in claims for financial benefits. Treatment outcome is not influenced by lifetime or current psychiatric diagnoses.
The correlation between the predictors activity pattern and engagement in a claim was very low (r=.10, n.s.). Only 10% of the CFS patients was characterised by both predictors. Therefore, each of the predictors needs separate attention. Since 45% of the patients in the sample was characterised by one of both predictors, these findings had implications for our routine practice of CFS patients referred for CBT. First, it was concluded that all these patients should be screened for both variables. Second, our conclusion was that CBT will not be offered anymore to patients engaged in a claim during the time of the legal procedure. These patients have to prove that they are disabled in order to gain financial benefits. This is incompatible with recovery, the main goal of CBT.
Third, it was concluded that patients with a passive activity pattern were in need of a different treatment protocol. The emphasis in CBT as administered in our RCT was on a base level of daily activity. This is important for moderately active CFS patients, but seemed to increase the fear of physical activity in CFS patients with passive activity patterns. In the latter group the subsequent gradual increase of physical activity was impeded. Meanwhile, we have developed a CBT protocol for passive CFS patients. They start with building up physical activity, whereas more active patients still start with a base level of daily activity.

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Chapter 8

Social support and the persistence of complaints in chronic fatigue syndrome

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Social support and the persistence of complaints in chronic fatigue syndrome

Abstract

Background Several studies suggested that the surroundings of CFS patients are of importance in the persistence of complaints. Contrary to expected, participation in support groups has not led to clinical improvement. The purpose of the present study was to describe social support in CFS patients as compared to other fatigued and non-fatigued groups. Further, changes in social support and the influence of social support on the course of CFS over a period of more than one year were studied in patients with and without treatment.

Methods Baseline data were assessed in 270 CFS patients, 150 disease-free breast cancer patients, 151 fatigued employees on sick leave and 108 healthy subjects using the Social Support List and Significant Others Scale. CFS patients were followed in cognitive behaviour therapy (CBT), guided support groups and natural course at 8 and 14 months.

Results CFS patients and fatigued employees reported more negative interactions and insufficiency of supporting interactions than cancer patients and healthy controls. No differences in frequency of supporting interactions were found. Negative interactions decreased significantly after treatment with CBT, but did not change in support groups or natural course. In the natural course, higher fatigue severity at 8 months was predicted by more negative interactions at baseline.

Conclusions In CFS patients and fatigued employees social support is worse than in disease-free cancer patients and healthy controls. Lack of social support was identified as a new factor in the model of perpetuating factors of fatigue severity and functional impairment in CFS.

Introduction

Chronic fatigue syndrome (CFS) is characterised by persistent or relapsing unexplained chronic fatigue of new or definite onset and lasting for at least six months. Fatigue is not the result of an organic disease or ongoing exertion, rest does not alleviate it, and it results in substantial reduction in previous levels of occupational, educational, social and personal activities[1]. Causes for CFS have not been found and most patients do not recover. No somatic or pharmacological treatments have proven to be effective. So far, cognitive behaviour therapy (CBT) and graded exercise therapy (GET) are the only interventions for CFS patients, which consistently have shown positive results[2,3]. In our study, in which the effectiveness of CBT was shown, CBT was compared to guided support groups and the natural course[4]. Guided support groups were intended to control for the absence of specific cognitive-behavioural interventions and the presence of therapist's attention and treatment expectations. We assumed that support groups, as in other chronic diseases, might contribute to a feeling of mutual understanding, acceptance, and

support, and thereby would have a healing effect[5,6]. An unexpected finding was that support groups were no more effective than the natural course. However, 80% or more of the patients experienced mutual understanding in the support group, and rated the contact with the therapist and the atmosphere in the group as good[4]. This discrepancy between the absence of clinical improvement and patients' satisfaction raised questions about the role of social support in CFS.

Social support is a very broad concept referring to the help and protection of others. Social support is not a unitary concept, but rather a metaconstruct of conceptually different components, ranging from the quantity of social interactions or the size of the social network to the perceived availability or quality of supporting interactions[7]. Different types of social support are distinguished, like emotional support, instrumental support, esteem support or informational support. Cobb[8] was the first to describe the positive influence of social support on health, like accelerated recovery and enhanced compliance. He saw social support as a buffer against stress. Next, several theories were offered to explain the mechanisms, by which social support directly or indirectly affects health.

Several studies found a relation between social support and CFS. Prior to illness, CFS patients perceived less social support compared to patients with irritable bowel syndrome and healthy controls in a retrospective study[9]. We have hypothesised that after onset of CFS perceived social support also may be less, since medical professionals consider CFS to be a controversial condition[10]. The quantity of social support also seems affected. CFS patients were found to report a substantial reduction of social relationships due to functional impairment in work and pastimes[11]. As a result of changes in social networks, family members and partners have become increasingly important resources of social support. CFS patients, whose partners were more optimistic about the course of the illness, reported less functional impairment[12]. A solicitous attitude of the partner was associated with worse patient functioning[13]. As to illness course and outcome of CFS, cross-sectional studies have shown that perceived social support was associated with improvement[14] and with less aggravation of CFS complaints after a natural disaster[15]. In our study of CFS patients with a relatively short illness length, we found that persistence of complaints after one-year follow-up was associated with higher levels of insufficiency of social support at baseline[16]. Although the results of all these studies suggest that the surroundings of CFS patients are of importance in the persistence of complaints, many questions concerning the exact relation between social support and CFS remain. For example, are demographic characteristics, like age, gender or civil status of importance for social support of CFS patients? Does social support of CFS patients differ from social support of other patients with fatigue complaints, patients with a chronic disease or healthy controls? Does social support of CFS patients change as a result of treatment with CBT or after participation in support groups?

The objectives of the present study were to assess the relation between social support and several demographic characteristics and to describe quantitative and

qualitative aspects of social support in CFS patients. Further, we were interested in comparing social support of CFS patients to other patients with fatigue complaints, to other patients with a chronic disease and to healthy subjects. In addition, we intended to study changes in social support of CFS patients over a period of more than one year and the relation between social support and the course of CFS in patients with and without treatment.

Patients and methods

Patients, design and procedure

The sample consisted of 270 CFS patients, who entered a multicentre randomised controlled trial of cognitive behaviour therapy[4]. All patients had a major complaint of fatigue and were referred to the outpatient clinic of the departments of internal medicine of two university medical centres in the Netherlands. Patients aged between 18 and 60 years were assessed by means of detailed history, physical examination and computer assessment of questionnaires and had to fulfil criteria for CFS[1], with the exception of the criterion of four out of eight additional symptoms[17]. Severe fatigue was assessed with a score of 40 or more on the subscale fatigue severity of the Checklist Individual Strength and severe impairment with a score of 800 or more on the Sickness Impact Profile.

Comparison groups

The sample of disease-free cancer patients consisted of 150 patients who participated in a cross-sectional study on determinants of chronic fatigue[18]. The 151 fatigued employees on sick leave had severe fatigue for more than four months without a somatic explanation and complete absenteeism from work for 6 to 26 weeks[19]. Healthy control subjects were family members, friends or colleagues of the patients participating in one of the above mentioned studies on CFS or breast cancer[4,18].

Assessments

Fatigue severity, functional impairment and social support were assessed at baseline, 8 months and 14 months. Relations with significant others were assessed at baseline.

Fatigue severity A subscale of the Checklist Individual Strength (CIS) assessed fatigue severity. In this questionnaire, the patient is asked about fatigue in the two weeks preceding the assessment. The subscale consists of eight items, each scored on a 7-point Likert scale (range 8-56). The CIS has good reliability and discriminative validity[4,20-22].

Functional impairment The Sickness Impact Profile (SIP) measured functional impairment. A total score was calculated by addition of the weights of items in eight subscales: home management, mobility, alertness behaviour, sleep/rest, ambulation, social interactions, work, and recreation and pastimes (SIP-8). This measure has good reliability and content validity[4,23].

Social support Social support was measured by the Social Support List[24], consisting of two 34-item questionnaires, interactions (SSL-I) and discrepancies (SSL-D), and a 7-item questionnaire negative interactions (SSL-N). Both SSL-I and SSL-D assess six types of social support: emotional interactions (range 4-16), problem-focused emotional support (range 8-32), esteem support (range 6-24), instrumental interactions (range 7-28), social companionship (range 5-20) and informational support (range 4-16). In the SSL-I, the frequency of supporting interactions is assessed. The SSL-D measures the perceived discrepancy in actual support and wanted support, further called insufficiency of supporting interactions. Total scores of SSL-I and SSL-D range from 34-136, total score of SSL-N from 7-28. The SSL has good reliability (Cronbach's alpha 0.93 (SSL-I) and 0.95 (SSL-D)) and content validity[25].

Significant others Twelve questions concerning the relationship with spouse/partner, relatives, friends, chief, colleagues, and general practitioner were administered and subjected to an exploratory principal component analysis with a subsequent orthogonal rotation. One item concerning the spouse/partner was too skewed and was therefore excluded. With an eigenvalue over 1, factor analysis resulted in 3 factors explaining 66% of the variance. Items that loaded at least .45 on one factor and a difference in loading on another factor of >.30 were retained. All items had a sufficient factor loading. The first factor consisting of 4 items explained 24% of the variance and was described as 'relationship with general practitioner' (REL-GP). The score ranged from 4 to 16, with a higher score reflecting a better relationship (Cronbach's alpha 0.91). 17% of the variance was explained by the second factor, which consisted of 4 items and reflected the 'relationship with family and friends' (REL-FF). The score ranged from 5 to 21, with a higher score reflecting a better relationship (Cronbach's alpha 0.63). The third factor consisting of 2 items explained 15% of the variance and was described as 'empathy from colleagues and chief' (EMP-CC). The score ranged from 4 to 8, with a higher score reflecting more empathy (Cronbach's alpha 0.75). If a patient did not work, no score was obtained for this factor.

Statistical analyses

The relation between baseline data of social support and several demographic characteristics, like age, gender, education, civil status, job status and illness length was analysed by comparing categories of the demographic variables using t-tests.

Baseline social support data of CFS patients were compared with data of disease-free breast cancer patients, fatigued employees on sick leave and healthy controls. Since these samples were not similar in age and gender, pairwise group comparisons were made with estimated marginal means standardised for age and gender using ANCOVA with Bonferroni corrections.

Changes in social support during the 14 months of the study were analysed with a multivariate analysis of variance (GLM) repeated measures within-subjects design.

Predictors of treatment outcome were selected by computing correlations between the variables concerning social support and significant others, and the primary outcome variables fatigue severity and functional impairment at 8 months for each of the three conditions. The baseline value of the dependent variable and significantly correlating variables were entered as independent variables in two blocks in separate multiple regression analyses for each of the dependent variables using the method enter. Variables not adding substantially to the variance in the dependent variable were removed. Factors were entered in the multiple regression which related to the outcome measures at $p<0.05$ or added substantially to the variance in the dependent variable.

Results

Relation between social support and demographic characteristics

In table 1 the baseline characteristics of the CFS sample concerning social support and significant others are shown. Female patients reported significantly more supporting interactions and a better relationship with family and friends than male patients. Patients older than 35 years had significantly less supporting interactions, reported significantly more insufficiency of social support, but had a significantly better relation with the general practitioner than younger patients. Lower educated patients had a significantly better relation with the general practitioner than higher educated patients. No differences were found between patients with and without a partner, with and without a job, or with a shorter or longer illness length.

Comparisons between CFS patients, disease-free breast cancer patients, fatigued employees on sick leave and healthy controls

In table 2 the means and standard deviations of supporting interactions and negative interactions of CFS patients, disease-free breast cancer patients, fatigued employees on sick leave and healthy controls are shown. In the three mixed samples, gender differences were found in the total score of supporting interactions, in social companionship, problem-focused emotional support and emotional interactions. Females reported significantly more supporting interactions than males. In the two samples of patients selected on fatigue severity, equal gender differences were also observed in instrumental interactions. Esteem support was significantly higher for female than for male fatigued employees on sick leave. No gender differences occurred for informational support and negative interactions.

Table 2 also depicts group differences while controlling for age and gender. No significant differences between the groups were found in the total score of supporting interactions and in esteem support and informational support. However, significant differences were found in some other types of supporting interactions. CFS patients had significantly more instrumental interactions than disease-free breast cancer patients and healthy controls. Fatigued employees on sick leave had significantly less emotional interactions compared to the other three groups. The three patient

groups had significantly more problem-focused emotional support than healthy controls. CFS patients had significantly less social companionship than disease-free breast cancer patients and healthy controls, and fatigued employees on sick leave less than healthy controls. CFS patients and fatigued employees on sick leave reported significantly more negative interactions than disease-free breast cancer patients and healthy controls.

Table 1. Baseline scores of social support and relation with significant others

		Social support			Significant others		
	% of sample	SSL-I mean(sd) n=270	SSL-D mean(sd) n=270	SSL-N mean(sd) n=270	REL-GP mean(sd) n=268	REL-FF mean(sd) n=269	EMP-CC mean(sd) n=149
Condition							
CBT	34%	79.6(11.3)	46.9(10.5)	11.1(3.5)	12.6(3.1)	14.9(2.6)	6.2(1.6)
SG	33%	78.9(12.9)	47.9(12.1)	11.8(3.0)	12.7(2.7)	14.7(2.9)	6.4(1.5)
NC	33%	81.3(12.4)	46.4(10.8)	11.0(2.8)	12.8(2.9)	14.9(2.5)	6.4(1.5)
p		0.410	0.626	0.209	0.912	0.844	0.734
Gender							
male	21.5%	73.4(9.9)	46.9(11.2)	11.3(2.9)	12.6	14.2	6.3
female	78.5%	81.7(12.2)	47.1(11.1)	11.3(3.2)	12.7	15.0	6.4
p		0.000***	0.904	0.920	0.742	0.042*	0.799
Age							
< 35 years	44.8%	82.7(11.1)	45.5(9.3)	11.4(3.0)	12.3	15.1	6.4
>= 35 years	55.2%	77.7(12.6)	48.3(12.3)	11.3(3.2)	13.1	14.6	6.3
p		0.001**	0.036*	0.842	0.019*	0.093	0.540
Civil status							
partner	69.9%	79.7(12.4)	46.4(10.6)	11.2(3.2)	12.9	14.9	6.3
no partner	30.1%	80.5(11.9)	48.7(12.3)	11.5(3.0)	12.3	14.8	6.4
p		0.629	0.126	0.520	0.114	0.768	0.916
Education							
lower	33.5%	78.6(11.5)	45.3(10.2)	11.1(3.2)	13.3	15.1	6.2
higher	66.5%	80.6(12.5)	48.0(11.5)	11.4(3.1)	12.4	14.7	6.4
p		0.207	0.061	0.471	0.017*	0.308	0.337
Job							
no	48.3%	80.3(13.3)	47.2(11.5)	11.6(3.3)	12.8	14.7	6.0
yes	51.7%	79.5(11.3)	47.1(11.0)	11.2(3.1)	12.6	14.9	6.5
p		0.618	0.923	0.341	0.477	0.728	0.083
Illness length							
<= 2 years	35.6%	81.8(12.1)	46.2(10.5)	10.9(3.1)	12.7	15.2	6.2
> 2 years	64.4%	78.9(12.2)	47.5(11.5)	11.5(3.2)	12.7	14.5	6.5
p		0.061	0.356	0.109	0.967	0.054	0.252

CBT: cognitive behaviour therapy - SG: guided support groups - NC: natural course
*p<0.05, **p<0.01, ***p<0.001

Table 2. Means and standard deviations of supporting interactions (SSL-I) and negative interactions (SSL-N) for patients with CFS, disease-free breast cancer patients, fatigued employees on sick leave and healthy controls, and pairwise group comparisons of estimated marginal means standardised for age and gender

	CFS 37 yr **1**		Disease-free breast cancer 46 yr **2**	Fatigued employees 43yr **3**		Healthy controls 45 yr **4**		Significant pairwise comparisons between estimated marginal means standardised for age and gender	
Supporting interactions	Female n=211 M (sd)	Male n=58 M (sd)	Female n=149 M (sd)	Female n=83 M (sd)	Male n=68 M (sd)	Female n=99 M (sd)	Male n=9 M (sd)	groups	p
Emotional interactions	11.2 (2.4)	10.0 (2.3)***	11.1 (2.5)	10.1 (2.2)	9.2 (2.2)*	11.1 (1.9)	9.4 (1.7)*	1 vs 3	<0.001
								2 vs 3	<0.01
								3 vs 4	<0.05
Esteem support	15.9 (2.8)	15.1 (2.5)	15.7 (2.9)	16.5 (3.2)	14.6 (3.3)**	15.7 (2.7)	14.5 (2.1)		
Emotional support problems	19.1 (3.7)	16.2 (3.2)***	18.2 (4.1)	18.8 (4.3)	16.7 (4.0)**	16.9 (3.4)	13.1 (3.6)**	1 vs 4, 3 vs 4	<0.001
								2 vs 4	<0.05
Informational support	8.4 (1.7)	8.0 (1.7)	8.1 (2.1)	8.4 (2.1)	8.0 (2.3)	8.4 (1.8)	7.3 (2.0)		
Instrumental interactions	14.4 (3.3)	12.6 (2.8)***	12.8 (2.9)	13.6 (3.6)	12.1 (2.9)**	12.9 (3.1)	10.9 (2.6)	1 vs 2,1 vs 4	<0.05
Social companionship	12.7 (2.7)	11.6 (2.3)**	13.9 (2.5)	13.4 (2.9)	11.6 (2.9)***	14.2 (2.5)	11.3 (2.1)***	1 vs 2,1 vs 4	<0.001
								3 vs 4	<0.05
Total (SSL-I)	81.7 (12.2)	73.4 (9.9)***	79.8 (12.5)	80.7 (13.8)	72.2 (13.3)***	79.2 (11.6)	66.7 (9.7)**		
Negative interactions	11.3 (3.2)	11.3 (2.9)	9.8 (2.5)	11.5 (3.5)	11.6 (3.4)	9.5 (2.0)	9.0 (1.8)	1 vs 2,1 vs 4	<0.001
								2 vs 3,3 vs 4	<0.001

gender differences *p<0.05, **p<0.01, ***p<0.001

Table 3. Means and standard deviations of insufficiency of supporting interactions (SSL-D) for patients with CFS, disease-free breast cancer patients, fatigued employees on sick leave and healthy controls, and pairwise group comparisons of estimated marginal means standardised for age and gender.

	CFS 37 yr **1**		Disease-free breast cancer 46 yr **2**	Fatigued employees 43yr **3**		Healthy controls 45 yr **4**		Significant pairwise comparisons between estimated marginal means standardised for age and gender	
Insufficiency of supporting interactions	Female n=211 M (sd)	Male n=58 M (sd)	Female n=149 M (sd)	Female n=83 M (sd)	Male n=68 M (sd)	Female n=99 M (sd)	Male n=9 M (sd)	groups	p
Emotional interactions	5.8 (2.3)	5.9 (2.3)	5.7 (2.3)	6.1 (2.3)	6.5 (2.1)	5.4 (2.0)	5.8 (1.6)	3 vs 4	<0.05
Esteem support	7.7 (2.0)	7.6 (1.9)	7.6 (2.1)	7.4 (1.7)	8.6 (2.6)**	7.2 (1.6)	7.1 (1.2)		
Emotional support problems	11.9 (3.9)	11.9 (4.1)	10.7 (3.3)	11.9 (3.9)	13.0 (3.9)	10.6 (3.0)	9.7 (2.7)	1 vs 2	<0.05
								1 vs 4, 2 vs 3	<0.01
								3 vs 4	<0.01
Informational support	5.5 (1.7)	5.2 (1.4)	5.6 (1.8)	5.7 (2.0)	6.0 (2.0)	5.4 (1.5)	5.4 (1.9)		
Instrumental interactions	9.1 (2.4)	9.3 (2.4)	8.7 (2.2)	9.4 (2.9)	9.7 (2.5)	8.5 (1.8)	7.7 (1.3)	1 vs 4, 2 vs 3	<0.05
								3 vs 4	<0.01
Social companionship	7.1 (2.6)	7.0 (2.1)	6.2 (2.1)	6.5 (2.2)	7.0 (2.1)	5.8 (1.6)	6.7 (1.7)	1 vs 2	<0.01
								1 vs 4	<0.001
								3 vs 4	<0.05
Total (SSL-D)	47.1 (11.1)	46.9 (11.2)	44.5 (11.0)	47.1 (11.1)	50.7 (12.2)	42.9 (8.5)	42.3 (9.1)	1 vs 4	<0.01
								2 vs 3	<0.05
								3 vs 4	<0.001

gender differences **p<0.01

Data pertaining to insufficiency of supporting interactions are shown in table 3. CFS patients had a significantly higher total score of insufficiency of supporting interactions than healthy controls, and employees with work-related fatigue had a higher total score than disease-free breast cancer patients and healthy controls. As to the different types of insufficiency of supporting interactions, CFS patients experienced significantly more insufficiency of social companionship and problem-focused emotional support than both disease-free breast cancer patients and healthy controls. The same pattern was found in fatigued employees on sick leave, although the comparison of social companionship with disease-free breast cancer patients did not reach significance. CFS patients experienced significantly more insufficiency of instrumental interactions than healthy controls and fatigued employees on sick leave significantly more than disease-free breast cancer patients and healthy controls. Fatigued employees on sick leave reported more insufficiency of emotional interactions than healthy controls. No group differences in esteem support and informational support were found. No gender differences occurred for the total score of insufficiency of supporting interactions.

Table 4. Course of supporting interactions (SSL-I), insufficiency of supporting interactions (SSL-D), and negative interactions (SSL-N) over 14 months for each of the three treatment arms

	baseline	8 months	14 months	Repeated measures	
	mean (sd)	mean (sd)	mean (sd)	F	p
CBT (n=57)					
SSL-I	82.3 (10.0)	80.6 (12.0)	79.7 (11.7)	4.661	0.013*
SSL-D	45.5 (8.8)	43.3 (8.4)	43.0 (8.9)	2.830	0.068
SSL-N	10.9 (3.1)	9.9 (2.0)	9.6 (2.4)	4.705	0.013*
SG (n= 62)					
SSL-I	78.9 (12.2)	78.3 (11.4)	78.1 (11.9)	0.326	0.723
SSL-D	48.2 (12.5)	47.3 (11.8)	45.7 (10.7)	1.820	0.171
SSL-N	11.6 (3.1)	11.2 (3.4)	11.2 (3.0)	0.707	0.497
NC (n=75)					
SSL-I	81.9 (12.0)	79.9 (10.2)	78.7 (11.6)	3.244	0.045*
SSL-D	46.2 (10.9)	46.7 (10.2)	45.0 (10.6)	1.741	0.183
SSL-N	10.8 (2.7)	10.5 (2.8)	10.4 (3.1)	1.460	0.239

CBT: cognitive behaviour therapy - SG: guided support groups - NC: natural course
* $p<0.05$

Course of social support over 14 months in CFS patients

Table 4 shows the mean scores of supporting interactions, negative interactions and insufficiency of supporting interactions of CFS patients at baseline, 8 months and 14 months in each of the treatment groups, as well as differences within groups

reflecting changes over time. In patients treated with CBT, supporting interactions and negative interactions decreased significantly after 14 months. In this group a decrease in insufficiency of supporting interactions was also found, although this change did not reach significance. Patients in guided support groups showed no significant changes during 14 months. Patients in the natural course group reported significantly less supporting interactions after 14 months. Insufficiency of supporting interactions and negative interactions did not change significantly in this group.
Significant differences between groups after 14 months were only found in negative interactions (F=4.555, df=2, p=0.012), and not in supporting interactions (F=0.107, df=2, p=0.898) or insufficiency of supporting interactions (F=1.193, df=2, p=0.305). Post-hoc analyses showed a significant difference in negative interactions between patients treated with CBT and patients in guided support groups (p=0.009).

Table 5. Predictors of fatigue severity and functional impairment after 8 months

	adj R^2	beta
Fatigue severity		
Cognitive behaviour therapy		
model 1: baseline fatigue severity	0.073**	0.290**
model 2: baseline fatigue severity	0.126**	0.285*
insufficiency emotional support problems		0.252*
Natural course		
model 1: baseline fatigue severity	0.046*	0.243*
model 2: baseline fatigue severity	0.106**	0.260*
negative interactions		0.257*
Functional impairment		
Cognitive behaviour therapy		
model 1: baseline functional impairment	0.250***	0.509***
model 2: baseline functional impairment	0.325***	0.460***
relationship with family and friends		-0.172
insufficiency emotional interactions		0.190
Guided support groups		
model 1: baseline functional impairment	0.288***	0.556***
model 2: baseline functional impairment	0.355***	0.491***
social companionship		-0.190
empathy from colleagues and chief		-0.196
Natural course		
model 1: baseline functional impairment	0.193***	0.451***
model 2: baseline functional impairment	0.271***	0.454***
relationship with general practitioner		0.294**

* p<0.05, **p<0.01, ***p<0.001

Predictors of fatigue severity and functional impairment

Higher fatigue severity after CBT was predicted by higher fatigue severity (7%) and more insufficiency of problem-focused emotional support (5%) at baseline (table 5). No predictors were found for fatigue severity after guided support groups. In the natural course group, higher fatigue severity (5%) and more negative interactions at baseline (6%) predicted fatigue severity at 8 months. Higher functional impairment after CBT was predicted by higher functional impairment (25%) and by a worse relationship with family and friends and more insufficiency of emotional interactions at baseline. Although the latter variables just did not reach significance, together they added 7.5% to the variance in fatigue severity. After guided support groups, higher functional impairment was predicted by higher functional impairment (29%) and by less social companionship and less empathy from colleagues and friends at baseline. Together these variables added 6.5% to the explained variance in fatigue severity, although they did not reach significance. In the natural course group, baseline functional impairment (19%) and a better relationship with the general practitioner (8%) predicted functional impairment.

Discussion

Our study of social support in CFS patients revealed several new findings.

Relation between social support and demographic characteristics

Demographic variables, like age, gender, and education, appeared to represent relevant factors in the quantitative and qualitative aspects of social support of CFS patients. Female CFS patients did report more supporting interactions than males. In this respect, CFS patients did not differ from other samples in our study in which similar gender differences were found. Insufficiency of supporting interactions and negative interactions were similar for both genders, in CFS patients and in both other mixed samples. Marriage and work are both sources for social support, and were therefore expected to coincide with higher levels of social support. However, the presence of a partner or a job seemed not to be related to the quantity or quality of social support of CFS patients. Nor did illness length, while we supposed that changes in social networks due to increasing illness length would result in a decrease of social support.

Comparisons between CFS patients, disease-free breast cancer patients, fatigued employees on sick leave and healthy controls

Based on the group comparisons, we concluded that CFS patients and fatigued employees differed in qualitative aspects of social support from disease-free breast cancer patients and healthy controls and not in quantitative aspects. CFS patients and fatigued employees on sick leave reported more negative interactions and more insufficiency of supporting interactions than disease-free breast cancer patients and healthy controls. In the sample of disease-free breast cancer patients 38% was severely fatigued. These patients also had significantly more negative interactions and insufficiency of supporting interactions than those patients who were not

fatigued[18]. Severe fatigue seems to be related to a worse quality of social support.
No significant differences between the four samples in the frequency of supporting interactions were found, although some differences in types of supporting interactions were identified. Roughly, fatigued persons, CFS patients as well as fatigued employees on sick leave, had more instrumental and problem-focused interactions and less social or emotional interactions than one or both of the other groups, which were not selected on fatigue severity. CFS patients reported more instrumental support, but at the same time also experienced more insufficiency of instrumental support than healthy subjects. Evidently, they were not fulfilled in their need for instrumental support.
As to the quality of social support, fatigued patients had more negative interactions and more insufficiency of support than healthy controls. This finding is of interest, because negative aspects of social relationships are supposed to reduce the helpful effect of social support.
There is one methodological point which should be considered. The way of recruiting healthy control subjects, who were family members, friends or colleagues of the patients participating in our studies, might have introduced some selection bias. Since these subjects were willing to join the patient in the study and thereby were showing support, they possibly had a more positive network interaction than other people in the normal population.
Course of social support over 14 months in CFS patients
Perceived support rather than quantity of social relationships is considered to affect health-related behaviours[7]. Therefore, we were especially interested in the effect of CBT and guided support groups on negative interactions and insufficiency of supporting interactions. We found that negative interactions and to a lesser extent insufficiency of supporting interactions decreased after CBT. The statistically significant decrease of negative interactions was also clinically significant, since the mean score at 14 months was similar to the mean score of healthy subjects. Insufficiency of supporting interactions and negative interactions did not change significantly during natural course and guided support groups. Supporting interactions decreased after CBT, as was the case in the natural course group. Clinically, this finding was of little importance, since after 14 months the frequency of supporting interactions was still at a level considered as normal for healthy subjects. The new contacts in the guided support groups may explain the finding that the supporting interactions of the patients in the guided support groups did not decrease significantly. In addition to our former conclusion that guided support groups were not effective in decreasing fatigue and functional impairment in CFS patients, we concluded that support groups also did not contribute to a decrease of negative interactions or insufficiency of supporting interactions. Higher levels of functional impairment, less social companionship and less empathy from colleagues and chief at baseline were found to predict higher levels of functional impairment in the support groups. Apparently, participation in support groups did not satisfy the need for

companionship and empathy. There might be another explanation for the ineffectiveness of support groups for CFS patients. Despite the fact that only in the first two meetings attention was paid to symptoms and functional impairment, in all of the subsequent meetings CFS patients remained focused on each other's symptoms and frequently exchanged information about aids to facilitate daily life. A strong focus on bodily symptoms was found to predict a worse outcome in our trial[4].

Predictors of fatigue severity and functional impairment

In the patients with CBT, insufficiency of supporting interactions and a worse relationship with family and friends predicted higher fatigue severity or functional impairment. Therefore, in the treatment protocol of cognitive behaviour therapy for CFS patients more attention for insufficiency of social support is needed. In the patients without treatment more negative interactions predicted higher fatigue severity.

Our conclusion was that insufficiency of social support and negative interactions are important factors in the persistence of CFS. Lack of social support should be added as a new factor to the model of perpetuating factors of fatigue and functional impairment in CFS[26]. Until now, the model was limited to complaint-related cognitions and behaviours, like somatic attributions, sense of control over complaints, physical activity and a strong focus on bodily symptoms. From the results of this study it is obvious that cognitions and behaviours concerning the individual's support system need equal attention. Further studies especially should pay attention to different ways in which social support might be of influence for CFS patients, helping them to accept and tolerate symptoms and disability or reinforcing illness behaviour. Also the mediating role of psychological distress should be considered. In general, patients with low levels of perceived social support report more psychological distress.

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Chapter 9

Doctor-patient relationship in primary care of chronic fatigue syndrome: perspectives of the doctor and the patient

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Doctor-patient relationship in primary care of chronic fatigue syndrome: perspectives of the doctor and the patient

Abstract

Background. Chronic Fatigue Syndrome (CFS) is characterized by severe debilitating fatigue for at least six months. The lack of a known origin could have consequences for the way general practitioners deal with the diagnosis CFS and their perception of CFS patients.

The aims of the study were to investigate the use of the diagnosis CFS by GPs and their reactions to self-diagnosis and to explore opinions of GPs about causes of CFS and the communication with CFS patients as well as opinions of CFS patients about their GPs.

Method. 121 GPs completed questionnaires and 12 were interviewed. Data of 211 CFS patients were analyzed as well.

Results. Only half of the GPs used the diagnosis CFS. The main reason for not diagnosing CFS was ignorance of the criteria. GPs reported self-diagnosis in 68% of the CFS patients. More than half of the GPs could sympathize less with the complaints of CFS patients compared with other patients. These GPs experienced more problems in communicating with CFS patients and judged co-operation and contact as poor. As to the causes for CFS a discrepancy was found. GPs mainly attributed the complaints to psychosocial factors, whereas patients mainly had physical attributions.

Conclusion. In CFS, GPs should be explicit about the diagnosis. As to the discrepancy in presumed causes of CFS between GPs and CFS patients, it may be helpful for GPs to discuss the distinction between initiating and perpetuating factors of CFS. We argue that this attitude of GPs would be beneficial to the course of the complaints of CFS patients.

Introduction

Fatigue is a complaint regularly presented by patients attending general practitioners (GPs)[1]. Fatigue is the third symptom on the list of most frequently presented complaints in general practices in the Netherlands[2]. If complaints of fatigue persist for more than six months and no somatic explanation can be found, chronic fatigue has developed[3]. Chronic fatigue syndrome (CFS) is defined by the presence of persistent or relapsing unexplained chronic fatigue that is of new or definite onset and lasting for at least six months. Fatigue is not the result of ongoing exertion, it is not alleviated by rest and results in substantial reduction in previous levels of occupational, educational, social and personal activities.

In prevalence studies among all GPs in the Netherlands the estimated prevalence of CFS was 1.1 per 1000 inhabitants[4,5]. This means an average of 2 CFS patients per GP, corresponding with Irish primary care[6]. In the UK GPs reported a prevalence of 1.3 per 1000 patients[7]. The results in these prevalence studies are in probability an

underestimation of true prevalence as not all CFS is presented to and diagnosed by GPs. In CFS, GPs may not be familiar with the criteria for the diagnosis or do not acknowledge the disease as a distinct clinical entity[8], which may contribute to the iceberg of complaints. If patients confront the practitioner with the self-diagnosis of myalgic encephalomyelitis (ME) or CFS, GPs consider these patients less likely to comply with treatment and more likely to pose difficult management problems and to take up a lot of time[9]. CFS patients report that doctors do not understand or accept their symptoms[10,11].

It seems obvious that the perspectives of CFS held by GPs and patients are quite different. However, it is not clear to what extent opinions about CFS differ. Diagnosis and self-diagnosis may be perceived from a different perspective, as well as opinions about causes of CFS, which will have its consequences for the communication between medical practitioners and CFS patients. The role of the GP seems especially important, because often the GP is the first professional confronted with the complaints of chronic fatigue. How this first consultation passes off may determine the future course of the CFS patient considerably[12]. Will the patient accept the fact that no known cause is available and no effective treatment? Or will the patient persist in further medical examinations and the testing of all kinds of non-proven treatments? In our opinion the GP has a crucial role in the further course of the complaints of chronic fatigue. More information about the behavior and opinions of GPs in cases of CFS is necessary for the development of management programs in primary care.

The aims of the present study were to investigate the use of the diagnosis CFS by GPs and their reactions to self-diagnosis. Furthermore, it was explored if discrepancies exist between the ideas of GPs and CFS patients about possible causes of CFS and about communication and mutual understanding.

Method

Questionnaires for GPs

In figure 1 the questionnaire developed for GPs is shown. The questionnaire was presented to 121 GPs preceding courses about CFS, 73 GPs in 1995 and 48 GPs in 1997. All of them agreed to complete the questionnaire. The GPs varied in years working as GP (range 1–28, mean 11.5). The questions concerned frequency of diagnosing cases of CFS, causes and attributions for the complaints, expectations of patients, the opinions about the communication with CFS patients and the need for expert knowledge. Completion of the questionnaire lasted about four minutes.

Questionnaires for CFS patients

Questionnaire data of 211 patients, not being the patients of the GPs in the study, were analyzed as well. These patients were consecutively referred from a university hospital outpatient clinic and met the criteria for CFS[13]. Data were gathered before participation in a randomized clinical trial. The questions concerned the doctor-patient relationship and attributions for the complaints.

Figure 1. Questionnaire for general practitioners about Chronic Fatigue Syndrome

This questionnaire contains 15 multiple-choice questions. These questions concern the relationship of general practitioners and patients with Chronic Fatigue Syndrome (CFS). CFS patients also use the name Myalgic Encephalomyelitis (ME). We should be grateful if you fulfilled this questionnaire. If there are no CFS patients in your practice, please fulfil the answer you would expect in the relationship with CFS patients.

1 Did you ever diagnose Chronic Fatigue Syndrome (CFS)?
- o No
- o Yes, namely ..... patients

2 If not, what is the reason? (you may select several answers)
- o These complaints do not occur in my practice
- o CFS is unknown to me
- o The diagnosis CFS does not exist (I disbelieve in CFS)
- o I am not familiar with the criteria to diagnose CFS
- o another reason, namely .....

3 Did any of your patients had a self-diagnosis of CFS or ME?
- o None
- o Yes, namely ..... patients

3b If yes, did you agree with the patients?
- o Yes
- o No

4 In your opinion, what is the main cause of CFS?
- o Only psychological
- o Mainly psychological and physical as well
- o Mainly physical and psychological as well
- o Only physical

5 To which of the following aspects are the complaints of CFS patients related? (You may select several answers)
- o Virus
- o Immune system
- o Physical abnormalities
- o Situation at work or at home
- o Consequence of a busy daily life
- o Distress
- o Problems in childhood
- o Too much worrying

6 Do you think CFS patients can be treated ?
- o Yes
- o Sometimes
- o I do not know
- o No

7 What do you think a CFS patient expects from the general practitioner? (You may select several answers)
A CFS patient feels the general practitioner to be a person:
- o to whom one may give vent to one's feelings
- o who gives advice
- o who prescribes an evident treatment
- o who prescribes a doctor's referral

How is your relationship with CFS patients compared with other patients? If you do not have any CFS patients in your practice, please try to answer these questions according to your present opinion. Please mark the box corresponding to your answer. The middle box means 'equal to other patients'.

8 Consultation of a CFS patient takes more / less time

more time ☐ ☐ ☐ ☐ ☐ less time

9 In your opinion CFS patients give more / less problems in communicating

more problems ☐ ☐ ☐ ☐ ☐ less problems

10 The complaints of CFS patients are more / less empathising to you

more empathising ☐ ☐ ☐ ☐ ☐ less empathising

11 Co-operation with CFS patients is better / worse

better ☐ ☐ ☐ ☐ ☐ worse

12 Contact with CFS patients is more flexible / tense

flexible ☐ ☐ ☐ ☐ ☐ tense

13 Are there any difficulties you encounter regularly with CFS patients?
o No
o Yes
Could you please mention these difficulties? .....
.....

14 Do you feel capable of informing CFS patients sufficiently?
o Yes
o Could be better
o No

15 Do you want more information about CFS?
o Yes
o No

16 For how many years have you been practising as a general practitioner?
..... years

Interview of GPs

Twelve GPs were extensively interviewed. They were not among the GPs who attended the courses and filled in the questionnaire. The practices of the GPs were located throughout the Netherlands, in cities as well as the country. The semi-structured interview consisted of 33 questions covering the same subjects as the questionnaire for GPs, but more extensively. Especially, the acknowledgement of CFS as a distinct clinical entity and the attitude to CFS patients were paid attention to. The tape-recorded interviews took place in 1995 and lasted about 45 minutes each.

Comparison of data from interviews and questionnaires

The answers of the interviewed GPs were in agreement with those given in the questionnaires. The data of the questionnaires will be used to answer the research questions. The content of the interviews will be used to explain and clarify the results.

Results

Diagnosis, self-diagnosis and need for expert knowledge

As is shown in table 1, half of the 121 GPs reported to use the diagnosis CFS. GPs diagnosing CFS had an average of 3.3 CFS patients in their practice. Reasons for not diagnosing CFS were ignorance of the criteria for CFS (69%) and not acknowledging CFS as a diagnosis (20%). Eleven percent gave no reason. In the interviews, half of the 12 GPs reported reluctance to the diagnosis, and this appeared to be an important reason for not diagnosing CFS. Interviewed GPs with reluctance to the diagnosis CFS had fewer CFS patients in their practice (3.2 vs. 5.5 patients). Differences between 1995 and 1997 showed an increased percentage of GPs diagnosing cases of CFS (45% vs. 62%).

Table 1. Percentage of GPs diagnosing CFS, reporting self-diagnosis and agreeing with self-diagnosis

	Did the GP ever diagnose CFS?			
	yes	no		
	n/total	n/total		
	63/121 (52%)	58/121 (48%)	Chi^2	p
Self-diagnosis of CFS/ME present?	yes	yes		
n = 113	49/60 (82%)	33/53 (62%)	5.27	<0.05
Agreement of GP with self-diagnosis?	yes	yes		
n = 67	28/36 (78%)	14/31 (45%)	7.46	<0.01

In the questionnaires 121 GPs reported self-diagnosis in 68% of the CFS patients. Table 1 shows that GPs not diagnosing CFS reported significantly less self-diagnoses than GPs diagnosing CFS (82% vs. 62%; $Chi^2=5.27$, $p<0.05$). Agreement with the self-diagnosis was mentioned by 35% of the GPs (n=42), whereas 21% disagreed (n=25); 44% (n=54) did not answer this question. Table 1 shows that GPs not diagnosing CFS reported significantly less agreement with self-diagnoses than GPs diagnosing CFS (78% vs. 45%; $Chi^2=7.46$, $p<0.01$).

Only 10% of the GPs felt capable of giving sufficient information about CFS to patients. GPs not diagnosing CFS felt significantly less capable of informing patients than GPs diagnosing CFS ($Chi^2=9.22$; $p<0.01$). Not surprisingly, nearly all of the GPs participating in the courses about CFS wanted more information about CFS (94%).

Doctor-patient relationship: perspective of the doctor

GPs' opinions about the relationship with CFS patients compared with other patients were analyzed as well. Most of the GPs (89%) reported that the visits of CFS patients took more time, 73% regularly experienced all kinds of problems with these patients, 43% reported problems in the communication and 31% rated the contact and co-operation as bad. Comparing their attitude to CFS patients with the attitude to other patients, 54% of the GPs reported less empathy to CFS patients. Less empathizing GPs had significantly more problems in communicating with CFS patients than more empathizing GPs ($t=2.49$, $p=0.014$) and the quality of the contact ($t=4.20$, $p=0.000$) and co-operation was significantly worse ($t=4.14$, $p=0.000$). Consultations of CFS patients by empathizing GPs did not take more time. A strong tendency was found that GPs working more years in general practice (12.7 vs. 10.5, $p=0.08$) and having more CFS patients in their practice (4.0 vs. 2.7, $p=0.09$) are more empathizing than less experienced colleagues.

Statements from the interviews were analyzed to illustrate the kind of problems GPs experience with CFS patients. The strong tendency to somatization, the vagueness of the complaints and the compelling attitude of CFS patients were mentioned as most problematic.

Questionnaire items about the expectations of CFS patients revealed that three-quarters of the GPs believed that CFS patients want to give vent to their feelings and take medical advice as well. One third of the GPs believed that CFS patients expect a treatment for their complaints or want to be referred to a specialist.

Doctor-patient relationship: perspective of the patient

In 43% CFS patients rated their relationship with the GP as good, as rather good in 37% and as not good or even bad in 20%. Seventeen percent of the CFS patients reported to have no confidence in the GP. Patients' opinions about the degree to which doctors take their complaints seriously and sympathize with them differed for categories of doctors. According to the opinion of 21% of the CFS patients GPs did not take their complaints seriously and 23% of the patients stated that the GP does not sympathize with them. In the patients' opinions more than half of medical specialists did not take their complaints seriously and did not sympathize with CFS patients (53% and 54%). Contrary, according to patients, doctors in a university outpatient clinic with a dedicated program for CFS nearly always took the complaints seriously and sympathized with the patient (both 99%). It should be noted that these last observations concerned the doctors who gave the diagnosis CFS to the patient.

Opinions about causes

As to the presumed causes for CFS a large discrepancy between GPs and CFS patients was found. Table 2 shows to which specific aspects CFS is attributed.

It is obvious that patients mainly have physical attributions for their complaints, whereas GPs mainly attribute the complaints to psychological factors. However, a

significant difference exists between GPs not diagnosing CFS and GPs diagnosing CFS. Ninety-one percent of GPs not diagnosing CFS attributed complaints to psychological factors compared to 76% of GPs diagnosing CFS (Chi^2=4.65, $p<0.05$).

Table 2. Percentage of GPs and CFS patients believing that CFS is related to one of the following aspects

Causes for CFS	GPs n = 121	CFS patients n = 211
Physical		
virus	41	63
immune deficiency	37	78
physical abnormalities	23	77
Psychological		
distress	82	—*
work or family	58	9
being busy	37	27
worrying	23	24
problems in childhood	23	12

* data not available for CFS patients

Discussion

In 1994 guidelines for the clinical evaluation of fatigued persons and a case definition of the chronic fatigue syndrome were provided[13]. However, the results in our study indicate that GPs are not familiar with the diagnosis CFS. In CFS, self-diagnoses are even more prominent than diagnoses by GPs. An exceptional situation in general practices.

Nearly half of the GPs never diagnose CFS. These GPs report fewer self-diagnoses of CFS and are less inclined to agree with self-diagnoses. Also, these GPs feel less capable of giving information about CFS to patients and are more inclined to attribute complaints of CFS patients to psychological causes. These results indicate that GPs never diagnosing CFS differ from GPs occasionally diagnosing CFS in knowledge of the disease and attitudes to CFS patients. Although there appear some problems in diagnosing CFS, there are indications from our comparisons at 1995 and 1997 of a substantial and rapid change in this respect.

Self-diagnosis is reported by GPs in 68% of the CFS patients. Confronted with a self-diagnosis nearly half of the GPs do not agree or disagree with the patient in a straightforward fashion. In cases of self-diagnosis, the tables are turned: the patient diagnoses in stead of the doctor. The self-diagnosis may easily evoke irritation of GPs, especially if the GP is uncertain about the diagnosis[14]. In our study nearly all GPs reported insufficient knowledge of CFS. However, CFS patients expect a diagnosis. Most CFS patients attribute complaints to a physical disease and may therefore expect an effective treatment as well.

Differences between GPs and CFS patients in causal attributions were found. Patients mainly had physical attributions for their complaints. GPs mainly attributed the complaints to psychological factors. Although no data are available about the reactions of GPs to physical attributions of CFS patients, caution is advised. Denial or resistance of the patient's opinion about physical causes by the GP may easily strengthen the patient's physical attributions. Strong physical attributions were found to be unfavorable for the prognosis[15]. Paying attention to somatic attributions and to the meaning of the diagnosis for the patient will be more beneficial to the patient than arguing about possible causes.

Although the GPs and the CFS patients in this study do not in anyway relate to each other, it is worthwhile to compare their views about clinical encounters. GPs' opinions about the relationship with CFS patients compared to other patients were not favorable. It is of interest that GPs experience more problems in the doctor-patient relationship than CFS patients. This may be due to self-diagnoses. A vicious circle of debating about causes and diagnosis may easily develop. Not diagnosing CFS when the patient fulfils the criteria, resistance to the patient's opinion as well as the unfavorable attitude of GPs to CFS patients may be important factors in determining the doctor-patient relationship. GPs may therefore decide to refer CFS patients to a medical specialist. However, patients will not profit from referral to a medical specialist, because of the lack of adequate medical treatments and the risk of increasing somatic fixation by further medical examinations. Moreover, CFS patients in this study reported that GPs took their complaints more seriously than most medical specialists did.

Despite these interesting results some side-notes should be discussed. The GPs involved in the study were not a representative sample, being those who had gone on courses about CFS and thus being more interested in CFS. The CFS patients in this study were all involved in a randomized clinical trial, perhaps indicating that they are a more co-operative and satisfied group than usual. However, in the case of interested doctors and co-operative patients the study highlights the most optimistic view of how CFS is dealt with in primary care. The methodological limitations of two separate samples of doctors and patients prevents us from presenting evidence for the supposed relation between not acknowledging the diagnosis CFS and an unfavorable doctor-patient relationship. Despite these shortcomings some recommendations may be drawn from the study.

The diagnosis and management of CFS patients in primary care seems of crucial importance in the future course of the illness. More specific guidelines for GPs in the identification and management of CFS patients are definitely needed. GPs capable of diagnosing CFS and adequate counseling may be able to prevent worsening of the complaints and long-term disability in CFS patients. Fuller and Morrison[16] described in detail a primary care approach to diagnosis and management of CFS. Although this approach will be of great support in the relationship with all patients in general practice and especially those with unexplained complaints, it is far too general for

patients with CFS.

In our opinion extensive evaluation of patients complaining of chronic fatigue is also necessary to be certain about the diagnosis CFS. Moreover, such evaluation of the patient's complaints has the advantage that the patient feels taken seriously by the GP and that a solid foundation is laid for management of the complaints in general practice.

A solution to the huge discrepancies in causal attributions between GPs and CFS patients may be found in the empirical fact that the cause of CFS is still unknown. GPs capable of distinguishing initiating and perpetuating factors in CFS may refrain from conflicts about presumed causes of CFS.

Objections made by GPs that these approaches to diagnosis and presumed causes are too time-consuming are refuted by the findings in this study that CFS patients already take more time of the GP than other patients in general practice. Moreover, the investment of the GPs valuable time will be recompensed by fewer conflicts with CFS patients about diagnosis and causes. Both willingness to diagnose CFS and expert knowledge of CFS seem to be important factors for improvement of the perceived relationship with CFS patients. This attitude may be beneficial to the course of the complaints too.

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Chapter 10

The transferability of the treatment protocol 'Cognitive Behaviour Therapy for Chronic Fatigue Syndrome'

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The transferability of the treatment protocol 'Cognitive Behaviour Therapy for Chronic Fatigue Syndrome'

Abstract

Recently, the treatment manual 'Cognitive behaviour therapy for Chronic Fatigue Syndrome' (CBT for CFS) was published. In the context of a research programme thirteen therapists applied an earlier version of this manual in 82 CFS patients. The results of this study showed that the treatment is effective. Hence, it was opportune to investigate whether the treatment manual was suitable to be transferred to peripheral therapists. The therapists participating in the research programme were thoroughly trained and supervised. But did they actually do what they were supposed to do? And what did they think of the usability of the treatment manual? In order to shed some light on these issues, following completion of the study the thirteen therapists were asked to complete a questionnaire. Also, analyses of audiotaped sessions were conducted to verify whether the therapists had complied with the various treatment aspects included in the manual. In 89% of the sessions this appeared to be the case. The questionnaire revealed that the therapists found it more difficult to treat CFS patients than patients with psychological or other physical problems. The treatment aspects posing the most problems were integrating individual problems into the standardised treatment, dealing with the patients' lack of confidence in the treatment and handling insufficient motivation. For these aspects in particular, extra training seems necessary. The treatment manual will have to be revised in such a way that it will leave therapists room to individualise the prescribed interventions and it will need to provide them with guidelines for interventions aimed at motivating patients.

Introduction

There have been manual-based psychotherapy treatments, for both research purposes and training and practice, for well over 25 years[1]. In 1993 the American Psychological Association (APA) appointed a task force to advise on the use of empirically validated treatments in the clinical practice and in the training of psychotherapists. The report of this Task Force on Promotion and Dissemination of Psychological Procedures[2] formed the starting point of a heated debate about the desirability and/or introduction of research-based treatment manuals in the clinical practice.

Much of the debate concerned the strengths and weaknesses of such *'evidence-based treatments'* and the differences between research and practice[3-6]. The discussions revealed that resistance to the use of standardised treatments was highest in psychotherapists working in clinical practice. It is their impression that the limitations of scientific research, the implications of the differences between client and therapist characteristics, the role of non-specific factors and the necessity to adjust the therapeutic interventions to the client- or patient-specific complaints are

not sufficiently taken into account[7]. Objections to manual-based treatments have been discussed and refuted frequently[3,6,8-10]. The arguments challenging standardised treatments include:

- their failure to take comorbidity and the more complex problems of the clinical practice into account;
- their lack of flexibility and adjustability preventing customisation;
- the idea that the patient or client is not served adequately by a standardised treatment;
- their failure to do justice to the role of the holistic theory and function analysis;
- the negative effect they have on the patient-therapist relationship;
- their negative impact on the competency and work satisfaction of the therapist;
- their poor practicability.

Despite these realistic objections many defend the notion that the clinical practice should nevertheless take advantage of the empirical evidence on the effectiveness of treatment procedures or manuals, even though further research is needed[9,11-15].

Recently, an American study investigated the attitude of psychotherapists toward treatment manuals[16]. Of the 2970 psychologists approached, all of who were APA members, 30% responded by returning the questionnaire they had been sent. Such a response can be said to be low and this raises doubts as to whether the collected data accurately reflect the general attitude of therapists. Nevertheless, a striking result was that the majority of the respondents had expressed an opinion about treatment manuals even though 25% of them were unfamiliar with the existence of such manuals and nearly 50% had never worked with them. This led the authors to conclude that the attitude of therapists regarding treatment manuals seems, to a great extent, to be based on what the psychologist has heard or read, rather than on any hands-on experience. The respondents' attitudes could be differentiated according to those who emphasised the negative aspects of the treatment process and those who underlined a positive treatment outcome. The negatively inclined respondents characterised a standardised treatment as dehumanising the psychotherapeutic process and focusing solely on the technical aspects at the expense of treatment flexibility and the patient-therapist relationship. Those psychologists emphasising a positive treatment outcome regarded the manuals more as guidelines provided to help the therapist to apply empirically validated interventions[16].

The debate on the pros and cons of standardised treatments in the clinical practice has also yielded suggestions as to the desired content of such a treatment manual. Many of these suggestions underpin the importance of a manual that leaves room for customisation and flexible application. In Schulte's view[17] for instance, the use of particular treatment techniques for specific symptomatology or disorders should be standardised as much as possible. Translating this general strategy into an actual intervention for a specific client or patient, however, will always involve tailoring the therapy to an individual patient, taking the patient-specific perpetuating factors into

account. According to Schulte[17], this also holds for establishing a workable basic attitude in the patient and motivating him or her, thus ensuring that interventions can be successfully applied. Davison[18] advocates basing interventions both on the treatment manual and the individual function analysis. According to Eifert, Schulte, Zvolensky, Lejuez, & Lau[19] a treatment manual should incorporate optional modules that may or may not be used depending on the patient's function analysis. Wilson[6] finds that many manuals would be more user-friendly if they would provide practical examples and specify non-specific factors.

Kendall, Chu, Gifford, Hayes, & Nauta[20] state that a manual should offer a general framework outlining the treatment and treatment goals per session, that the manual should specify strategies and means to achieve these goals and that it should provide the therapist with guidelines to challenge problems that may arise in the course of the treatment. It is also desirable that the manual provides examples on how to customise the treatment. Addis[11] argues that in order to facilitate a successful transfer of a manual-based treatment, a systematic description of the non-specific factors (such as the patient-therapist interaction and the generation of positive expectations) and the clinical techniques to be used should be included in the manual.

Some authors seem to be under the impression that learning to work according to a manual is easier than learning to apply other psychotherapeutic methods. Vakoch and Strupp[21], for instance, are concerned that when, during training, too much attention is paid to learning to apply manual-based treatments, this will go at the expense of acquiring the ability to make more complex clinical judgments. By contrast, Heimberg[8] claims that learning to apply manual-based therapies requires more training. On the one hand the therapist needs to be able to fit his or her activities within the framework of the manual, while on the other hand he or she also needs to be able to improvise, but again within these boundaries. To be able to accomplish this requires experience with the symptomatology or disorders to be treated, the treatment itself and its theoretical context. Addis[11] suggests a training with one level addressing the more technical aspects of the treatment and a level dedicated to the non-specific factors. Iwamasa and Orsillo[22] state that before therapists are to apply manual-based treatments, they first need to acquire general cognitive-behavioural therapeutic skills. And finally, Addis, Wade, & Hatgis[3] mention that making an inventory of the therapists' objections to standardised treatments is an important ingredient for future training courses. Apart from teaching therapeutic techniques, attention needs to be paid to the patient-therapist relationship.

Recently, the treatment manual 'Cognitive behaviour therapy for Chronic Fatigue Syndrome', CBT for CFS, was published[23]. In the context of a research programme considerable practical experience had been acquired using an earlier version of the manual[24]. In a multicentre randomised controlled trial cognitive behaviour therapy was compared with guided support groups and natural course[25]. The study included 270 CFS patients. Intention-to-treat analyses showed CBT to be more effective than

the two other conditions for both of the two main outcome measures, i.e. fatigue severity and functional impairment.
Since the standardised treatment has proved effective, it has become opportune to try and investigate whether the manual is also suitable for transferral. Two questions are relevant in this context.
First, to what extent did the therapists, who were extensively trained and supervised, comply with the various aspects of the treatment manual during the actual sessions? In other words, did they do what they were expected to do? This is the so-called integrity check. Secondly, what is their judgment as to the manual's suitability for transfer? What are, in their views, the difficult and less difficult aspects of the prescribed treatment, what are the manual's shortcomings, and which of the treatment aspects do they think are suitable to be applied by therapists without additional training? To find answers to these questions, following conclusion of all treatment sessions, each of the therapists was presented with a questionnaire.

Method

Treatment manual

The treatment manual 'CBT for CFS' was founded on empirical knowledge and experience with CFS patients in the clinical practice. The rationale of the intervention was based on the model of perpetuating factors in CFS[24,26,27]. This model claims that a negative self-efficacy (the idea the patient has that he/she has no control over the complaints), strong somatic attributions, a low activity level and a tendency to focus on bodily sensations negatively affect fatigue severity and functional impairment in CFS patients. When complaints are attributed to a somatic cause (somatic attributions) this will lead to a reduced level of physical activity, which in turn affects the severity of the fatigue. A negative self-efficacy and strong focus on physical sensations will, again according to the model, have a direct impact on the severity of the fatigue. The standardised cognitive behaviour therapy for the treatment of CFS was therefore aimed at decreasing somatic attributions, increasing self-efficacy, and restoring the balance in activity patterns. The underlying principle of the treatment was that although we do not know what actually causes the complaints, we do know which factors help maintain the symptoms. The treatment therefore challenged the perpetuating factors. The final treatment goal was the patient's full recovery and a resumption of his or her normal activities.
The manual starts with a general outline of the treatment (table 1). Next, for each session the goal is described, together with the associated target cognitions for the patient, the therapist's aims and objectives, and the session's programme. Also, an indication of time, in minutes, to be allotted to each treatment aspect was provided. The manual further contained practical suggestions on how to effectuate the various interventions, sometimes with verbatim descriptions and detailed examples using the same two fictitious patients throughout the manual. The treatment consisted of 16 sessions distributed over a period of eight months. The first sessions were on a

weekly basis with the frequency of the subsequent sessions decreasing from once every two to once every three weeks down to once a month.

Table 1. Outline of the treatment manual

Step [1)]	Session	Methodology	Homework assignment
1. Referral and intake	1	- introduction - discussion report - fine-tuning expectations - role spouse - modus operandi	
2. Preparing patient for treatment and explanation of treatment goal	1, 2	- discussion goal - return to work	
3. Explanation of the model	1, 2	- views on somatic factors - role of cognitions and behaviours	
4. Exercises to prevent the fatigue from getting worse	1, 2, 3 ... (through-out)	- learning to think differently - accepting cognitions - peak-stop exercise	- registration of cognitions - peak-stop exercise
5. Learning to recognise and respect limitations, and following this through	2, 3, 4 ... (through-out)	- peak-stop exercise, learning to rest, base level - rationale activity programme - coping with the environment: learning to say no - lowering demands: changing way of thinking	- registration of cognitions - peak-stop exercise - writing down base level
6. Practising gradual expansion of limits	5, 6, 7 ... (through-out)	- activity programme: graphs - drawing up a plan for a return to work	- peak-stop exercise - activity programme: graphs - plan for return to work
7. Changing lifestyle and relapse prevention	8, 9, 10, 11, 12,... (through-out)	- first step return-to-work plan - discussion of impeding circumstances, environmental factors, cognitions and other likely problems	- activity programme: graphs - steps for return to work
	13, 14, 15, 16	- dealing with setbacks - preparing for therapy completion - evaluation	

[1)] These steps refer to the treatment aspects as described on pages 14 to 17 of the chapter on Chronic fatigue from 'Handboek Klinische Psychologie' (Bleijenberg, Vercoulen, & Bazelmans, 1996)

The content of the first eight sessions was fully structured. The subsequent sessions left more room to allow them to be tailored to the individual patient. The manual comprised 79 pages. Preparation and evaluation forms were provided separately. With these forms the therapists were encouraged to reflect, both prior to and following each session, on how to integrate the patient's complaints with the manual.

Therapists, training and supervision

Thirteen psychotherapists participated in the research project 'Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial'[25]. The therapists worked at three different locations, viz. Leiden, Maastricht and Nijmegen. They were psychologists, psychiatrists or health scientists and all were qualified or assistant behaviour therapists. At the start of the project none had any earlier experience with CBT for CFS. Prior to the start of the treatments all therapists received extensive training in the use of the manual 'CBT for CFS'. The training course lasted two two-day meetings, followed by several follow-up sessions.

Table 2. The main topics discussed during the plenary supervision sessions

- recognising individual cognitions, defining new (target) cognitions, and achieving the desired changes in cognitions (Socratic dialogue)
- enhancing the patient's self-efficacy
- use of a wheelchair
- use of medication
- sleeping problems and sleeping during the day
- base level and peak-stop exercise: balancing periods of rest and activity
- what constitutes a good programme to build up activity levels, and how to respond to the activity graphs
- passive patients
- company doctors and work-related problems
- what is improvement, what is recovery?
- how flexible can/are you allowed to be with the manual?
- making function analyses
- integrating additional patient-specific problems and comorbidity in the CBS treatment
- balancing permissiveness and authoritativeness
- the therapist's cognitions regarding the treatment
- emotions patients may evoke in the therapist
- resistance and motivation of therapist and patient

Preceding the training sessions all therapists had studied the treatment manual as well as literature on CFS and cognitive behaviour therapy[24]. For the training sessions and subsequent supervisions use was made of, among other techniques, video recordings, audiotapes, fictitious problems, role plays with simulated patients and the therapists' own cases. The in-situ supervisions were initially conducted on a weekly basis and, at a later stage, every other week. Every other month a plenary

supervision was arranged to discuss those issues that had caused the therapists problems. The therapists of one of the three locations selected these topics, together with their supervisor, and they provided their own CFS cases. During these central supervisions, additionally, role plays were practised or the supervisor raised specific points for discussion based on the experience of the preceding months. In total eight such plenary sessions were held over a period of 18 months. The main topics discussed in these sessions are listed in table 2. Together, the participating therapists treated 82 CFS patients.

Integrity check

For evaluation purposes, i.e. to verify whether the therapists had complied with the guiding principles of the treatment manual, all therapy sessions were audiotaped. In total 1,097 sessions were conducted. A *random* sample of 61 audiotapes (a good 5%) was analysed by an independent rater. In 49 of the cases the tapes comprised a full session; 12 of the recordings were incomplete. The manual was subdivided and scored for the following treatment aspects: cognitive restructuring, setting limits, activity programme, return to work (or resumption of other personal goals) and other CBT. The sessions were analysed by means of the audiotapes, their so-called *verbatims*, and a checklist. For each of the treatment aspects the time dedicated to this aspect during a session was noted down. In addition, the checklist was used to indicate on a five-point scale (minimal, some, reasonable, considerable, extensive) for each session how much attention the therapist had paid to the treatment aspect the manual prescribed for that session. An overall judgment on the session as a whole was given using a three-point scale (insufficient, sufficient, good).

Questionnaire for the psychotherapists

As regards the questions about the treatment to be put to the therapists, the manual was subdivided into the same treatment aspects as used for the integrity check, i.e. cognitive restructuring, setting limits, activity programme, return to work or resumption of other personal goals, and other CBT. In addition, for the questionnaire these aspects were further subdivided into subcategories (table 3).

The therapists were asked to evaluate the CBT for CFS manual for these subcategories on a scale ranging from 1 (agree) to 6 (disagree) on the basis of the following statements:

- I think this is important for a successful treatment
- I can adequately apply this myself
- In my view, patients understand the rationale of this aspect well
  (this item was not assessed for the questions relating to 'other CBT')
- Can, in my view, be adequately applied by an untrained psychotherapist, i.e. a (cognitive) behaviour therapist working solely on the basis of the manual
- How this aspect is to be effected, is sufficiently described in the manual.

In addition, the following statements were included:

- CFS patients are more difficult to treat than other patients with somatic complaints.
- CFS patients are more difficult to treat than patients with psychological complaints.

Similarly, these statements were scored on a scale from 1 (agree) to 6 (disagree). Of this 6-point scale the therapists primarily used score 1 (40% of the answers). The scores 2 (26% of the answers) and 3 (17% of the answers) and 4, 5 and 6 (together 17% of the answers) were used far less frequently. This is why, except for the overall judgment, in the representation of the therapists' evaluations we only show the percentages of score 1, reflecting the proportion of therapists who fully agreed with that specific statement.

Table 3. The therapists' views on the CBT for CFS treatment manual

	doable in my opinion	understood well by the patient	important for a successful treatment	sufficiently described in the manual	not practicable for an untrained therapist
Cognitive restructuring					
explanation rationale	85%	54%	100%	39%	23%
making an inventory of cognitions	31%	8%	62%	15%	23%
challenging cognitions	39%	8%	69%	8%	46%
Setting limits					
explanation limits	69%	62%	92%	46%	23%
implementing peak-stop exercise	54%	46%	62%	15%	15%
Activity programme					
explanation activity programme	69%	62%	85%	31%	15%
implementing activity programme	46%	31%	77%	15%	23%
Return to work / Other personal goals					
defining goals	39%	31%	77%	23%	15%
action plan return to work / personal goals	31%	23%	62%	8%	23%
implementing plan return to work / personal goals	31%	23%	69%	15%	31%
Other CBT					
lack of confidence	31%		85%	8%	54%
insufficient motivation	23%		92%	8%	46%
integrating individual problems	31%		77%	8%	39%
dealing with comorbidity	18%		85%	0%	31%

Results

Did the therapists do what they were expected to do?

During all sessions themes were dealt with as described by the manual. In 89% of the sessions this was rated as sufficient. In 25% of the sessions issues were raised that were not related to CBT for CFS (other non-CBT). The proportion of time allotted to these non-relevant topics was, on average, 8%. The *overall* judgment revealed that the rater considered 87% of the sessions to be sufficient or good.

A comparison of the proportion of time to be allocated to the various subjects as stipulated in the manual with the time actually spent on these themes showed many similarities, particularly with respect to the aspects cognitive restructuring, setting limits and building up activity levels (figure 1).

As regards the percentage of time allocated to return to work and other CBT the differences were greater. Compared to the manual, less time was dedicated to a return to work and more time was spent on other CBT.

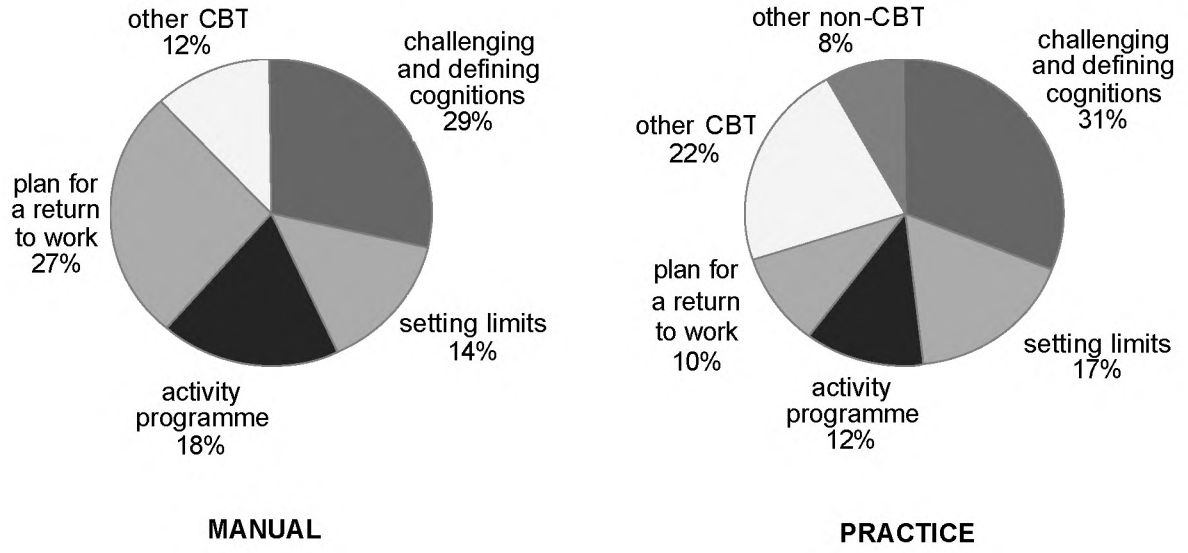

Figure 1. Discrepancy between what the therapists practised and what was prescribed by the manual

Overall judgment of CBT for CFS

Many of the therapists indicated that they found CFS patients more difficult to treat than other patients with somatic complaints and patients with psychological complaints (figures 2a and 2b).

Which treatment aspects were practicable for the therapists?

It was remarkable that for a majority of therapists explaining the treatment's rationale, the activity programme and setting limits posed the least problems, whereas at the stage of having the patient comply with the peak-stop exercises and activity

programme already fewer therapists stated this was practicable. Moreover, with respect to challenging and defining cognitions, formulating the final goal, drawing up and realising a plan for a return to work, integrating individual problems and dealing with a lack of confidence, only a third of the therapists indicated that the manual was workable. Merely 18% reported that challenging insufficient motivation and dealing with comorbidity was viable.

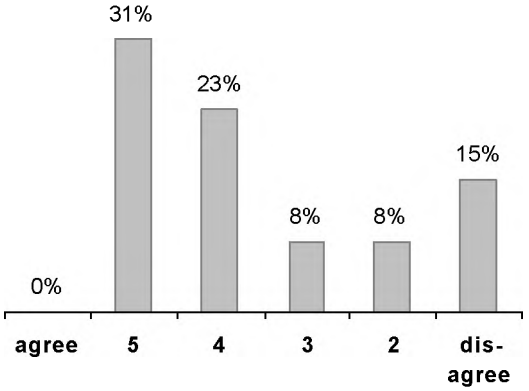

Figure 2[a]. CFS patients are more difficult to treat than other patients with somatic complaints

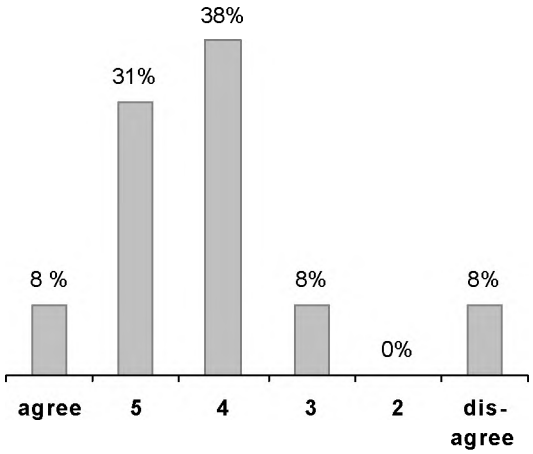

Figure 2[b]. CFS patients are more difficult to treat th than other patients with psychological complaints

Which aspects were understood adequately by the patients?
Again, the explanation of the rationale, setting limits and the activity programme come top of the list, followed by maintaining the peak-stop exercise and activity programme, defining targets and drawing up and executing a plan for a return to work. The most striking finding is that a mere 8% (a single therapist) had the impression that the patients grasped what defining and challenging cognitions entailed.

Which aspects did the therapists regard as important for a successful treatment?
When we look at which aspects of the treatment were important or less important in the eyes of the therapists to ensure a successful treatment outcome, it is surprising that for the element rated as the least significant still 62% of the therapists indicated this as important. In addition to explaining the treatment, 75% of the therapists regarded coping with low motivation, handling comorbidity and integrating individual problems as central to the treatment. Compared to the other treatment elements, particularly defining and challenging cognitions and making and having the patient follow up the plan aimed at a return to work was considered less relevant.
What was described adequately in the manual?
Only with respect to the aspects explaining limits, the rationale and activity

programme did 31% to 46% of the therapists state that these were amply described in the manual. For the aspects having the patient comply with the peak-stop exercise and activity programme, and also for work resumption, cognitive restructuring, and the elements categorised as 'other CBT', only one therapist indicated these as having been adequately described in the manual.

Which aspects would pose problems for an untrained therapist?
Table 3 lists for each treatment aspect the percentage of psychotherapists who thought that the particular aspect could not be applied by an untrained therapist. Specifically lack of confidence, insufficient motivation and challenging cognitions was seen by 50% of the therapist as likely to pose problems for an untrained therapist. Only two therapists (15%) were convinced that an untrained therapist would not be capable to apply the activity programme and have the patient comply with the peak-stop exercise and achieve the targets set.

Discussion
As evidenced by the integrity check, the therapists have overall applied the treatment as prescribed by the manual and, as shown by the effect study, successfully[25]. However, it needs to be said that the therapists found several aspects of the manual-based CBT for CFS treatment hard to administer.
They managed explaining the treatment rationale and having the patients comply with their limits and activity programme quite well. However, with respect to bringing about a change in the patient's behaviour and cognitions, as well as having the patients draw up and follow up on the action plan aimed at a return to work (or reaching other personal goals), already fewer therapists indicated that they had found this viable. Integrating patient-specific problems and managing a lack of confidence and motivation had posed them the most problems. Particularly for comorbidity and dealing with lack of motivation the therapists expressed a need for the manual to be more explicit. These aspects, together with challenging cognitions, were also the treatment components of which the therapists stated that these could not be easily applied without additional training in the use of the manual. Since it is difficult to describe these aspects explicitly in a manual, we feel that specifically these components of the therapy need to be mastered through training and supervision. It needs to be noted that the results as derived from the questionnaire are in line with the topics discussed in the plenary supervision sessions. These frequently involved cognitive restructuring, tailoring the programme to the individual patient, and the patient-therapist interaction.
This study has several methodological limitations. For instance, since the questionnaire could only be put to the 13 therapists who had participated in the study, our sample was small. In addition, only a limited number of scores of the six-point scale were used. This may possibly be due to the respondents' desire to give socially acceptable answers. Nevertheless, the scores clearly indicated at which

aspects the manual was found to be lacking. The responses to the various items, moreover, are consistent in that they show which treatment aspects the therapists considered less or more difficult. Despite these limitations, we can safely say that the responses to the questionnaire constitute a useful supplement to the acquired clinical experience in the use of the manual and the associated training and supervision.

The fact that defining and challenging cognitions posed serious problems may also be attributed to the therapists' prior training and experience. They had been selected on the basis of their experience in behavioural therapy, but the extent of practical experience with cognitive therapy was not the same for all therapists. Similarly, their therapeutic experience with patients suffering form somatic complaints was quite diverse and ranged from 0 to 24 years. Furthermore, the fact that the therapists indicated that putting the manual to practice had not always been easy may also be related to the version of the manual they were working with; this first version did not yet differentiate between passive and active CFS patients[28]. The effect study[25] had shown that the standardised treatment had proved specifically suitable for the treatment of the relatively active CFS patients but had hardly worked for the passive CFS patients. As passive CFS patients are characterised by a fear and avoidance of activity, complying with preset activity limits proved to be of no use to these patients. We now know that for this group the stage at which activity levels are raised needs to be brought forward drastically. In contrast, active CFS patients still undertake too many activities regularly. Since they exceed their limits, for them learning to observe the limits agreed upon is useful. Passive CFS patients already undertake so little that maintaining limits only perpetuates their pattern of complaints. Because during the study the passive patients were also required to comply with this aspect of the treatment, this may have frustrated the therapeutic process.

On the basis of the experiences as reported by the 13 participating therapists, their supervisions and the results of the effect study, the treatment manual has been revised. In the most recent version[23] the manual now makes a distinction between the treatment of passive and relatively active CFS patients. Also with respect to flexibility the manual has been modified. It is now stressed that the therapist will always need to investigate for each individual patient which the key factors are that help maintain the complaints. Is this a passive or a relatively active CFS patient? Is there any comorbidity? In the course of the treatment a function analysis of the patient-specific perpetuating factors is recommended. The manual may be used to support this process of differentiating the essentials from the side issues. It describes the treatment in broad outlines and offers suggestions and examples, founded on empirical evidence, of possible cognitions and behaviours, the appropriate interventions and the likely problems to be encountered. Pivotal to the treatment will, however, always be to relate to each individual patient.

It is our view that a sound treatment manual should provide insight into and contain detailed information about the function analysis of the patient group as a whole, the specific cognitions and behaviours of the patient or client population, the

interventions specifically targeted at these specific symptoms, likely motivational and interaction problems, as well as provide strategies, interventions and additional recommendations illustrating ways to deal with such problems. The function analysis and the specific cognitions and behaviours of the patient group as a whole need to be founded on scientific findings. Furthermore, a treatment manual should offer a solid framework and firm foothold, and should provide the psychotherapist with a sound basis for the individual function analysis and the subsequent interventions[29,30]. This facilitates the treatment for the therapist, but he or she will, however, always have to tailor the treatment to the individual patient. The difficulty here is that in order to integrate the patient-specific function analysis with the manual the therapist needs to have full control over two different aspects. He or she will need to combine both the manual and the individualised treatment on the basis of a therapeutic programme that has only been defined in broad terms. This implies that the therapist may need specific, additional skills and the process will always place high demands on his or her basic technical and interaction skills, as well as on the preparation and evaluation of the sessions.

Applying a standardised, manual-based therapy may seem straightforward. It is ready-made and everything is primed and as long as you stick to the manual, the treatment will run its course. Nothing is further from the truth. Although the outlines are provided, it is vital that the therapist fine-tunes the manual to each individual patient. For the developers of manuals it is essential that they allow enough room for manoeuvre in the manual so that the therapist is able to cater for each specific patient, but the manual should also offer sufficient degrees of freedom to provide for differences between therapists. Working with the present manual requires solid cognitive behavioural and interaction skills of the therapist, as well as a sound knowledge of the scientific state of affairs concerning CFS. A standardised, empirically validated practice does not necessarily make treatment easier, but it may at least enhance the quality.

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Chapter 11

Cost effectiveness analysis of cognitive behaviour therapy for patients with chronic fatigue syndrome

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Cost effectiveness analysis of cognitive behaviour therapy for patients with chronic fatigue syndrome

Abstract

Cognitive behaviour therapy (CBT) can be considered to be an efficacious treatment for chronic fatigue syndrome (CFS). This study reports a cost-effectiveness analysis as part of a randomised controlled trial of CBT for CFS patients compared to guided support groups (SG) and the natural course (NC, no protocolised intervention). Patients were treated for 8 months and followed up for another 6 months. Both a health care and a societal perspective were used, indicating either cost per patient clinically significant improved based on the CIS-fatigue scale or cost per quality adjusted life year. One way sensitivity analyses and bootstrap simulations were performed to study cost-effectiveness uncertainty.

Of the 270 patients complete cost and effectiveness data were available of 171 patients at 8 months and 128 at 14 months. At 8 and 14 months the percentages of improved patients were 31% and 27% for CBT, 9% and 11% for SG, and 12% and 20% for NC. The mean QALY gained until 14 months was for CBT, SG and NC respectively 0.0737, -0.0018, and 0.0458. CBT and SG mean treatment costs were €1,490 and €424. Other medical cost for CBT, SG, and NC for the first period were €324, €623, and €412 and for the second period €232, €561, and €378 respectively. The non-medical costs for the distinguished periods for CBT, SG and NC were €262, €550, €427 and €226, €439, €287. Productivity costs were considerable but not statistically significant different between groups. CBT was dominant over SG. Compared to NC, the baseline incremental cost-effectiveness of CBT is €20,516 CFS-patient clinically significant improved and €21,375 per QALY. The bootstrap per ratios indicate that compared to the current situation (NC) CBT can be dominant as well as inferior, or that an incremental cost-effectiveness has to be judged about. Future research should focus on productivity costs and use a longer period of prospectively following patients.

Introduction

Principles of economic evaluations in health care

Because of the tension between budget constraints and the growing possibilities of diagnosing and treating patients, economic evaluations of interventions in health care become more and more important. These economic evaluations intend to generate information about the relative efficiency of a diagnostic or therapeutic intervention on the basis of which decision-makers can decide about the implementation of this technology. After the efficacy of a health care technology has been established in a highly controlled situation for selected patients, the effectiveness and efficiency (or cost-effectiveness) has to be studied empirically in order to judge about the usefulness and possibilities of the technology in day-to-day health care.

The basic principle of an economic evaluation is the comparison of at least two

alternative courses of action, either being pharmaceutical products, medical devices or treatment procedures[1]. Because of this explicit comparison the difference in effectiveness and the differences in costs between the alternatives can be related to each other in order to be able to determine the relative efficiency of, in most economic evaluations, a newly introduced health care intervention. A comparison of the new intervention can be made with the regular intervention for the specific patient population, the most effective intervention so far, the cheapest, the intervention of first choice and so on. Of course, the choice of the comparator intervention is essential for the usefulness of the study findings to decision-makers[2].

Chronic fatigue syndrome

Chronic fatigue syndrome (CFS) is characterised by persistent or relapsing unexplained fatigue, of new or definite onset and lasting for at least six months, resulting in substantial reduction in previous levels of occupational, educational, social and personal activities[3]. Other symptoms such as musculoskeletal pain, sleep disturbance, impaired concentration and headaches might be present as well[4]. A large economic burden related to disability and health care use induced by CFS underscores the need for analysis of costs involved[5]. Cognitive behaviour therapy (CBT) can be considered to be an efficacious treatment for CFS. However, in the first randomised controlled trials[6,7], the therapy was administered by a highly skilled therapist in a specialised centre and therefore the generalisibility of these findings is subject to discussion[4]. Thus, before CBT for the treatment of CFS can be implemented in day-to-day health care practice, nowadays instead of efficacy only, information about effectiveness and cost-effectiveness is desirable.

A full economic evaluation aimed to determine the cost-effectiveness of health care interventions is only possible in case besides effectiveness measurement a cost analysis is integral part of the study. In this study we report the results of a cost-effectiveness analysis which was part of a randomised controlled trial. In this study we evaluate the differences in both costs and effectiveness of CBT for CFS patients compared to first another treatment, guided support groups, and secondly a control group, the natural course.

Methods

Study design

Design

The methods of the clinical part of this study have been previously described.[8]. The study was designed as a prospective, controlled, randomised multicentre clinical trial and was approved by the institutional review board.

Patients and treatment

The inclusion criteria for participation in the trial were as follows. Besides informed consent, the patients, between 18 and 60 years old, had to have a score of 40 or more on the subscale fatigue severity of the Checklist Individual Strength (criteria for

CFS or idiopathic chronic fatigue according to Fukuda et al.[3]), and a score of 800 or more on the Sickness Impact Profile. Exclusion criteria were previous or current engagement in CFS research, pregnancy or engaged in pregnancy- stimulating techniques and living more than one-and-a-half hour travelling time of one of the three centres. Between October 1996 and January 1998, consecutive patients with a major complaint of fatigue, referred to the outpatient departments of internal medicine of the University Medical Centre Nijmegen and the University Hospital Maastricht were enrolled in the study.

After inclusion in the study and baseline measurements, patients were randomised to cognitive behavioural therapy (CBT), guided support groups (SG) or natural course (NC). CBT lasted 8 months and consisted of 16 one-hour sessions by trained therapists. Patients in this group had to meet the requirements of no further medical examinations or additional treatments for CFS during the study. The SG group (11 one-and-a-half-hour meetings during 8 months) was introduced to show the additional effect of CBT next to therapist attention. The NC group (no protocolised intervention) was established to make comparison possible between the protocolised CBT intervention and the medical care seeking behaviour of CFS patients as is current practice. CBT and SG were performed in three treatment centres (Dept. Medical Psychology, University Medical Centre Nijmegen; Dept. Psychiatry, Leiden University Medical Centre; Dept. Psychotherapy, Maastricht Mental Health Institute). Thirteen therapists were available for CBT, one social worker for SG.

Before randomisation, at 8 months follow up (shortly after finalising CBT or SG), and at 14 months follow up (6 months after finalising CBT or SG) patient assessments were performed. Because fatigue is the main symptom of CFS patients, for the cost-effectiveness analysis we used the subscale CIS-fatigue (Checklist Individual Strength) as a disease-specific outcome measure to determine the fatigue severity during the last two weeks[9,10]. Besides this, because health related quality of life was considered to be an important outcome, the EuroQol was used as a preference-based measure[11]. Using the patients' answers on the EuroQol-questions indicating their health state of the past two weeks, a single utility value was calculated as an indicator for the quality of life[12].

Cost-effectiveness analysis

Study perspective and time horizon

In our study we used two perspectives. First, a health care perspective was basis for the cost-effectiveness analysis, indicating that only medical costs were relevant (either paid for by an insurance company or the patients themselves). Secondly, a societal perspective was used, which implies that also non-medical costs, such as travelling expenses and productivity costs (costs related to absence from work due to illness) were considered to be relevant. Both perspectives implied that the cost analysis was performed on the basis of real costs instead of using charges paid for treatment (for instance, neither patients nor insurance companies had to pay for the

experimental CBT and SG treatment, although these costs are a relevant part of our analysis). Costs initiated in the context of the study, but not related to day to day patient treatment, the so-called protocol-driven costs were left out of the cost analysis[1]. The time horizon used for the analyses was equal to the follow up of patients, thus 14 months after inclusion in the study. Given this short time horizon, the principle of discounting was not applied.

The cost analysis consisted of two main components: first, the measurement of the volumes of the resources used by each patient and second, the financial valuation (cost price) of the volumes measured. The volumes of care and other cost items that were not related to the protocolised CBT and SG treatment were measured by means of a monthly diary. Patients indicated on the monthly diary cards the number of CFS related visits to their GP, medical specialists, physical therapists, and practitioners for alternative medicine, number of hours of formal and informal home care support, hospital admission and number of days in hospital, and use of prescribed medication. Out-of-pocket costs, for instance OTC-medication, were based on actual expenses. The number of days not being able to perform paid or unpaid work was registered as well. Regarding the cost price analyses we followed the Dutch guidelines for costs analyses in health care[13]. Cost prices that were based on the 1998 price level and converted into Euros were used to value the registered volumes (table 1).

Table 1. Cost prices used to value the different volumes measured in the cost-effectiveness analyses (in Euro, €)

Volume parameter	Cost price (€)
General practitioner (per visit)	14.98
Medical specialist (per visit)	59.90
Physical therapist (per visit)	16.34
Company doctor (per visit)	83.05
Non-physician alternative medicine practitioner (per visit)	44.47
Prescribed medication (average costs per day)	2.27
Unprescribed medication (average costs per day)	2.41
Home care (per hour)	14.48
Informal home care support (per hour)	6.13

Regarding CBT and SG integral prices were determined, thus costs were based on actual therapist time, use of medical materials and including overhead costs such as costs for therapist training and facilities. The cost prices for GP visits, medical specialist visits, physical therapists, and travelling were based on the guidelines. Visits to psychotherapists, home care, and use of alternative treatment were based on reported expenses or recommended prices from the professional associations. Market prices were used for valuing medication. In order to prevent coincidental differences in productivity costs between the trial groups, the days of lost work were

valued using the Dutch general wage rate rather than the actual wages of individuals. The diagnostic protocol was identical for all participating patients. However, in daily practice only patients who are eligible for CBT will be diagnosed extensively, thus these costs were only relevant for the CBT-patients and were left out of the cost analysis for the other groups. For SG, the costs for an intake visit were calculated, as is current practice.
For each patient, the volumes measured were multiplied by the specific cost price, leading to the cost of CFS. A distinction was made between the costs of CFS diagnosis and treatment, other medical costs being reimbursed by the insurance company, patients' expenses, and costs of lost productivity. Besides this, the phases of the therapy period (intake to 8 months) and the follow-up (9 to 14 months) were discerned.

Analyses
Analyses were performed on the basis of intention to treat. The patients who were included in our analyses had to have complete data regarding the effectiveness measures and at least 75% of the cost diaries had to be available. Missing cost data due to missing diaries were constructed by using the patient year approach, thus extrapolating the available cost data to the end of follow-up[14]. The CIS-fatigue was used to determine the percentage of patients for each randomisation group that was clinically significant improved. As a criterion for improvement we used both a significant change index and a cut off score of 36 or lower of the CIS-fatigue[8]. The EuroQol utility score was used to calculate the quality adjusted life years (QALY) regarding the period of follow-up. In the QALY concept, the quality of life is expressed in a utility figure between 0 (health state equal to death) and 1 (perfect health) and multiplying time in a health state with this figure leads to the QALY score. Costs were expected to be skewed and therefore the non-parametric Mann Whitney U test was used to detect differences in costs between the groups. The analyses of the cost-effectiveness data were aimed to compare CBT to both SG and NC. For the effectiveness regarding the percentage of patients that clinically significantly improved, the incremental cost-effectiveness ratio (ICER) was based on the total treatment costs for each specific patient group. The ICER regarding quality of life was calculated based on the difference in mean costs and difference in mean effectiveness between groups. These ratios indicate the financial investment that is needed to gain the additional effectiveness. To test the robustness of the findings of the cost-effectiveness analysis regarding deterministic variables such as cost prices, one way sensitivity analyses were performed by varying the values of these parameters[15]. For this analysis, we used the most important cost prices in these analyses, being the costs of the CBT therapist and the overhead costs for training. Besides, the uncertainty of an ICER was estimated by using non-parametric bootstrapping, a method that is based on randomly sampling with replacement of the number of the patients in the trial from the original data[16]. For each of the 1,000

bootstrap replicates a bootstrap ICER was calculated. Following, this information is translated and readily presented to decision-makers using the cost-effectiveness acceptability curve which plots the probability that a particular intervention is optimal, over a range of cost-effectiveness values[17]. For the bootstrap analyses we used the costs and effectiveness data regarding the 14 months follow up.

Results

In the study 270 patients were included (for CBT, SG, and NC respectively 92, 90, and 88). The effectiveness and costs data were complete for 171 patients until the 8 months measurement (52, 55, and 64 for CBT, SG, and NC respectively) and for 128 patients until the 14 months measurement (for CBT, SG, and NC respectively 37, 36, and 55). The missing data were related to 10 patients in CBT and 8 patients in SG who did not start therapy. Lost to follow-up for the clinical assessments for CBT, SG, and NC were 28%, 21%, and 10% respectively during the eight months period, and 7%, 6%, and 11% between the 8 to 14 months follow-up. Missing cost diaries were the reason for additional lost to follow-up of 7 of 59 remaining patients in CBT, 10 of 65 SG, and 15 of 79 in NC at 8 months follow-up and, respectively, 18 of 55, 25 of 61, and 15 of 70 at 14 months follow-up. Extensive analysis of differences between patients who completed the study and patients who were lost to follow-up for the cost-effectiveness analysis showed no differences at baseline measurement regarding age, sex, duration of CFS complaints, treatment centre, CIS fatigue score and the clinical assessment measures.

From the clinical results of the study it was concluded that there were no centre effects on the main outcome variables. CBT proved to be statistically significant more effective regarding improvement on CIS fatigue and other measures such as Karnofsky performance status and Sickness Impact Profile as described in detail elsewhere[8]. Regarding the criterion clinical significant improvement as defined by the cut off score of 36 or lower of the CIS-fatigue, at 8 and 14 months the percentages of improved patients in the cost-effectiveness study were 31% and 27% for CBT, 9% and 11% for SG, and 12% and 20% for NC. The utility at intake, 8, and 14 months of follow up are reported in table 2. Based on these utility scores the mean QALY gained from intake until 14 months follow up was for the three groups respectively 0.0737, -0.0018, and 0.0458.

Table 2. Mean utility scores at intake, 8, and 14 months of follow up and the differences between the measuring moments

	Intake	8 months	Difference 0 - 8 months	14 months	Difference 8 – 14 months
CBT	0.4859	0.5817	0.0958	0.6014	0.0197
SG	0.5036	0.4930	- 0.0106	0.5035	0.0105
NC	0.5257	0.5779	0.0522	0.5999	0.0220

CBT: cognitive behaviour therapy - SG: guided support groups - NC: natural course

Cost results

The analysis of the cost involved in diagnosis and both protocolised treatment strategies, e.g. CBT and SG resulted in €1,490 and €424 respectively. In detail, for the treatment modality SG the diagnostic activities were considered to be limited to one intake session by a social worker, costing €34. The cost for the more extensive diagnostic protocol before CBT treatment were €411, consisting of €265 for personnel, €48 for the use of medical equipment and materials, and €65 overhead costs. €34 considered travelling costs by patients. In both cases, main component of the diagnosis and treatment costs were costs for personnel €830 (of which €192 was related to the training CBT-therapists) and €194 (for SG).

Table 3. Volumes of care used

	CBT			SG			NC		
	Mn	Md	IQR	Mn	Md	IQR	Mn	Md	IQR
0-8 months									
General practitioner	1.3	1	0-2	2.2	1	1-4	2.2	1	0-3
Medical specialist	0.4	0	0-0	0.9	0	0-1	0.7	0	0-0
Physiotherapist	1.4	0	0-0	5.1	0	0-7	3.7	0	0-6
Psychologist	0.5	0	0-0	2.1	0	0-3	1.3	0	0-0
Alternative caregiver	0.3	0	0-0	4.9	0	0-9	3.4	1	0-5
9-14 months									
General practitioner	1.0	0	0-1	1.8	1	0-2	1.4	1	0-2
Medical specialist	0.2	0	0-0	0.8	0	0-2	0.6	0	0-0
Physiotherapist	1.9	0	0-0	3.2	0	0-3	2.9	0	0-4
Psychologist	0.0	0	0-0	1.3	0	0-1	1.5	0	0-0
Alternative caregiver	1.3	0	0-0	4.2	0	0-7	1.4	0	0-2

CBT: cognitive behaviour therapy – SG: guided support groups – NC: natural course
Mn: mean – Md: median – IQR: interquartile range

In table 3 the volumes of non-protocolised care used are reported. These volumes were the basis for calculating the mean medical cost per patient (the above mentioned treatment costs excluded): for CBT, SG, and NC for the period from 0 to 8 months €324, €623, and €412 respectively and for the period from 9 to 14 months €232, €561, and €378. The non-medical costs for the distinguished periods for CBT, SG and NC were €262, €550, €427 and €226, €439, €287. In table 4 a more detailed break-down is given regarding these figures. Thus, the 8 months average total costs (productivity costs excluded) for the three groups were €2,487, €1,631, and €839, and for the whole 14 months period €2,534 for CBT, €2,597 for SG and €1,504 for NC.

In the three groups the percentage of patients having a paid job at the start of the study were 36.8%, 23.5% and 39.7% and the mean number of working hours were 28.0, 31.7, and 24.7. Based on the absence from paid work (mean number of hours

Table 4. Mean and median cost (€) per patient and interquartile range regarding the 14 months study period, distinguishing the 'treatment' period of 8 months and 6 months 'follow up'

0-8 months	CBT			NC			SG		
	Mn	Md	IRQ	Mn	Md	IRQ	Mn	Md	IRQ
Medical costs									
General practitioner	20	15	0-30	34	15	15-60	34	15	0-45
Specialist	22	0	0-0	55	0	0-60	39	0	0-0
Physiotherapist	24	0	0-0	83	0	0-114	62	0	0-98
Company doctor	38	0	0-0	177	0	0-249	105	0	0-0
Prescribed medicine	35	0	0-3	80	22	0-85	70	10	0-93
Home care	173	0	0-0	182	0	0-0	94	0	0-0
Non-medical costs									
Non physician alternative practitioner	17	0	0-0	128	0	0-152	137	11	0-189
Unprescribed medicine	32	0	0-11	70	8	0-90	62	12	0-90
Informal home care	97	0	0-25	155	0	0-230	104	0	0-57
Other costs	79	0	0-0	166	0	0-45	71	0	0-18
Travelling costs	51	0	0-50	44	9	0-48	61	0	0-70
Total medical costs	324	51	0-373	623	349	75-883	412	176	34-554
Total non-medical costs	262	34	1-422	550	342	851-3728	427	243	5-771
Total 0 – 8 months	586			1173			839		
9 - 14 months									
Medical costs									
General practitioner	15	0	0-15	26	15	0-30	20	15	0-30
Specialist	13	0	0-0	45	0	0-90	35	0	0-0
Physiotherapist	31	0	0-0	52	0	0-41	48	0	0-65
Company doctor	2	0	0-0	104	0	0-42	121	0	0-0
Prescribed medicine	29	0	0-9	75	16	0-94	93	5	0-44
Home care	132	0	0-0	250	0	0-0	101	0	0-0
Non-medical costs									
Non physician alternative practitioner	33	0	0-0	94	0	0-179	55	0	0-68
Unprescribed medicine	19	0	0-2	55	1	0-14	23	0	0-14
Informal home care	82	0	0-0	146	0	0-208	75	0	0-0
Other costs	69	0	0-0	115	0	0-0	89	0	0-0
Travelling costs	31	0	0-5	40	9	0-48	44	12	0-70
Total medical costs	232			561			378		
Total non-medical costs	226			439			287		
Total 9 – 14 months	458			1000			665		
0-14 months (sum of means)									
Medical costs	556			1184			790		
Non-medical costs	488			989			714		
Total 0-14 months	1044			2173			1504		

CBT: cognitive behaviour therapy – SG: guided support groups – NC: natural course
Mn: mean – Md: median – IQR: interquartile range

absence from paid work during 4 weeks for CBT, SG and NC were 33.4 and 23.1, 23.1 and 20.1, and 37.0 and 25.3 for the two periods respectively), the productivity costs from intake to 8 month and for the 9 to14 months period were calculated, but due to the large, overlapping ranges no significant difference were found (table 5)

Table 5. Productivity costs in Euro (€)

	Intake to 8 months			9 to 14 months			0 to 14 months
	Mn	Md	IQR	Mn	Md	IQR	Sum of means
CBT	13,248	4,030	0 – 26,838	7,242	1,072	0 – 12,325	20,490
SG	8,728	0	0 – 10,896	6,437	0	0 – 13,168	15,165
NC	14,564	3,684	0 – 28,177	7,788	2,322	0 – 10,717	22,353

CBT: cognitive behaviour therapy – SG: guided support groups – NC: natural course
Mn: mean – Md: median – IQR: interquartile range

Incremental ratios

An important finding before calculating incremental cost-effectiveness ratios is that SG is more expensive and less effective, both regarding percentages of improved patients and QALYs , than the experimental treatment (CBT). Therefore SG can be considered to be inferior to CBT and only the incremental cost-effectiveness of CBT versus NC was calculated.

Table 6. Incremental cost-effectiveness of CBT versus NC based on the number of CFS patients showing clinically significant improvement and costs regarding treatment and other medical costs at 8 months and 14 months follow up

	Costs CBT	Explanation	Costs NC	Explanation	Cost difference	Effectiveness difference	Costs CFS-patient improved
8 months	€159,168	64* €2,487	€53,696	64* € 839	€105,472	11.69	€ 9,024
14 months	€161,975	55* €2,945	€82,720	55* €1,504	€ 79,255	3.86	€20,532

CBT: cognitive behaviour therapy – SG: guided support groups – NC: natural course

The incremental cost-effectiveness regarding the percentage of patients that clinically significant improved showed that an investment of respectively €9,024 and €20,516 was needed to have one CFS patient clinically significant improve at 8 months and 14 months follow up. In table 6 the underlying calculation is explained in detail. The cost per QALY using the 14 month follow up related to respectively 1) treatment costs, 2) treatment costs, other medical costs and patients costs, and 3) these costs including productivity costs are respectively €60,108, €51,642 and €21,375.

Table 7. Distribution of the bootstrapped incremental cost-effectiveness ratios over the four quadrants of the cost-effectiveness plane

	1st quadrant	2nd quadrant	3rd quadrant	4th quadrant
Medical and patient cost per CFS-patient improved	78%	22%	0%	0%
Medical- patient and productivity cost per CFS-patient improved	37%	10%	13%	40%
Medical and patient cost per QALY	64%	36%	0%	0%
Medical- patient and productivity cost per QALY	31%	15%	20%	34%

CBT: cognitive behaviour therapy; NC: natural course
1st quadrant: CBT more effective and more costly than NC
2nd quadrant: CBT inferior compared to NC
3rd quadrant: CBT less effective and less costly than NC
4th quadrant: CBT dominant over NC

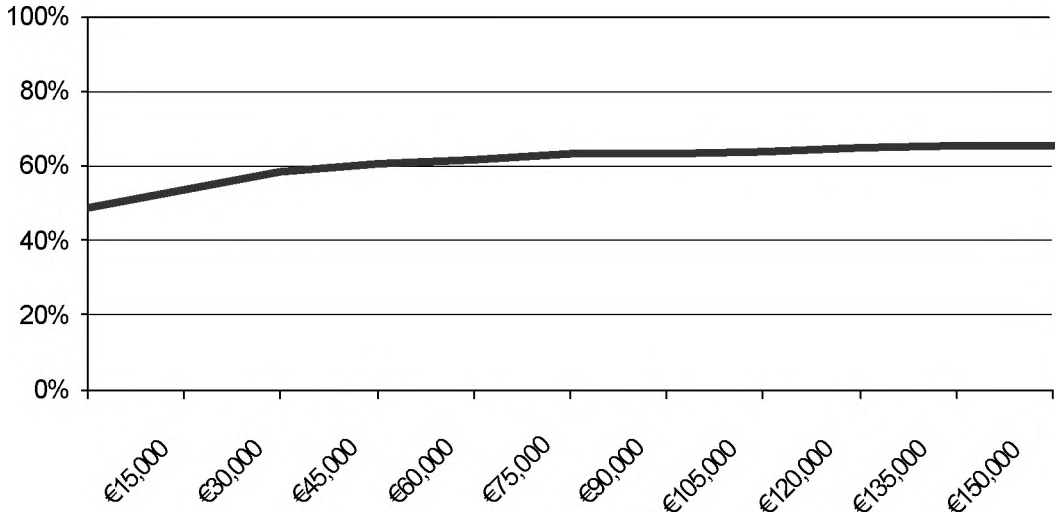

Figure 1. Acceptability curve showing the probability that CBT is cost-effective over a range of cost-effectiveness thresholds regarding medical-, patient-, and productivity costs per QALY

Varying the costs of the CBT therapist and costs for training in a sensitivity analysis showed that this did influence the cost-effectiveness estimates. In the situation that training costs are set at zero, the additional treatment cost per extra patient clinically significant improved changed from €9,024 to €7,971 regarding the 8 months time horizon and from €20,516 to €17,778 for the 14 months time horizon. The cost per QALY based on total costs (productivity costs included) changed into €14,482.
The bootstrap simulations based on the costs and effectiveness data regarding the 14 months follow up showed that the uncertainty surrounding the incremental cost-effectiveness ratios is considerable. The bootstrap ratios indicate that compared tothe current situation (NC) CBT can be dominant as well as inferior, that it is necessary to invest cost to gain effectiveness, or to accept effectiveness loss at

lowerlower cost (table 7). However, from the cost-effectiveness acceptability curve it can be seen that regarding prefering CBT over NC, uncertainty remains over a wide range of cost-effectiveness thresholds (figure 1).

Discussion

To our knowledge, cost-effectiveness of CBT in CFS patients has not been studied prospectively before. An extensive literature review did not reveal any prospective randomised study reporting the cost-effectiveness of CBT in CFS patients (our search strategy is available on request). Especially since CBT is the only therapy for CFS with evidence based efficacy, cost-effectiveness information is relevant[18]. Our main finding suggests that CBT leads to a higher clinical efficacy and that total costs to society are lower than the natural course, however, the statistical uncertainty of this finding is considerable.

Compared to the results of the clinical study as reported by Prins et al.[8] our results are based on a smaller number of patients due to the cost diaries lost to follow up in a larger number of participants, in the treatment period as well as the whole study period. Although this is a known phenomenon when using cost diaries, this method to collect cost-effectiveness data is considered to be feasible and valid[19]. An extensive comparison between participants in the cost-effectiveness analyse (N=171) and the remaining clinical study participants (N=99) did not reveal any statistically significant differences regarding age, duration of CFS-complaints, and scores on Sickness Impact Profile, Karnofsky score, physical activity, a self-efficacy scale, a causal attribution list, and functional impairment. Selection bias due to missing data is not expected, and we regard the cost estimates to be a valid reflection of the medical costs of CFS patients.

In our study, we found that CBT resulted in a better outcome and a lower use of medical care facilities than the control treatment (SG) and the natural course (NC). The phenomenon that patients receiving active treatment for disorders manifest reduced utilization of other medical services is referred to as the medical-offset. This is explained by, first, the situation that patients with untreated mental disorders frequently present with physical symptoms and persistent complaints that resolve with appropriate mental health treatment and, second, the idea that physical disorders may contribute to emotional distress, which in turn may exacerbate patients' symptoms or delay recovery. In the literature a medical-offset was reported for patients who were treated for depression and had CFS complaints, thus bringing about less reimbursed costs compared to the period before they were actively treated[20]. Health care visits to either GP and specialists or non-physician practitioners were found to be higher in SG than in CBT and control. During CBT, as part of the therapy, patients were discouraged to use other treatment in order to facilitate attribution of improvement to themselves in stead of other treatments. Some CBT patients violated this advice given the fact that the range of medical costs (CBT costs excluded) was zero to €4,122 (mean €324) during the first 8 months. However,

given a similar period of follow-up, the number of visits to GP and specialist in our control group was considerably less than found in the literature[5],[21]. This might be explained by the Dutch yearly subscription payment system, which discourages physician-induced follow-up visits. The number of non-physician alternative medicine practitioner visits, characterised by a fee for service payment was comparable. In our study no patient reported CFS-related hospital admission. Lloyd et al.[21] found a mean CFS-related hospital stay of 0.7 days after making a correction for three exceptional situations. It can be assumed that the costs we reported are underestimations of the total costs involved in current CFS treatment because, since besides visits to care providers and use of drugs we were not able to examine other services and non-drugs costs such as special diets. However, it can be argued that including these costs would enlarge the cost difference between successfully and unsuccessfully treated patients. Besides this, an important contribution to the reduction in costs was generated by the ability of successfully treated patients to return to their work. This finding was in accordance with previous studies because resuming work was clearly related to improvement of CFS symptoms. The best predictors to explain resuming work were found to be changes in the number of physical signs and psychiatric diagnosis[22]. Regarding our limited follow up we expect the cost-effectiveness to improve in case of a longer time horizon. Besides this, on an experimental basis CBT is offered as a group therapy which reduces costs and in case effectiveness persists, this might lead to a more favourable cost-effectiveness.

However, the statistical uncertainty of the cost-effectiveness estimates we found is considerable as the bootstrap simulations showed. This might be due to the fact that the clinical trial that was basis for this economic evaluation was powered to show an effect on physical activity, a measure that is not ideal for a cost-effectiveness analysis because its focus may be too narrow[1]. Using a societal perspective, thus including productivity costs, has a large impact on the cost-effectiveness estimates. However not statistically significant, the differences in productivity costs between the groups were considerable due to the fact that a small number of patients that were employed were absent from work during a longer period. Therefore, the results have to be interpreted with caution and we intend to further investigate the longer term working situation of our patients. The societal perspective is of importance, since in the trial of 270 CFS patients 76% had been employed before the onset of CFS, whereas only 33% had a job at the start of the study[8]. In the mean time the conclusions of this work should be based on the health care perspective as expressed in the medical and patient costs per CFS patient clinically significant improved, being €20,516. The difference in utility between the experimental treatment and the current situation is small. Given this fact and the short time horizon, the cost per QALY seem high. However, extrapolating the utility values and the cost figures another four years indicates that the cost per QALY will become more acceptable and even indicates dominance in case the productivity costs are included. This finding has to be interpreted with caution because in our study the

productivity costs were based on a small number of patients. Thus, to be able to estimate the cost-effectiveness of treatment of CFS patients more accurately, future research should give more focus on productivity costs and use a longer period of prospectively following patients.

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Chapter 12

General discussion

General discussion

Introduction

In this thesis, we concluded that cognitive behaviour therapy (CBT) is an effective treatment for patients with chronic fatigue syndrome (CFS). The effectiveness of CBT was found by comparing the treatment with guided support groups and the natural course of CFS in a randomised controlled trial (*Chapter 4*). Three systematic reviews endorsed effectiveness of CBT for patients with CFS[1-3]. The conclusion of these reviews was that CBT and graded exercise therapy (GET) are beneficial interventions for CFS patients, while for immunological therapy the evidence was inconclusive and for all other interventions insufficient evidence of effectiveness was found. In our opinion, CBT and GET are similar therapies, since there is no CBT without exposure to graded exercise and no GET without cognitive interventions needed to encourage graded exercise. All forms of CBT and GET encompassed a graded exercise programme, in which the main exercise was daily walking or cycling. In both CBT and GET, therapists express the opinion and entertain the expectation that exercise is helpful, the cognitive aspect that motivates patients to continue graded exercise for several weeks or months.

In other trials reporting positive results of CBT/GET a single therapist[4-6] or only a few highly skilled therapists[7-9] administered CBT in specialist centres. Therefore the generalisability of the positive results to settings outside specialist centres remained uncertain[1]. In our study 13 therapists with no prior experience in CBT for CFS who were participating in three different centres established the effectiveness of CBT. We showed that CBT could be transferred from CFS research clinics to therapists working in different settings with no previous experience in CBT for CFS patients (*Chapter 10*).

Our conclusion that CBT is an effective treatment for CFS patients brought about reactions both in scientific journals[10-16] and in letters and comments by patient organisations[17,18]. In several comments patient selection was questioned and methodological issues concerning our study came up. Compared to other studies we reported lower percentages of improved patients, which raised questions about the effectiveness of CBT. The curative intention of CBT was under discussion as well as our choice for a psychological model of CFS as the basis for therapy.

In this chapter, we will discuss these comments and questions. Furthermore suggestions for implementation of CBT and for future directions of CFS research will be made.

Patient selection

A frequently raised objection was that in our study less impaired patients with chronic fatigue had been selected and that therefore the results could not be generalised to patients with CFS. The suggestion that we selected relatively healthy patients with chronic fatigue without additional symptoms rather than patients with CFS was

incorrect[19]. Apparently our statement that we did not include the CDC criterion of four additional symptoms led to misunderstanding. In previous studies we showed that the number of additional symptoms is highly dependent of the assessment method and more importantly there are no differences in fatigue severity between chronic fatigue syndrome patients fulfilling the CDC criteria and patients who did not[20]. Besides, we did assess additional symptoms at baseline. In our sample 252 patients had the diagnosis CFS and 18 the condition idiopathic chronic fatigue[19]. Cut-off scores for fatigue severity and functional impairment guaranteed that all these patients were severely disabled. We agree that we can only generalise the results of our study to patients who are able to attend an outpatient clinic. However, this is a large group. During the trial we were never short of CFS patients and still there is a steady flow of patients to our chronic fatigue outpatient clinic. Large numbers of bedridden or homebound CFS patients are claimed by patient organisations. One of our studies concerned non-institutionalised bedridden CFS patients. The Dutch ME-association was asked to contact CFS patients among their thousands of members who were willing to participate in CFS-related research, but were incapable to visit the research centre because of severe functional limitations. We received participation forms of 29 patients living all over the Netherlands, of whom 20 were included after screening[21].

It was also suggested that patients in our study suffered from other somatic or psychiatric diagnoses than CFS[10,15]. All patients with a major complaint of fatigue, referred to the outpatient clinic of the departments of internal medicine, were eligible for the study. Extensive screening of patients with a CFS protocol, consisting of guidelines for the anamnesis and physical examinations as well as supplementary diagnostics, prevented misdiagnosis of CFS before they were approached for participation in the trial. First, before we diagnosed a patient as CFS, according to the CDC criteria[22] a thorough medical examination was being done to rule out somatic disorders, which might explain the complaint of chronic fatigue. Further, patients with complaints of chronic fatigue were screened with computerised questionnaires to verify whether they fulfilled the CDC-criteria for CFS (*Chapter 2*). In addition, a structured clinical interview for DSM-III-R was done to prevent confounding of CFS and psychiatric diagnoses. Nevertheless, like in other CFS samples[23], we found psychiatric co-morbidity in the CFS patients in our study. Compared to the general population, CFS patients reported significantly more lifetime and current mood disorders, while the prevalence of anxiety disorders did not differ (*Chapter 6*). We also found somatic co-morbidity in our CFS sample, but the internists evaluated the somatic co-morbidity as insufficiently accounting for the complaint of chronic fatigue and diagnosed these patients as CFS (publication in preparation).

Study methods

Also methodological aspects of our study were criticised. Our choice of control conditions was questioned. It was suggested that active management in a primary-

care situation would have been better as a control condition[12]. This might have been true for studies in the United Kingdom. In our study concerning the use of the diagnosis CFS by general practitioners (GPs) and their attitude towards CFS we found that GPs in the Netherlands were not familiar with CFS and reported insufficient knowledge of CFS (*Chapter 9*). Support groups and natural course were chosen as control conditions, since these were closest to the health care situation of CFS patients in the Netherlands. Our choice of control groups yielded the interesting finding that support groups were significantly less effective than CBT and no more effective that the natural course. Similar results were found in a study showing that membership of support groups of CFS patients was predictive of a worse outcome after GET. The authors suggested that these groups might play a part in reinforcing illness beliefs and advising against graded exercise interventions[24].

Our statistical analyses raised questions, since there was a large dropout rate in the trial, especially in both treatment arms. However, most patients dropping out were willing to participate in assessment. There was a post-treatment dropout rate of 25%, but only 11% of the patients had missing data. Before the trial we decided that no imputation techniques would be used to estimate missing data, since as in leaving out patients with missing data bias may also result from using imputed data. Regarding the intention-to-treat (ITT) population we used the usual definition: all patients randomised. Since the variables we analysed were differences from baseline values, the actual ITT population did not include patients with missing values at 8 and/or 14 months. Patients who withdrew from treatment were included in the analyses[10,11]. We provided enough circumstantial evidence to substantiate our results and "explain" the missing data. Proper methodology was used in our study, and the results clearly show that patients receiving CBT improved more than patients in both other conditions, also in blinded functional assessments like the Karnofsky performance status[16].

The cost-effectiveness study of CBT for CFS patients was under discussion. The cost-effectiveness estimates appeared to vary largely, depending of the choice of a health-care perspective or a societal perspective. The prevailing method is the health-care perspective. Therefore, conclusions were based on the assessment of medical and patient costs. However, we assumed that these were underestimations of the total costs involved in the treatment of CFS. Productivity costs were not included, although these have a large impact in CFS (*Chapter 11).* In our opinion, the societal perspective would have shed more light on the costs of CFS patients. The amount of sick leave of CFS patients was impressively higher than in other general medical outpatients[25]. In our trial of 270 CFS patients 76% had been employed before the onset of CFS, whereas only 33% had a job at the start of the study.

Clinical significant improvement

Less patients showed clinically significant improvement in our trial than in the two comparable CBT studies[5,7]. Various aspects may account for this finding. Our criteria

for clinical significant improvement were more stringent than in both other CBT trials. To define clinical significant improvement in fatigue severity, first a reliable change index was calculated for each patient to decide if statistical significant improvement occurred. Second, a cut-off score was calculated to decide if a patient's score had moved from the range of CFS patients to the range of healthy subjects. Normative comparisons of CFS patients and healthy subjects perhaps have led to an overly stringent criterion for improvement. In an evaluation of the concept of clinically significant improvement[26] it was questioned if patients should be compared to a non-representative "supernormal" sample of healthy subjects, from which all (psycho)-pathology is excluded (*Chapter 4*). Further, therapists in our study had no clinical experience with CFS patients at the onset of the trial, while the therapists in the two other CBT studies were very experienced. After participating in the trial, many of our therapists agreed with the statement that CFS patients were more difficult to treat than patients with psychological complaints and than patients with somatic complaints (*Chapter 10)*. Finally, predictors of treatment outcome showed that the treatment protocol was not suitable for CFS patients with a passive activity pattern and for CFS patients engaged in a claim for disability related financial benefits.

Predictors of treatment outcome

We agree with suggestions for further identification of subgroups of CFS patients benefiting from CBT[12]. In our studies we found several predictors of treatment outcome. Some of these predictors pointed in the direction of subgroups, like patients with a passive activity pattern or patients engaged in claims for disability related benefits, while other predictors highlighted weaknesses in the treatment protocol or in the way CBT was performed by the therapists. Starting with the latter, patients with a strong focus on bodily symptoms or with a low sense of control had a worse outcome in respectively functional impairment and fatigue severity after CBT (*Chapter 4*). We did not expect these factors as predictors of a worse outcome, since both were factors in the model of CFS, which was the basis for CBT. This might indicate that CFS patients characterised by a strong focus on bodily symptoms or by a lower sense of control were less sensitive to the treatment protocol we developed or that therapists were less competent in handling aspects of the treatment concerning these characteristics of patients. It might have been difficult for therapists to detract patients from complaining about bodily symptoms to more health-promoting cognitions and behaviours. To facilitate this aspect for both therapists and patients, in the later revised treatment protocol we skipped the daily registration of fatigue during the first sessions of CBT. The emphasis came on impeding cognitions and behaviours rather than on symptoms. Further, therapists might have experienced problems in establishing sense of control in CFS patients with a relatively long duration of somatic complaints who used to be dependent on treatments rather than taking the initiative for active participation in therapy. Pre-therapy assessment of sense of control might alert the therapist to pay special attention to this important

aspect before starting CBT.

Of all 270 CFS patients in our study 24% was subtyped as pervasively passive (*Chapter 5*). For the subgroup of patients with a passive activity pattern a new treatment protocol was developed[27]. The early accent in CBT on a base level of daily activity, so important for relatively active CFS patients, seemed to enhance the fear of physical activity in patients with a passive activity pattern and might be impeding for the subsequent gradual increase of physical activity. In the new treatment protocol, CBT for passive patients directly starts with building up physical, mental and social activities, whereas relatively active patients still start with attaining and maintaining a base level of physical activity.

During the trial, we noticed the impact for CFS patients of being engaged in a claim for disability related benefits of the Disablement Insurance Act. Thirty-one percent of the patients in our study appeared to be engaged in a claim between the baseline and post-treatment assessments (*Chapter 7*). Afterwards, it turned out that these patients had significantly less improvement than CFS patients not engaged in claim. In our opinion, it was impossible to benefit from a treatment directed at recovery of complaints, while in the meantime a patient was convincing work-related institutions of complaints and the need of financial benefits. Therefore, in our outpatient clinic patients engaged in disability claims only are assigned to CBT after finishing these legal procedures.

Variables failing to predict treatment outcome were as interesting as the predictive factors we identified. Demographic variables like age, gender and education were not found to be of importance for clinical response. Treatment outcome also was not predicted by duration of complaints suggesting that CBT is equally effective for patients with differing duration of illness. This finding was supported by recent results of a similar outcome study[24]. The majority of CBT/GET studies in CFS pertained to samples with median illness duration of about five years. In one of our natural course studies we found that prognosis for total recovery was poor from 18 months after onset of CFS[28]. If CBT will be offered to CFS patients in an earlier stage of the illness, medical and societal costs might be reduced importantly.

We found that CFS patients with and without lifetime or current psychiatric co-morbidity equally benefited from CBT (*Chapter 6*). Similar results were reported in a previous CBT trial[5]. Therapists' attention for psychiatric diagnoses might explain this finding. From the start of our study therapists were trained to deal with psychiatric co-morbidity during CBT. In one of the GET studies with considerably less face-to-face sessions, concurrent emotional difficulties were predictive of a worse outcome[24]. Since in our sample of CFS patients treated with CBT psychological wellbeing and depressive symptoms also considerably improved, we continued our routine to refuse CBT to those CFS patients who were not willing to stop antidepressant pharmacotherapy. In earlier studies, antidepressants were not found effective in either treating the symptoms of depression of CFS patients or any other outcomes[29]. In our opinion, antidepressant therapy interferes with one of the main goals of CBT

acquiring control over symptoms instead of dependence on medication.
The identification of the above predictors of treatment outcome prompted us to clarify indications and contra-indications of CBT for patients with CFS[30]. CBT is not recommended if patients disagree with the diagnosis and insist on further medical examinations, if patients are not willing to co-operate in CBT, if they are engaged in other therapies or if they are involved in legal procedures for disease- related financial benefits. Activity pattern and psychiatric co-morbidity have to be considered to optimise the treatment plan.

Cognitive behaviour therapy: rehabilitation or cure
Patient organisations and colleagues questioned the curative intention of our therapy and claimed that the ultimate goal could be rehabilitation[16,31]. However, the intention of CBT as practised in our research group was definitely curative. We elaborated our opinion in a reaction to Christopher Clark and colleagues' commentary on the Report of the Working Party on CFS/ME to the Chief Medical Officer for England and Wales, in which they state that none of the rehabilitation approaches is intended to be curative[31,32]. With each CFS patient who enters CBT, the therapist discusses the individual and specific meaning of recovery. As in other chronic diseases the meaning of cure differs tremendously among patients. At the beginning of CBT recovery seems vague and unattainable for most CFS patients. By contemplating life after recovery, a CFS patient is formulating his own personal goals for CBT. Under which conditions will a patient consider himself as basically healthy? Which activities would he undertake in this situation? Too often therapists agree to far less concrete and less achievable aims, still within the scope of chronically ill patients. The art of CBT is to broaden the patients' vision to a future life as a well person. After reaching most of the personal goals, one of the last cognitive interventions in CBT is to stop labelling oneself as a CFS patient. Our case study of a patient with CFS who was treated with CBT and was followed up two-and-a-half years after the start of CBT is a good example of the way we deal with cure in CBT (*Chapter 3*). In our opinion it helps CFS patients to strive for a cure, since a personal goal can never be completed if it is not aimed for. By questioning or denying the curative intentions of CBT therapists may deprive CFS patients from a potential cure. We agree that CBT may not be a cure for all CFS patients. As in other chronic diseases not one therapy is effective in curing all patients or in establishing the same effect for all patients. However, CBT certainly has been effective for at least thirty five percent of the CFS patients who fulfilled the stringent criteria for recovery in our trial. Recovered patients returned to work and other activities. Everyday bodily signs and symptoms were no longer interpreted as indicating CFS. Most importantly, these persons no longer labelled themselves as having CFS. If this is not cure, what is?

The psychological model of CFS

CBT for patients with CFS was based on a statistically tested model of perpetuating factors in CFS[33]. Our use of this model was questioned. Unlike correspondents[10,12,13] and patients' organisations[13,14] suggested, the use of a psychological model does not preclude neurobiological components. There is still little consistent evidence for underlying organic pathology in CFS. The findings in CFS concerning subtle changes in the hypothalamus-pituitary adrenal axis (of which pathogenetically the importance is unknown), have led to two randomised controlled trials , from which neither we nor the investigators of these trials[34,35] do derive the suggested conclusion that steroids are treatment of choice[15]. Adherents of biopsychosocial models and pathological models made some slight steps towards agreement on definition and diagnosis, but large gaps concerning treatment still remain[31]. Patients' organisations in the Netherlands share the opinion that the success of CBT affirms the bias that CFS has a psychogenic cause[17]. This argument enforces the old paradigm, in which diseases or complaints were considered as either somatic or psychiatric in origin. In modern medicine, the biopsychosocial approach guarantees that both aspects are equally attended to[36]. Problems with a somatic cause, like diabetes may be aggravated or alleviated by psychological consequences (medication adherence or lifestyle). Psychological factors were involved in the persistence of fatigue in patients with a known somatic cause as multiple sclerosis[33]. Initiating psychological factors, like a reactive depression following bereavement, may be aggravated by somatic consequences (fatigue, weight loss) or alleviated by medical therapy.

A known somatic or psychic cause is not conditional for an effective treatment of a disorder. In our study on co-morbid psychiatric disorders (*Chapter 6*), we showed that CFS patients with and without current or lifetime psychiatric disorders equally benefited from CBT, not only concerning physical symptoms, like fatigue severity and functional impairment, but also in psychological symptoms, like depression and psychological distress. The latter results are remarkable since CFS patients treated with CBT were not allowed to use anti-depressants. Apparently, co-morbid psychiatric diagnoses, like anxiety disorder or depression, also benefit from CBT specially tailored for the somatic complaint of fatigue.

Our model of perpetuating factors in CFS was limited to complaint-related cognitions and behaviours, like somatic attributions, sense of control over complaints, physical activity and a strong focus on bodily symptoms. From the results of our study of social support in CFS patients it is obvious that cognitions and behaviours concerning the individual's support system need equal attention (*Chapter 8*). Insufficiency of social support and negative interactions were found to be important factors in the persistence of CFS. Lack of social support should be added as a new factor to the model of perpetuating factors of fatigue and functional impairment in CFS.

Implementing CBT for CFS patients

The effectiveness of CBT for patients with CFS was proven. We showed that CBT could be transferred from a CFS research clinic to therapists with no previous experience in treating CFS patients with CBT. This transfer is essential to detach the treatment from medical research settings, in which only a limited number of CFS patients can be treated. To increase accessibility of this treatment for more CFS patients, CBT will have to be implemented in general (mental) health settings.

The societal costs of CFS are high and consist of medical costs, productivity costs and costs as a result of legal procedures concerning claims. Extrapolating cost-effectiveness estimations over four years indicated dominance of CBT compared to the natural course if case productivity costs were included (*Chapter 11).*

Based on these results we proposed to make CBT available for CFS patients in the Netherlands. In comparing two prevalence studies among general practitioners we found that the population of CFS patients was growing[37,38]. The estimated prevalence of CFS patients in 1999 was 27.000. The incidence was estimated at 6000 new patients every year[17]. To increase accessibility of CBT for all CFS patients in future, this treatment will have to be implemented outside university medical settings. Ideally, general practitioners should diagnose CFS, without detours to medical specialists, and refer CFS patients to general mental health settings for CBT. During several years CFS expert centres should transfer expertise to both general practitioners and mental health settings.

Acceptance of CBT as an effective treatment for CFS patients by both CFS patients and general practitioners is a crucial condition for implementation. There is evidence from several sources that CBT is an acceptable treatment for half to three-quarter of CFS patients. First, in our trial 75% of the eligible patients in the general internal medicine outpatient clinic was willing to participate in a psychotherapy study. Next, after informed consent and before randomisation patients' preference for one of the treatment arms was investigated. Sixty-two percent of the patients preferred CBT compared to 19% expressing preference for each of the control conditions[17]. Further, in a study among members of the Dutch ME-association 54% of 2600 respondents reported previous psychosocial treatments[39]. Acceptance by general practitioners of CFS as a medical diagnosis and of CBT as a treatment seemed also favourable. In 1997, we concluded that in the majority of cases general practitioners should diagnose CFS[40], only a small percentage of patients needed to be referred for further diagnostics. The willingness among general practitioners to diagnose CFS was growing. Compared to our first prevalence study the percentage general practitioners reporting to have no CFS patients dropped from 27% in 1993 to 13% in 1999[37,38]. In the latest prevalence study we found that 75% of the general practitioners still referred CFS patients to medical specialists. At the same time half of the general practitioners reported to counsel CFS patients. However, almost all of the general practitioners were willing to refer CFS patients in case of an evidence-based treatment[38].

Future directions

Like others we are interested in the long-term results of CBT. Since at the end of our study CBT was offered to all patients in the control conditions, a long-term comparison between CBT and natural course was not possible. In a retrospective study of the effects of CBT after 5 years the first results concerning lasting benefits of CBT were promising[41]. In future CBT studies, fatigue and physical functioning of CFS patients should be monitored during several years to elucidate patterns of cure and relapse. To estimate the cost-effectiveness of CBT in CFS patients more accurately, future research should give more focus on productivity costs and use a longer period of prospectively following patients.

The essential mechanisms responsible for improvement after CBT are still unknown. Do cognitive and behavioural interventions equally need attention? Is graded exposure to exercise essential to recovery? Or do illness beliefs or a strong focus on bodily symptoms need to be changed first? Does a changed sense of control over symptoms precedes or results from these changes? Once we know which mechanisms mainly cause improvement, more efficient and less expensive treatments can be developed.

In a CFS expert centre, GET with minimal individual treatment sessions and telephone follow-up calls showed promising results for patients without strong illness beliefs and without concurrent emotional difficulties[4,24]. Active management of CFS patients in a primary-care situation by family physicians or members of primary-care health teams might be another alternative[12]. Co-operation with patient support groups was suggested as a way to spread evidence-based advices among CFS patients[24]. Perhaps in some patients, group CBT might be a more effective alternative in combining patients' support and evidence-based interventions. Our first clinical results showed effectiveness in symptom reduction and improved physical functioning[42].

Essential mechanisms of improvement might be located in the patient's functioning as well as in the patient's surroundings. Lack of social support was identified as a new perpetuating factor in CFS. Support might come from the general practitioner diagnosing CFS, the psychotherapist offering CBT, other CFS patients in a therapy group, family members and friends. All these support systems deserve more attention in future studies concerning the natural course or treatment of CFS patients.

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Summary

Chronic fatigue syndrome (CFS) is the term that is usually accepted by clinicians and scientists for the range of complaints that patients often refer to as ME (myalgic encefalomyelitis). CFS is characterised by severe disabling fatigue, for which no somatic explanation can be offered, lasting for more than six months and resulting in severe impairment in daily functioning. Health care costs are high and productivity loss occurs frequently.

From 1990, the Nijmegen Fatigue Research Group studied causes, natural course, consequences and treatments of CFS. No cause of CFS was found and most patients did not recover. Pharmacological treatment was not effective. Psychological processes were found to be involved in perpetuating fatigue and functional impairment in CFS patients. Based on these findings a model of CFS was developed, which showed that a low sense of control, low levels of physical activity and strongly focusing on bodily symptoms contribute to increasing severity of fatigue and functional impairment. Factors in the model concern psychological processes, which can be treated with cognitive behaviour therapy (CBT). CBT is a psychotherapeutic method directed at changing condition-related cognitions and behaviours.

The studies presented in this thesis are primarily concerned with the effectiveness of cognitive behaviour therapy for CFS patients and factors influencing the outcome in CFS patients with and without treatment.

In *Chapter 2* we describe how the patients for these studies were selected. During the last decade our outpatient clinic has seen large numbers of patients suffering from chronic fatigue, both in the context of outpatient care and within the framework of scientific research. In both settings guidelines and measuring instruments have been developed to help improve CFS diagnostics. At our outpatient clinic a chronic fatigue protocol is applied. In our scientific studies patients fill in several computerised questionnaires (MID TestOrganizer) to establish whether they meet the operational and CDC *(Centers for Disease Control)* criteria for CFS. Retrospectively the medical records and the computerised questionnaires of 516 patients referred to an internal medicine outpatient clinic with complaints of chronic fatigue, were checked separately and compared to see whether the diagnosis of CFS had been met. Agreement between the physicians' and the researchers' evaluations was 84%. Disagreement mostly concerned severity of fatigue and functional impairment, or premorbid exclusion criteria.

Studying CBT for CFS, we first subjected the treatment protocol for CFS patients to systematic evaluation in several case studies. In *Chapter 3* the case of a 26-year old woman with CFS is presented. Multidimensional assessment showing severe debilitating fatigue and considerable psychological, social and occupational impairment confirmed the diagnosis. CBT was based on a tested causal model of CFS and individual behavioural analyses. Key elements in CBT were process

variables from the CFS model, like sense of control, causal attributions, physical activity and focusing on bodily functions. Goals were recovery of fatigue, returning to work and relapse prevention. The course of therapy is described in detail to illustrate difficulties in treating CFS. Assessments were made five times, at baseline and at 8, 14, 21 and 33 months. Comparison of the pretest, post-test and follow-up scores of the outcome variables, fatigue and functional impairment and of the process variables showed clinically significant improvement from the range of CFS patients to the range of healthy controls. CBT was successful and resulted in clinically significant improvement.

Our next step was studying the effectiveness of CBT for patients with CFS. This study is presented in *Chapter 4*. In a multicentre randomised controlled trial we compared CBT with guided support groups and the natural course. CBT was administered in three different settings by 13 recently trained behaviour therapists of three different disciplines. CBT consisted of 16 sessions of one hour during eight months. Central components of CBT were explanation of the model of perpetuating factors, motivating for CBT, challenging fatigue-related cognitions, attaining and maintaining a base level of physical activity, gradual increase of physical activity, and planning work rehabilitation or rehabilitation in other personal activities. The CFS patient learned to acquire control over symptoms instead of dependence on physicians prescribing treatments or medications. Multidimensional assessments were done at baseline, 8 months, and 14 months. Results showed that CBT was significantly more effective than both control conditions for the two primary outcome variables fatigue severity and functional impairment. Depending of the different criteria, one third of the patients was clinically significant improved and half of the patients was more improved in the ratings by an independent judge or in the self-rated improvement. Prognostic factors for outcome after CBT were higher sense of control predicting more improvement, and a passive activity pattern and focusing on bodily symptoms predicting less improvement.

Changes in physical activity are thought to play an important role in maintaining symptoms in CFS. The aim of the study presented in *Chapter 5* was to describe intra-individual physical activity patterns in more detail and to identify pervasively passive patients. With help of a movement-sensing device (ActiLog), physical activity levels were registered continuously over a 12-day period in CFS patients. Within this registration period, the ten largest activity peaks were computed. The intensity and duration of these activity peaks and their subsequent rest periods were described and compared to those of healthy controls. In addition, the patients' 12 daily activity scores were used to identify patients who were characterised by low levels of physical activity throughout the registration period. The results showed that the CFS sample had less intense and shorter activity peaks than the healthy controls, while the average rest periods that followed these peaks lasted longer. Approximately one fourth of the CFS sample differed distinctly from the control group and was labelled as pervasively passive. We concluded that the measurements and classification of

actual physical activity levels reduced heterogeneity in the CFS population and therefore could provide the opportunity to optimise behavioural intervention protocols for CFS.

Lifetime and current psychiatric disorders have been associated with poor outcome in the prognosis of patients with CFS. The impact of psychiatric disorders on treatment withdrawal and outcome of CBT for CFS patients is not known. In *Chapter 6* lifetime and current psychiatric diagnoses were assessed at baseline with a structured psychiatric interview in a multicentre randomised controlled trial of 270 patients allocated to CBT, support groups or natural course during 14 months. The proportions of psychiatric diagnoses in CFS patients were compared to data of a general population study. Proportions of patients with and without psychiatric diagnoses were compared concerning treatment withdrawal and clinical improvement. Outcomes of patients with and without current psychiatric diagnoses were examined in general linear models. Lifetime and current psychiatric disorders were found in 50% and 32% of the CFS patients. The proportions of mood disorders were higher than in the general population. No significant differences were found between patients with and without current or lifetime psychiatric diagnoses in treatment adherence or clinical improvement in each of the conditions. In CBT, support groups and natural course patients with a current psychiatric diagnosis had outcomes of fatigue severity and functional impairment identical to patients without a current psychiatric diagnosis. CFS patients with psychiatric co-morbidity have not a higher withdrawal rate or worse outcome than patients without, when treated with cognitive behaviour therapy.

In *Chapter 7* two categories of CFS patients are described which did not benefit from CBT. One third of the CFS patients appeared to be engaged in a legal procedure concerning financial benefits. We found that patients engaged in disability claims had a worse outcome after CBT than those patients to whom this did not apply. We concluded that patients who are involved in legal procedures in connection with their illness – involving insurance issues and/or invalidity benefit claims – should not be offered CBT. During such procedures patients need to convince the medical board of the severity of their complaints and impairments and this does not accord with a treatment aimed at improvement or recovery from the symptoms involved. Based on these findings CFS patients still actively involved in such procedures are no longer prescribed CBT in clinical practice. In Chapters 4 and 5 we described that the quarter of CFS patients characterized by a passive activity pattern had a worse outcome. None of the patients in CBT with a passive activity pattern was clinically improved after treatment. We concluded that patients with a passive activity pattern were in need of a different treatment protocol, which we have developed by now.

Several studies suggested that the surroundings of CFS patients are of importance in the persistence of complaints. Contrary to expected, in Chapter 4 we found that participation in support groups did not result in more clinical improvement than the natural course. The purpose of the study presented in *Chapter 8* was to describe

social support in CFS patients as compared to other fatigued and non-fatigued groups. Social support data were assessed in 270 CFS patients, 150 disease-free breast cancer patients, 151 fatigued employees on sick leave and 108 healthy subjects. The results showed that CFS patients and fatigued employees reported more negative interactions and insufficiency of supporting interactions than cancer patients and healthy controls. In CFS patients and fatigued employees the quality of social support was worse than in disease-free cancer patients and healthy controls. However, no differences in quantity of supporting interactions were found. Further, changes in social support of CFS patients and the influence of social support on the course of CFS over a period of more than one year were studied in patients with and without treatment. CFS patients were followed in CBT, guided support groups and natural course at 8 and 14 months. Negative interactions decreased significantly after treatment with CBT, but did not change in support groups or natural course. In the natural course, higher fatigue severity at 8 months was predicted by more negative interactions at baseline. Lack of social support was identified as a new factor in the model of perpetuating factors of fatigue severity and functional impairment in CFS.

The general practitioner (GP) is part of the social environment too. The role of the GP seems especially important, because often the GP is the first professional confronted with the complaints of chronic fatigue. How this first consultation goes may determine the future course of CFS considerably. The lack of a known origin for chronic fatigue could have consequences for the way GPs deal with the diagnosis CFS and their perception of CFS patients. The aims of the study presented in *Chapter 9* were to investigate the use of the diagnosis CFS by GPs and their reactions to self-diagnosis and to explore opinions of GPs about causes of CFS and the communication with CFS patients as well as opinions of CFS patients about their GPs. The results showed that only half of the GPs used the diagnosis CFS. The main reason for not diagnosing CFS was ignorance of the criteria. GPs reported self-diagnosis in 68% of the CFS patients. More than half of the GPs could sympathize less with the complaints of CFS patients compared to those of other patients. These GPs experienced more problems in communicating with CFS patients and judged co-operation and contact as poor. As to the causes for CFS a discrepancy was found. GPs mainly attributed the complaints to psychosocial factors, whereas patients mainly had physical attributions. In communicating with the CFS patient it may be helpful for GPs to discuss the distinction between initiating and perpetuating factors of CFS.

In *Chapter 10* the transferability of CBT for patients with CFS is considered. The results of the trial in Chapter 4 showed that CBT can be transferred from CFS research clinics to therapists with no previous experience in CBT. In order to implement CBT in general health settings, transferability of the treatment is essential. The therapists in the effect-study were thoroughly trained and supervised. The question was if they sufficiently followed the treatment protocol. Analyses of audiotaped sessions were conducted to verify whether the therapists had complied

with the various treatment aspects included in the manual. In 89% of the sessions this appeared to be the case. The opinions of the therapists concerning the usability of the treatment manual were investigated with questionnaires completed by the thirteen therapists following completion of the study. The questionnaire revealed that the therapists found it more difficult to treat CFS patients than patients with psychological or other physical problems. The treatment aspects posing the most problems were integrating individual problems into the standardised treatment, dealing with the patients' lack of confidence in the treatment and handling insufficient motivation. For these aspects in particular, extra training seems necessary. The treatment manual will have to be revised in such a way that it will leave therapists room to individualise the prescribed interventions and it will need to provide them with guidelines for interventions aimed at motivating patients.

Implementation of CBT for CFS not only depends on transferability of the treatment to other therapists, but also on the economic evaluation of the intervention. In *Chapter 11*, the first prospective randomised study reporting the cost-effectiveness of CBT in CFS-patients is presented. Especially since CBT is the only therapy for CFS that is evidence based, cost-effectiveness information is relevant. The cost-effectiveness analysis was part of the randomised controlled trial of CBT for CFS patients, presented in Chapter 4. Both a health care and a societal perspective were used, indicating either cost per patient clinically significant improved or cost per quality adjusted life year (QALY). CBT resulted in a better outcome and a lower use of medical care facilities than both control conditions. Regarding our limited follow up we expect the cost-effectiveness to improve in case of a longer time horizon. However, the statistical uncertainty of the cost-effectiveness estimates we found is considerable, as the bootstrap simulations showed. The use of a societal perspective, thus including productivity costs, has a large impact on the cost-effectiveness estimates. Although not statistically significant, the differences in productivity costs between the groups was considerable due to the fact that a small number of patients that were employed were absent from work during a longer period. Therefore the results have to be interpreted with caution and we intend to investigate the longer term working situation of our patients further. The societal perspective is of importance, since in the trial of 270 CFS patients 76% had been employed before the onset of CFS, whereas only 33% had a job at the start of the study. In the meantime the conclusions of this work should be based on the health care perspective. The difference between utility in the experimental treatment and the current situation is small. Given this fact and the short time horizon, the costs per QALY seem high. However, extrapolating the utility values and the cost figures another four years indicates, that the cost per QALY will become more acceptable and even indicates dominance of CBT in case the productivity costs are included.

Finally, in *Chapter 12* the results of the studies in this thesis are considered as a whole. We go into questions and critical remarks which our studies evoked, discuss practical implications of our studies and our ideas concerning implementation of CBT

for CFS, and indicate the direction for future studies. It was concluded that with proper indications CBT may be a cure for a considerable part of the CFS population. Future research should be directed at long-term effectiveness and cost-effectiveness to give implementation a fair chance of succeeding. Essential mechanisms of CBT should be investigated to contribute to further improvement of effectiveness and cost-effectiveness.

Samenvatting

Chronisch vermoeidheidssyndroom (CVS) is de door clinici en wetenschappers algemeen aanvaarde naam voor het geheel van klachten, dat door patiënten vaak ME (myalgische encefalomyelitis) wordt genoemd. CVS wordt gekenmerkt door ernstige invaliderende vermoeidheid, die minimaal zes maanden bestaat, waarvoor geen lichamelijke verklaring gevonden kan worden en die heeft geleid tot ernstige beperkingen in het dagelijks functioneren. De medische consumptie van CVS patiënten is hoog en arbeidsongeschiktheid komt veel voor.
Dit proefschrift bouwt voort op onderzoek vanaf 1990 verricht door de Nijmeegse Onderzoeksgroep Chronisch Vermoeidheidssyndroom naar de oorzaken, het beloop, de gevolgen en de behandelingsmogelijkheden van CVS. Lichamelijke oorzaken voor CVS werden niet gevonden en spontaan herstel bleek weinig voor te komen. Behandelingen met medicijnen waren niet effectief. Het onderzoek liet wel zien dat psychologische factoren een rol spelen bij het in stand blijven van de klachten. Op basis van deze bevindingen werd een model voor CVS ontwikkeld, dat liet zien dat het idee dat men zelf weinig aan de klachten kan doen, het blijven toeschrijven van de klachten aan een lichamelijke oorzaak en daarmee samenhangende verminderde lichamelijke activiteit, en een sterke gerichtheid op lichamelijke symptomen bijdragen aan het in stand blijven van vermoeidheid en beperkingen van CVS patiënten. De factoren in het model betreffen psychologische processen. Dergelijke processen zijn met cognitieve gedragstherapie (CGT) te beïnvloeden, waardoor de klachten van CVS patiënten kunnen verminderen. CGT is een vorm van psychotherapie die gericht is op het veranderen van cognities en gedragingen die met de lichamelijke klachten samenhangen.
De onderzoeken in dit proefschrift hebben betrekking op het bepalen van de effectiviteit van CGT voor patiënten met CVS en op factoren die het verloop van de klachten bij patiënten met en zonder deze behandeling beïnvloeden.
In *Hoofdstuk 2* wordt beschreven hoe patiënten voor deze onderzoeken geselecteerd werden. Op de polikliniek Algemeen Interne Geneeskunde (AIG) van het Universitair Medisch Centrum Nijmegen zijn in het afgelopen decennium zeer veel patiënten gezien met klachten van chronische vermoeidheid, zowel in de patiëntenzorg als in het kader van wetenschappelijk onderzoek. Vanuit beide invalshoeken werden richtlijnen en meetinstrumenten ontwikkeld om de diagnostiek te verbeteren. Op de polikliniek AIG gebruiken de artsen een protocol om de diagnose CVS te stellen. Daarnaast vullen de patiënten enkele vragenlijsten op de computer in met de MID TestOrganizer, een software programma ontwikkeld door de Medisch Instrumentele Dienst in samenwerking met de afdeling Medische Psychologie, om vast te stellen of zij voldoen aan de operationele criteria en CDC criteria (Centers for Disease Control) voor CVS. Bij 516 patiënten werden de uitkomsten van het onderzoek door de arts met behulp van het protocol en het geautomatiseerde vragenlijstonderzoek met

elkaar vergeleken. In 84% van de gevallen bestond overeenstemming over de aan- of afwezigheid van de diagnose CVS tussen de arts en de vragenlijsten. In de gevallen met tegenstrijdige bevindingen bleek meestal onduidelijkheid over de ernst van de vermoeidheid of de beperkingen een rol te spelen. De ernst van de klachten is goed in kaart te brengen met vragenlijstonderzoek. Twee korte vragenlijsten zouden als aanvulling op het protocol door artsen gebruikt kunnen worden om de diagnose CVS te stellen.

De behandeling met CGT voor patiënten met CVS werd systematisch geëvalueerd in enkele casestudies. In *Hoofdstuk 3* wordt verslag gedaan van CGT bij een 26-jarige vrouw met CVS. Haar vermoeidheidsklachten hebben geleid tot ernstige beperkingen in het beroepsmatig, sociaal en psychisch functioneren. Patiënte is volledig arbeidsongeschikt geraakt. De diagnose CVS werd gesteld en met multidimensioneel vragenlijstonderzoek bevestigd. Uit de metingen bleek dat de klachten van patiënte in vergelijking met andere CVS patiënten ernstig waren. De behandeling werd gebaseerd op zowel een wetenschappelijk model als individuele functionele analyses. Cognitieve herstructurering en activiteitenopbouw waren de belangrijkste elementen van de behandeling. Behandeldoelen waren herstel, werkhervatting en terugvalpreventie. Vergelijkingen van de metingen van vermoeidheid en beperkingen voor en na de behandeling lieten zien dat het niveau van functioneren van patiënte na de behandeling dichter bij het gemiddelde van gezonde proefpersonen lag dan bij het gemiddelde van CVS patiënten. Cognitieve gedragstherapie had succes en resulteerde in klinisch significante verbetering.

De volgende stap was het onderzoeken van de effectiviteit van CGT voor patiënten met CVS in wetenschappelijk onderzoek. Deze studie wordt in *Hoofdstuk 4* gepresenteerd. In een gerandomiseerd gecontroleerd onderzoek uitgevoerd in drie verschillende centra werd bij 278 CVS patiënten het effect van CGT vergeleken met lotgenotencontact en met de gangbare praktijk. Dertien therapeuten zonder ervaring met CVS kregen een training in het behandelen van patiënten met CVS. CGT bestond uit 16 sessies van één uur gedurende acht maanden. Belangrijke elementen in de behandeling waren uitleg van het model van instandhoudende factoren, motiveren voor CGT, herstructureren van aan moeheid gerelateerde cognities, tot stand brengen van een basisniveau van dagelijkse activiteiten, geleidelijk ophogen van lichamelijke activiteit en hervatting van werk of persoonlijke doelen. De CVS patiënt leerde zelf controle te krijgen over de klachten, in plaats van afhankelijk te blijven van voorschriften van artsen of andere behandelaars. Multidimensionele metingen hadden op drie momenten plaats: bij de start van het onderzoek, na 8 maanden (nameting) en na 14 maanden (follow-up). De resultaten lieten zien dat CGT effectiever is dan beide andere onderzoekscondities op de twee primaire uitkomstmaten vermoeidheid en beperkingen. Afhankelijk van het gehanteerde criterium was ruim een derde of de helft van de patiënten klinisch significant hersteld of verbeterd volgens de onafhankelijk beoordelaar en naar het eigen oordeel van de patiënt. Een positieve self-efficacy, het idee dat men zelf iets aan de klachten kan

doen, bleek meer verbetering na CGT te voorspellen, terwijl een passief activiteitenpatroon en een sterke gerichtheid op lichamelijke symptomen voorspellers waren van minder verbetering na CGT.
In *Hoofdstuk 5* wordt een onderzoek gepresenteerd over de lichamelijke activiteit van CVS patiënten. Doel van dit onderzoek was het gedetailleerd beschrijven van intra-individuele patronen van fysieke activiteit en het identificeren van patiënten met een passief activiteitenpatroon. Met behulp van de aktometer (ActiLog, Medisch Instrumentele Dienst), een apparaat ter grootte van een luciferdoosje dat dag en nacht om de enkel wordt gedragen, werden gedurende twaalf dagen niveaus van fysieke activiteit gemeten bij alle CVS patiënten die eerder beschreven werden in Hoofdstuk 4. Gedurende de periode van registratie werden de tien grootste pieken van activiteit berekend. De intensiteit en duur van deze pieken van activiteit werden beschreven, evenals de erop volgende periodes van rust. Deze werden vergeleken met dezelfde gegevens van gezonde proefpersonen. De resultaten van dit onderzoek lieten zien dat CVS patiënten minder intense en kortere pieken van activiteit hadden en langere periodes van rust dan de controlegroep met gezonde proefpersonen. Daarnaast werden de dagelijkse activiteitsscores van de CVS patiënten gebruikt om patiënten te identificeren met een voortdurend laag activiteitenpatroon. Een kwart van de CVS patiënten bleek een voortdurende lage lichamelijke activiteit gedurende twaalf dagen te vertonen. De classificatie in activiteitenpatronen werd in Hoofdstuk 4 gebruikt om het behandelingsresultaat van CGT te voorspellen.
In *Hoofdstuk 6* wordt een onderzoek gepresenteerd naar psychiatrische co-morbiditeit van de patiënten met CVS die deelnamen aan het onderzoek beschreven in Hoofdstuk 4. Psychiatrische stoornissen zijn in sommige onderzoeken geassocieerd met een ongunstig beloop van de klachten van patiënten met CVS. Niet bekend is de invloed van psychiatrische stoornissen op het resultaat van behandeling met CGT of op uitval tijdens de behandeling. Voordat de CVS patiënten startten met het gerandomiseerd gecontroleerd onderzoek naar het effect van CGT werd de aanwezigheid van eerdere of huidige psychiatrische stoornissen vastgesteld met een gestructureerd psychiatrisch interview. Psychiatrische stoornissen bleken bij 50% van de CVS patiënten in de loop van het leven voor te komen en waren aanwezig bij 32% van de patiënten op het moment van het onderzoek. De percentages stemmingsstoornissen en angststoornissen bij patiënten met CVS werden vergeleken met de resultaten uit een onderzoek bij de Nederlandse bevolking. Stemmingsstoornissen kwamen bij CVS patiënten meer voor dan in de algemene bevolking, maar angststoornissen waren in gelijke mate aanwezig bij beide groepen. In de drie onderzoekscondities CGT, lotgenotencontact en natuurlijk beloop werden tussen patiënten met en zonder psychiatrische stoornissen geen verschillen gevonden in behandelingsresultaat of in uitval tijdens de behandeling. Vermoeidheid en beperkingen waren in gelijke mate afgenomen. Op basis van deze bevindingen concludeerden wij dat psychiatrische co-morbiditeit geen voorspeller is van het behandelingsresultaat van CGT.

In *Hoofdstuk 7* worden twee categorieën patiënten beschreven die niet of nauwelijks bleken te verbeteren na behandeling met CGT. Een derde van de CVS patiënten was betrokken bij een beroepsprocedure met betrekking tot een WAO/AAW of WW-uitkering. In ons onderzoek naar het effect van CGT werd vastgesteld dat patiënten die tijdens behandeling betrokken zijn bij een dergelijke beroepsprocedure een significant slechter behandelingsresultaat hadden dan patiënten waarbij dit niet het geval is. Dit heeft er in de klinische praktijk toe geleid dat CGT voor CVS niet meer aangeboden wordt aan patiënten die nog actief bezig zijn met een beroepsprocedure. In een dergelijke procedure moeten patiënten de tegenpartij overtuigen van de ernst van hun klachten en beperkingen. Dit blijkt moeilijk samen te gaan met een behandeling die gericht is op herstel. Zoals in Hoofdstuk 4 en 5 werd beschreven had een kwart van de CVS patiënten in ons onderzoek een passief activiteitenpatroon. Na de behandeling met CGT bleek geen van deze patiënten hersteld te zijn. Op basis van deze resultaten werd voor de patiënten met een passief activiteitenpatroon een andere vorm van cognitieve gedragstherapie ontwikkeld.
In de literatuur wordt gesuggereerd dat de omgeving van CVS patiënten een rol speelt bij het in stand blijven van de klachten, zonder dat dit goed onderzocht is. In *Hoofdstuk 8* wordt een studie gepresenteerd, waarin de sociale steun van CVS patiënten wordt beschreven en vergeleken met andere groepen patiënten en met gezonde proefpersonen. Gegevens over sociale steun werden verzameld van 270 CVS patiënten, 150 ziektevrije borstkankerpatiënten, 151 zieke werknemers met vermoeidheidsklachten en 108 gezonde proefpersonen. De resultaten lieten zien dat CVS patiënten en vermoeide werknemers meer negatieve interacties en een groter tekort aan ondersteunende interacties rapporteerden dan kankerpatiënten en gezonde controles. De kwaliteit van sociale steun van CVS patiënten en vermoeide werknemers was slechter dan die van ziektevrije borstkankerpatiënten en gezonden, maar tussen deze groepen werden geen verschillen in de kwantiteit van sociale steun gevonden. Verder werden gedurende een periode van ruim een jaar veranderingen in sociale steun van CVS patiënten onderzocht en werd de invloed van sociale steun op het beloop van CVS nagegaan bij patiënten behandeld met en zonder CGT. Na behandeling met CGT namen de negatieve interacties van CVS patiënten significant af, terwijl dit niet het geval was in de lotgenotencontactgroepen en het natuurlijk beloop. In het natuurlijk beloop werd hogere vermoeidheid na acht maanden voorspeld door meer negatieve interacties bij de start van het onderzoek. De resultaten lieten zien dat sociale steun als variabele opgenomen moet worden in het model van vermoeidheid.
De huisarts maakt ook deel uit van de sociale omgeving van de patiënt. De rol van de huisarts is van belang, omdat de huisarts meestal de eerste professional is die geconfronteerd wordt met de klachten van chronische vermoeidheid. Hoe dit consult verloopt, kan mede het beloop van CVS bepalen. Het ontbreken van een somatische verklaring voor chronische vermoeidheid zou consequenties kunnen hebben voor de wijze waarop huisartsen omgaan met de diagnose CVS en voor hun perceptie van

CVS patiënten. Doel van het onderzoek gepresenteerd in *Hoofdstuk 9* was om te onderzoeken of huisartsen de diagnose CVS gebruiken en hoe zij reageren op een door de patiënt zelf gestelde diagnose. Verder was het onderzoek gericht op de opvattingen van huisartsen over oorzaken van CVS en over de communicatie met CVS patiënten. De opvattingen van CVS patiënten over hun huisarts werden ook onderzocht. De resultaten lieten zien dat slechts de helft van de huisartsen de diagnose CVS gebruikte. De belangrijkste reden om de diagnose CVS niet te stellen bleek onbekendheid met de criteria voor CVS te zijn. De huisartsen rapporteerden dat 68% van de CVS patiënten zelf de diagnose had gesteld. Meer dan de helft van de huisartsen gaf aan zich moeilijker te kunnen inleven in de klachten van CVS patiënten dan in die van andere patiënten. Deze huisartsen hadden meer problemen in de communicatie met CVS patiënten en beoordeelden de samenwerking en het contact als slecht. Over de oorzaken van CVS werd door huisartsen en door patiënten anders gedacht. Huisartsen schreven de klachten vooral toe aan psychosociale factoren, terwijl patiënten vooral lichamelijke oorzaken noemden. Bij de communicatie met CVS patiënten zou het de huisarts daarom kunnen helpen om onderscheid te maken tussen oorzakelijke en instandhoudende factoren van CVS.

In *Hoofdstuk 10* wordt de overdraagbaarheid van CGT voor patiënten met CVS onder de loep genomen. De resultaten van het effectonderzoek in Hoofdstuk 4 hebben laten zien dat het mogelijk is om CGT voor CVS vanuit onderzoeksinstituten over te dragen naar therapeuten zonder eerdere ervaring met deze behandeling. Voor de implementatie van CGT in de geestelijke gezondheidszorg is de overdraagbaarheid van de behandeling van groot belang. De psychotherapeuten in het effectonderzoek waren uitgebreid getraind en gesuperviseerd. De vraag was echter of zij de behandeling ook volgens protocol hadden aangeboden. Door analyse van audio-opnamen van de therapiesessies werd nagegaan in hoeverre de therapeuten de verschillende aspecten van de behandeling ook volgens protocol hadden uitgevoerd. In 89% van de sessies bleek dat in voldoende mate te zijn gebeurd. Wat therapeuten vonden van de uitvoerbaarheid van deze protocollaire vorm van CGT voor CVS werd onderzocht door aan het einde van het effectonderzoek aan de 13 psychotherapeuten die de behandelingen uitvoerden, een vragenlijst voor te leggen. Uit de resultaten bleek dat de psychotherapeuten vonden dat CVS patiënten moeilijker te behandelen zijn dan patiënten met psychische klachten en patiënten met andere lichamelijke klachten. Het moeilijkste vond men het integreren van individuele problemen in de behandeling, het gebrek aan vertrouwen in de behandeling van de patiënt en het omgaan met onvoldoende motivatie. Met name voor deze aspecten lijkt, naast het ter beschikking stellen van het protocol, extra training noodzakelijk. Het protocol zal zo geschreven moeten zijn dat de therapeut de behandeling kan individualiseren en handreikingen krijgt met betrekking tot het motiveren van de patiënten.

Implementatie van CGT voor patiënten met CVS hangt niet alleen af van de overdraagbaarheid van de behandeling naar andere therapeuten, maar ook van de

economische evaluatie van de behandeling. In *Hoofdstuk 11* wordt het eerste prospectieve gerandomiseerde onderzoek naar de kosteneffectiviteit van CGT voor patiënten met CVS gepresenteerd. Informatie over kosteneffectiviteit is speciaal van belang, omdat CGT de enige behandeling voor CVS patiënten is, waarvan de effectiviteit werd aangetoond. De kosteneffectiviteitsanalyse maakte deel uit van het gerandomiseerde gecontroleerde onderzoek, dat in Hoofdstuk 4 werd gepresenteerd. Zowel een gezondheidszorgperspectief (kosten per herstelde patiënt) als een maatschappelijk perspectief (kosten per quality adjusted life year) werden gebruikt. CGT resulteerde in een beter effect en een lager gebruik van medische faciliteiten dan beide controle condities. Gezien de beperkte follow-up is de verwachting dat de kosteneffectiviteit verbetert bij een langere tijdshorizon. Echter, bootstrap simulaties lieten zien dat de statische onzekerheid van de bevindingen aanzienlijk is. Met name het gebruik van het maatschappelijk perspectief, waarbij ook de productiviteitskosten in het onderzoek meegenomen worden, heeft veel invloed op de kosteneffectiviteit schattingen. Hoewel niet statistisch significant, was het verschil in productiviteitskosten tussen de onderzoeksgroepen aanzienlijk. De resultaten moeten daarom met voorzichtigheid geïnterpreteerd worden. De werksituatie van CVS patiënten moet verder onderzocht worden. Het maatschappelijk perspectief is zeker van belang, gezien het feit dat van de 270 patiënten in het onderzoek 76% werkte voordat de klachten ontstonden, terwijl ten tijde van het onderzoek nog maar 33% een baan had. Voorlopig moeten de conclusies van dit onderzoek echter op het gezondheidszorgperspectief gebaseerd worden. Het verschil tussen CGT en de huidige situatie is klein. Vanwege dit feit en de korte tijdshorizon, lijken de kosten per QALY hoog. Als de bevindingen echter geëxtrapoleerd worden naar een tijdshorizon van vier jaar, worden de kosten per QALY acceptabeler en is er zelfs sprake van dominantie van CGT als de productiviteitskosten mede beschouwd worden.

Tot slot worden in *Hoofdstuk 12* de resultaten van de onderzoeken in dit proefschrift in een groter geheel bezien. We gaan in op vragen en kritische reacties die ons onderzoek heeft opgeroepen, bespreken praktische implicaties alsmede onze ideeën over implementatie van CGT voor CVS en geven de richting aan voor toekomstig onderzoek. De belangrijkste conclusie is dat met een goede indicatiestelling CGT tot herstel kan leiden bij een belangrijk deel van de patiënten met CVS. Toekomstig onderzoek naar effectiviteit en kosteneffectiviteit van CGT op lange termijn is gewenst om implementatie een goede kans van slagen te bieden. Onderzoek naar de werkzame elementen van CGT kan bijdragen aan een verbetering van de effectiviteit en de kosteneffectiviteit.

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