Hans Knoop

Cognitive behaviour therapy for chronic fatigue syndrome

analysis of the treatment response

Financial support for the publication of this dissertation was kindly given by the Expert Centre Chronic Fatigue of the Radboud University Nijmegen Medical Centre

Cover illustration: Noon: rest from work by Vincent van Gogh, Musée d'Orsay, Paris
Cover design: Yvonne Keurentjes, Seña ontwerpers
Printed by: Ponsen & Looyen BV, Wageningen, the Netherlands

ISBN 978-90-9022786-3

Cognitive behaviour therapy for chronic fatigue syndrome

Analysis of the treatment response

Een wetenschappelijke proeve op het gebied
van de Medische Wetenschappen

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de Rector Magnificus Prof. mr. S.C.J.J. Kortmann,
volgens besluit van het College van Decanen
in het openbaar te verdedigen
op donderdag 3 april 2008 om 15.30 uur precies

door

Johannes Adrianus Knoop

geboren op 14 december 1966
te 's-Hertogenbosch

Promotores:	Prof. dr. G. Bleijenberg
	Prof. dr. J.W.M. van der Meer

Manuscriptcommissie:	Prof. dr. A.E.M. Speckens, voorzitter
	Prof. dr. P.M.G. Emmelkamp, Universiteit van Amsterdam
	Prof. dr. B.G.M. van Engelen
	Prof. dr. R.P.T.M. Grol
	Prof. dr. Ph. Spinhoven, Universiteit Leiden

Paranimfen:	Klaartje Verhoeven
	Peter Pilzecker

voor mijn vader

Contents

Contents

1

General introduction

Introduction

In this thesis, six studies are presented in which different aspects of the treatment of patients with chronic fatigue syndrome (CFS) were investigated. In this introductory chapter, some of the literature on this syndrome is reviewed and a cognitive-behavioural model of CFS is introduced. This model forms the basis for cognitive behaviour therapy (CBT), an evidence based treatment for CFS. The different elements of this mode of treatment are explained in detail and the controversies and unresolved issues surrounding CBT for CFS are discussed. Some of these unresolved issues are addressed in this thesis. Also, an attempt is made to further develop this form of treatment by testing the effectiveness of a new type of intervention. The chapter ends with a description of the research centre where the studies were undertaken.

Chronic fatigue syndrome

For most people, fatigue is a 'normal' and sometimes pleasant state that is experienced regularly. However, fatigue becomes a symptom when it is severe, chronic and interfering with daily live. In certain instances we then speak of CFS. CFS is characterized by severe fatigue lasting longer than six months and leading to a substantial reduction of activities. A somatic explanation for the fatigue is lacking.[1] Most patients have, aside from fatigue, additional symptoms. According to the US Center for Disease Control criteria for CFS[1 2] a patient must report four out of eight additional symptoms: unrefreshing sleep, post-exertional malaise, headache, muscle pain, multi-joint pain, sore throat, tender lymph nodes and concentration and memory impairment. Although some suggest that CFS is a 'modern disease', reports about patients with CFS-like symptoms date back to the end of the 19th century.[3 4]

The prevalence of CFS in the Netherlands is estimated to be between 30,000 to 40,000 patients.[5] The prognosis of CFS without treatment in adults is not favourable. A recent review showed that only 5% of the patients show spontaneous recovery.[6] In adolescents with CFS the prognosis is much better.[7]

What causes CFS?

The aetiology of CFS is still unknown. It is probable that CFS is multi-factorially determined. A distinction between factors that predispose someone for CFS, factors that precipitate CFS, and factors that perpetuate the symptoms has proven to be fruitful.[8]

Research into the factors that predispose someone for CFS has shown that physical inactivity, being female, and early adverse experiences (i.e. physical or emotional neglect or abuse) are risk factors for developing CFS.[8 9] There is also some evidence that a genetic disposition exists for CFS.[8]

Different somatic and psychological stressors, like an operation, infection or loss of a loved one, can precipitate CFS. They can all act as triggers of the symptoms of CFS.

Psychological processes seem to be the main factors in perpetuating CFS once the symptoms have been established. [8 10 11]

Although until now no consistent somatic impairment has been found in CFS, a recent and promising line of research investigated possible neurobiological abnormalities that are associated with CFS. The activity patterns in specific areas of the brain were shown to be different in patients with CFS when they were performing the same tasks as healthy controls. In a study of de Lange et al[12] areas in the brain that play a role in the emotional response to making an error showed less activity, suggesting some kind of motivational impairment in CFS. Other research showed that more areas in the brain were activated when CFS patients performed a complex cognitive task while their actual performance did not differ from healthy controls. The level of activity in the brain of CFS patients was associated with the reported severity of mental fatigue.[13 14] There are also two studies that show that patients with CFS have less grey matter. In one of those studies, the amount of grey matter was negatively correlated with the level of physical activity.[15 16] Furthermore, changes in functioning of the Hypothalamopituitary-adrenal (HPA) axis and serotonergic transmitter systems have been found.[8] To what extent these abnormalities reflect the consequences of CFS, are the biological correlates of the perpetuating factors, or are related to the aetiology of CFS is not yet clear.

A cognitive behavioural model of perpetuating factors of CFS

Vercoulen et al[11] developed a statistically tested model of the psychological factors that perpetuate fatigue and disabilities in CFS (see Fig. 1).

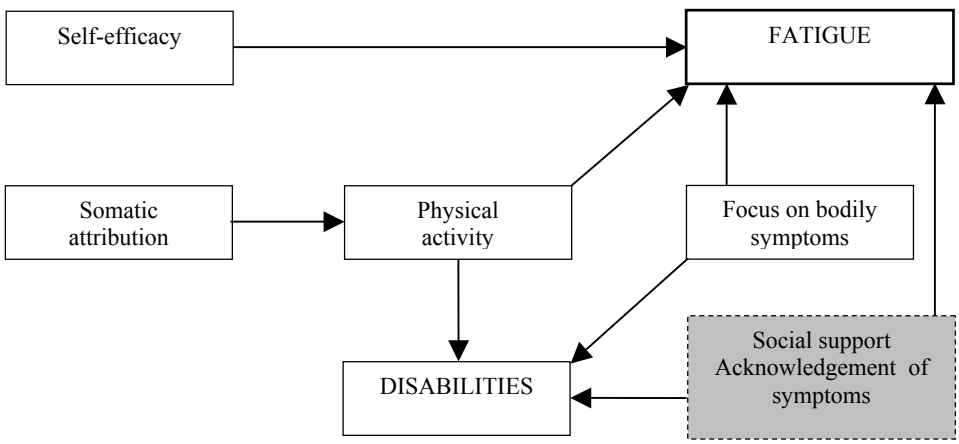

Fig. 1: Model of perpetuating cognitions and behaviour of CFS.[28]

Cognitions and behaviour are the maintaining factors in CFS. A low self-efficacy negatively influences the fatigue. The conviction that the symptoms have a somatic cause lowers the physical activity, which in turn increases the fatigue and leads to disabilities. Body consciousness or a strong focus on bodily symptoms also has a negative influence on

the level of fatigue and disabilities. A more recent study showed a perceived lack of social support and more negative social interactions in CFS patients. A lack of social support was identified as a factor that has to be added to the model of perpetuating factors of CFS.[17]

The treatment of CFS

Different treatment modes have been applied to CFS. In a systematic review, Whiting et al[18] concluded that behavioural interventions have shown the most promising results. A recent update[19] again showed that behavioural interventions appeared to reduce symptoms and improve the level of functioning when tested in randomized controlled trials (RCT).

Cognitive behaviour therapy (CBT) and graded exercise therapy (GET) are the most frequently used behavioural interventions for CFS. Both interventions involve a gradual exposure to activity. In GET, the gradual build up of physical exercise is a central element. In CBT, there are also interventions specifically aimed at changing CFS related beliefs and perceptions. Five RCT's have tested GET. Depending on the outcome variable used, GET results in a significant reduction of symptoms and disabilities in 18 to 63 per cent of the patients.[20] A higher success rate (69%) was reported by Powell et al[21] who combined GET with an educational intervention that explained both the reasons for ill health and the rationale for GET. Of the eight trials that tested the effects of CBT for CFS, six reported a positive effect of the intervention.[19] After CBT, between 50 to 70 percent of the patients report a significant reduction of symptoms, disabilities or both.[18 19 22]

Cognitive behaviour therapy for CFS

There are different CBT protocols for CFS.[23 24] All protocols aim at a change in fatigue related cognitions and a gradual increase of activity. These interventions should lead to a decrease of the severe fatigue and disabilities. It is (often implicitly) assumed that other symptoms, such as pain, difficulty concentrating, or forgetfulness will also decrease if patients become less fatigued. However, this is still a matter of discussion and the fact that the reduction of fatigue is the main focus of CBT while less attention is given to other symptoms is sometimes criticized.

The protocol that is used in the studies of this thesis is based on the model of perpetuating factors of Vercoulen et al.[11] The protocol was tested in two RCT 's, one in adults[25] and one in adolescents.[22] The treatment starts with the establishment of goals. In this phase, the model of perpetuating factors is explained to the patient and individualized to her situation (the female pronoun is used to denote both female and male patient). When the patient is invited to formulate the treatment goals, it is emphasized that recovery of CFS is possible. Recovery means that a patient no longer suffers from CFS, is no longer chronically and severely fatigued, and can resume her normal activities as a result of the therapy. This is different from the other CBT protocols in which, rather than recovery, the reduction of symptoms and disabilities is seen as the highest attainable goal of treatment.

A disruption of circadian rhythms as a consequence of changes in the sleep-wake cycle in response to the severe fatigue (e.g. sleeping during the day) is thought to be one of the

perpetuating factors in CFS. Therefore, after formulating the goals of the treatment, the patient learns to regulate her sleep-wake pattern, which means that she goes to bed at the same time everyday, gets up at the same time, and does not sleep or lies down during the day.

In the protocol of Bleijenberg et al[26] the pattern of physical activity determines the type of interventions that are used after the regulation of the sleep-wake cycle. An actometer, a motion sensing device that can quantify physical activity, is used to assess the activity pattern.[27] Two types of activity patterns are distinguished: relatively active and passive. The relatively active pattern is characterised by bursts of activity followed by periods of rest. Patients with a relatively active pattern have cognitions that enhance their symptoms. Examples of these cognitions are non-acceptance of symptoms and cognitions that lead to peaks of activity, such as wanting to do too much or making too many demands on ones self in light of current symptoms. Relatively active patients first have to attain a base level of activity and subsequently gradually increase their activity level. By means of a systematic program, they first increase their physical activity (walking of cycling), and then they gradually resume work and other activities of daily life. To do this successfully, the cognitions that enhance the symptoms and maintain the peaks of activity have to be systematically challenged. Patients with a passive activity pattern are characterised by an extremely low physical activity level and activity impeding cognitions. After entering treatment, they immediately start with a graded physical activity program followed by a systematic increase of mental, social and work related activities. It is assumed that the gradual resumption of mental activities will decrease the self-reported mental impairments. This has however never been empirically tested. When patients follow the graded activity program, the activity impeding cognitions are changed because patients stop avoiding activities.

For all patients, specific cognitive behavioural interventions are used. These interventions are aimed at decreasing the focusing on bodily symptoms, changing the way patients communicate with others about CFS and changing their attitude when dealing with the reaction of others to their symptoms. An important intervention for decreasing the focus of bodily symptoms is, no longer talk about the symptoms in therapy, but to talk about the ways in which to change the perpetuating behaviour and cognitions. When patients start with CBT they have to agree to stop all medical assessments aimed at finding the 'cause' of the fatigue. This also helps to decrease the focus on physical functioning. Finally, specific interventions are used to normalise the perception of signals of the body and to learn to give them less attention.[28] During treatment, it is stressed that patients have to learn to cope with a limited understanding of their symptoms by (a part of) their social environment. It is important that the patient takes responsibility for changing her situation, even if her environment is less supportive. At the same time, an attempt to increase the social support of a patient is made by educating the spouse, or other important proxy's, and colleagues about CFS in ways in which they can support the patient. Throughout the treatment, the focus of communication is on the resumption of activities (like work) and the reduction of

symptoms. The therapy ends with interventions aimed at the prevention of relapses. Bleijenberg et al[26] describe the treatment protocol in more detail.
CBT for adolescents for CFS is comparable to that of adults, however, the parents of the adolescent are involved in the therapy, and the treatment is shorter as a positive outcome can be reached more quickly than in adults.[22]

Research into CBT for CFS: outline of this thesis
Although there is substantial evidence that CBT is an effective treatment for CFS, there are a number of controversies surrounding this mode of treatment. Some seem related to the unwillingness of certain researchers and patient advocacy groups to accept that cognitions and behaviour play an important role in the perpetuation of CFS symptoms. Others are related to legitimate concerns about the effectiveness and scope of CBT. This thesis aims to address some of these unresolved issues surrounding CBT. Additionally, the thesis aims to further the development of CBT.

The effect of CBT on pain symptoms
Although chronic fatigue is an important symptom of CFS, it is not the only one. Most patients also complain of chronic pain.[29 30] Four of the eight additional symptom criteria of the CDC definition of CFS are pain symptoms: headache, muscle pain, multi joint pain and a sore throat. The pain symptoms lead to significant disabilities in patients.[31]
The question addressed in *chapter 2* is whether CBT for CFS is also effective for pain symptoms. To answer this question, data of two previous studies testing the effectiveness of CBT for CFS in adults[32] and adolescents[22] were re-analysed. Also, the mechanisms of the change in pain symptoms and the predictive value of the pain symptoms for the outcome of CBT for CFS were studied.

The effect of CBT on neuropsychological test performance and self reported cognitive impairments
Most patients who are chronically fatigued also complain about difficulty concentrating and forgetfulness. As already mentioned, it is assumed that these symptoms will decrease following CBT but that has never been investigated systematically. The role of the impairments in cognitive functioning in CFS is unclear. Although a majority of patients complain about their mental functioning, their performance on neuropsychological tests that objectively measures mental capacities often shows no impairment.[33] There is a discrepancy between subjective cognitive functioning and objective neuropsychological test performance (see also Vercoulen et al[34]). This discrepancy is not limited to cognitive impairments but also occurs in sleep disorders and the perception of pain.[35 36] Furthermore, research also showed that the mental functioning of CFS patients is negatively influenced by a focus on bodily symptoms.[37] All these findings suggest that there is a disorder in the perception of bodily symptoms and mental functioning in CFS and not in the objective cognitive performance or bodily functioning. If this is true, one would expect that following

CBT the perception of the patient's own functioning will change rather than her performance on neuropsychological tests. In *chapter 3*, the question is addressed to what extent the self-reported cognitive impairments decreased and neuropsychological test performance increased following CBT for CFS.

The change in the experience of fatigue following CBT

For most people, fatigue is a pleasant and normal phenomenon after a period of activity. CFS patients not only report severe fatigue, the perceived quality of their fatigue is often very different from that of healthy people. For patients with CFS, fatigue has a profound negative connotation. An important goal of the treatment is to make the perception of the fatigue comparable to that of a healthy person, meaning that the patient experiences the fatigue as something normal, without persistent negative connotations. The scales used to assess fatigue mostly measure fatigue severity and not the subjective quality of the fatigue. We developed an adjective checklist, the Fatigue Quality List, to assess the experience of the fatigue. The psychometric properties of this list and the effect of CBT on the experience of fatigue were investigated. That study is reported in *chapter 4*.

Rehabilitation versus recovery

The majority of the studies that investigate the effects of CBT for CFS report a change in symptoms and disabilities. However, the nature of this change following treatment is controversial. Some suggest that patients learn to adapt to a chronic condition. Patients learn to manage their chronic condition better, will report less symptoms and disabilities, but remain impaired by CFS.[38] Others think that a full recovery from CFS is possible and that recovery should be the goal of CBT.[39] In the protocol used in the studies of this thesis, recovery is explicitly stated as the goal of treatment.

The question what the tenable goal is for CBT for CFS, adaptation or recovery, is not only an interesting research question but also one of clinical importance. If recovery is the goal of treatment, a therapist will select other interventions than when the goal is to cope better with chronic symptoms. Furthermore, the communication of the aim of the treatment by the therapist is in itself a cognitive intervention that can facilitate a behavioural change. *Chapter 5* will report on a study in which we measured the proportion of the patients that are (fully) recovered following CBT using different measures and definitions of recovery.

Long term effects of CBT for CFS

Several trials have shown a positive effect of CBT for CFS directly following treatment. Less is known about the long term effects of CBT. In other disorders for which CBT is an effective treatment, large discrepancies occur between short and long term effects. In affective disorders for example, a high relapse rate is common after a positive outcome directly following treatment with CBT.[40] There is only one study that systematically studied the long term outcome of CBT for CFS. This study of Deale et al[38] showed that CBT can produce lasting benefits in adult CFS patients five years after the treatment. We

investigated the long term outcome of CBT for CFS in adolescents. A previous study of our research group had already shown that CBT has a positive effect in adolescent CFS patients directly following treatment.[22] All patients who participated in the trial were contacted for a follow-up assessment to see if the positive effects of CBT were maintained. Furthermore, we tried to predict treatment outcome from the baseline assessment. The study is described in *chapter 6*.

The efficacy of self instructions based on CBT in the treatment of CFS

CBT for CFS is an intensive treatment. It consists of 16 individual sessions in a period of 8 months.[26] Licensed cognitive behavioural therapists need additional training and supervision to learn to treat CFS patients effectively. The current treatment capacity for CBT for CFS in the Netherlands is limited; yet it is unlikely that intensive treatment is necessary for all CFS patients. If a less intense form of CBT for CFS is available, treatment capacity will increase and it will become possible to better tailor the intervention to the specific needs of the CFS patient. We developed a minimal intervention based on the CBT protocol for CFS. It consisted of a self help booklet supported by two-weekly email contact with a CBT therapist. The efficacy of this minimal intervention was tested in a RCT where the effects of the self help booklet supported by email contact were compared with a waiting list condition. The objective of the study was twofold: first, we wanted to test the effectiveness of the minimal intervention in reducing CFS symptoms and second, we wanted to identify those patients for whom a minimal intervention sufficed. In *chapter 7* the results of this study are reported.

In the final chapter (*chapter 8*) the results of the aforementioned studies are discussed in light of the existing literature on CBT for CFS. The clinical implications of the findings will be formulated and possible directions for future research will be mentioned.

Expert Centre Chronic Fatigue

All studies reported on in this dissertation were performed at the Expert Centre Chronic Fatigue of the Radboud University Nijmegen Medical Centre (www.umcn.nl/chronicfatigue). The expert centre started in 1990 as the result of collaboration between the departments of Internal Medicine, Virology and Medical Psychology. Possible somatic and psychological determinants and consequences of CFS were studied systematically. This resulted in a model of perpetuating factors of CFS, which formed the basis for the development of the protocol of CBT for CFS. Several intervention studies testing CBT for CBS have been performed.[22 25 32 41] The expert centre implemented CBT for CFS in clinical routine and treated over 200 CFS patients in 2006. Current research focuses on the neurobiological correlates of CFS, the process of change (and somatic correlates of this change) during CBT for CFS and the development and implementation of a model of stepped care for CFS.

The expertise of the Expert Centre Chronic Fatigue is not limited to CFS but extends to chronic fatigue in other conditions, such as cancer[42], neuromuscular disorders[43] [44] and rheumatoid arthritis. A RCT has shown that CBT is effective in treating fatigue in disease-free cancer patients[45] and a trial testing the effectiveness of CBT in treating chronic fatigue in neuromuscular disorders is in preparation.

REFERENCES

1. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994; 121: 953-9.
2. Reeves WCC, Lloyd A, Vernon SD, Klimas N, Jason LA, Bleijenberg G, et al. Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. BMC Health Serv Res 2003; 31: 25.
3. Wessely S, Hotoph M, Sharpe M. Chronic fatigue and its syndromes. Oxford: Oxford University Press, 1998.
4. Bleijenberg, G. De ene vermoeidheid is de andere niet. Oratie. Katholieke Universiteit Nijmegen, 2003.
5. Gezondheidsraad. Het chronische-vermoeidheidssyndroom [Health council. Chronic fatigue syndrome]. Den Haag: gezondheidsraad, 2005, publicatie nr 2005/02.
6. Cairns R, Hotoph M. A systematic review describing the prognosis of chronic fatigue syndrome. Occup Med-C 2005; 55: 20-31.
7. Rimes KA, Goodman R, Hotoph M, Wessely S. Incidence, prognosis, and risk factors for fatigue and chronic fatigue syndrome in adolescents: a prospective community study. Pediatrics 2007; 119: 603-9.
8. Prins JB, Van der Meer JWM, Bleijenberg G. Chronic fatigue syndrome. Lancet 2006; 376: 346-355.
9. Heim C, Wagner D, Maloney E, Papanicolaou DA, Solomon L, Jones JF, et al. Early adverse experience and risk for chronic fatigue syndrome: results from a population based study. Arch Gen Psychiatry 2006; 63: 1258-1266.
10. Suraway C, Hackmann A, Hawton K, Sharpe M. Chronic fatigue syndrome: a cognitive approach. Behav Res Ther 1995; 33: 535-544.
11. Vercoulen JHMM, Swanink CMA, Galama JMD, Fennis JFM, Jongen PJH, Hommes OR, et al. The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: the development of a model. J Psychosom Res 1998; 45: 507–517.
12. de Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Werf SP, van der Meer JWM, et al. Neural correlates of the chronic fatigue syndrome- an fMRI study. Brain 2004; 127: 1979-1992.
13. Lange G, Stefferer J, Cook DB, Bly BM, Christodoulou C, Liu WC, et al. Objective evidence of cognitive complaints in chronic fatigue syndrome: A BOLD fMRI study of verbal working memory. NeuroImage 2005; 26: 513-524.
14. Cook DB, O' Connor PJ, Lange G, Steffener J. Functional neuroimaging correlates of mental fatigue induced by cognition among chronic fatigue syndrome patients and controls. NeuroImage 2007; 36: 108-122.
15. Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JWM, Toni I. Gray matter volume reduction in the chronic fatigue syndrome. NeuroImage 2005; 26: 777-781.
16. Okada T, Tanaka M, Kuratsune H, Watanabe Y, Sadato N. Mechanisms underlying fatigue: a voxel-based morphometric study of chronic fatigue syndrome. BMC Neurol 2004; 4: 14.
17. Prins JB, Bos E, Huibers MJ, Servaes P, van der Werf SP, van der Meer JW, et al. Social support and the persistence of complaints in chronic fatigue syndrome. Psychother Psychosom 2004; 73: 174-182.
18. Whiting P, Bagnall AM, Sowden AJ, Cornell JE, Mulrow CD, Ramirez G. Interventions for the treatment and management of chronic fatigue syndrome: a systematic review. J Am Med Assoc 2001; 286: 1360-8.

19. Chambers D, Bagnall A, Hempel S, Forbes C. Interventions for the treatment, management and rehabilitation of patients with chronic fatigue syndrome/myalgic encephalomyelitis: an updated systematic review. J Roy Soc Med 2006; 99: 506-520.
20. Edmonds M, McGuire H, Price J. Exercise therapy for chronic fatigue syndrome. Cochrane Database of Systematic Reviews, 2004, Issue 3. Art no: CD003200. DOI:10.1002/14651858.CD003200.pub2.
21. Powell P, Bentall RP, Nye FJ, Edwards RHT. Randomised controlled trial of patient education to encourage graded exercise in chronic fatigue syndrome. Brit Med J 2001; 322: 1-5.
22. Stulemeijer M, de Jong LWAM, Fiselier TJW, Hoogveld SWB, Bleijenberg G: Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. Brit Med J 2005; 330: 7481-6.
23. Deale A, Chalder T, Wessely SC, Keijsers GPJ, Hoogduin CAL. Protocollaire behandeling van patienten met het chonisch vermoeidheidssyndroom: graduele activering en cognitieve therapie [a protocol for the treatment of chronic fatigue syndrome: graded activity and cognitive therapy]. In: Protocollaire behandeling in the ambulante geestelijke gezondheidszorg. Keijsers GPJ, Van Minnen A, Hoogduin CAL, eds. Houten/diegem: Bohn Stafleu van Loghum, 1999.
24. Bleijenberg G, Bazelmans E, Prins J. Chronisch vermoeidheidssyndroom [chronic fatigue syndrome]. Houten/Diegem: Bohn Stafleu Van Loghum, 2001.
25. Prins JB, Bleijenberg G, Bazelmans E, Elving L, de Boo Th, Severens JL, et al. Cognitive behaviour therapy for chronic fatigue syndrome: A multicentre randomised controlled trial. Lancet 2001; 357: 841-7.
26. Bleijenberg G, Prins J, Bazelmans E. Cognitive behavioral therapies; in Jason LA, Fennell PA, Taylor RR (eds). Handbook of chronic fatigue syndrome. New York, Wiley & Sons, 2003, pp 493-526.
27. Van der Werf SP, Prins JB, Vercoulen JHMM, Van der Meer JWM, Bleijenberg G. Identifying physical activity patterns in chronic fatigue syndrome using actigraphic assessment. J Psychosom Res 2000; 49: 373-9.
28. Knoop H, Bleijenberg G. Belemmerende preoccupaties bij patiënten met het chronisch vermoeidheids-syndroom [preoccupations in chronic fatigue syndrome]. Tijdschrift voor directieve therapie 2005; 25: 205-217.
29. Vercoulen JHMM, Swanink CMA, Fennis JFM, Galama, JMD, Van der Meer JWM, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38: 383-392.
30. King C, Jason LA. Improving the diagnostic criteria and procedures for chronic fatigue syndrome. Biol Psychol 2005; 68: 87-106.
31. Meeus M, Nijs J, De Meirleir K. Chronic musculoskeletal pain in patients with the chronic fatigue syndrome: a systematic review. Eur J Pain 2007; 11: 377-386.
32. Knoop H, Bleijenberg G, Gielissen MFM, van der Meer JWM, White PD. Is a full recovery possible after cognitive behavioural therapy for chronic fatigue syndrome? Psychother Psychosom 2007; 76: 171-6.
33. Vercoulen JH, Bazelmans E, Swanink CM, Galama JM, Fennis JF, van der Meer JW, et al. Neuropsychological impairment in chronic fatigue syndrome. J Clin Exp Neuropsychol 1998; 20: 144-56.
34. Mahurin RK, Claypoole KH, Goldberg JH, Arguelles L, Ashton S, Buchwald D. Cognitive processing in monozygotic twins discordant for chronic fatigue syndrome. Neuropsychology 2004; 18: 232-9.
35. Van der Werf SW, De Vree B, Van der Meer JWM, Bleijenberg G. The relationship between body consciousness, somatic symptoms report and information processing speed in chronic fatigue syndrome. Neurol Neuropsychology Behav Neurol 2002; 12: 12-15.
36. Watson NF, Jacobsen C, Goldberg J, Kapur V, Buchwald D. Subjective and objective sleepiness in monozygotic twins discordant for chronic fatigue syndrome. Sleep 2004; 27: 973 –7.
37. Ullrich PM, Afari N, Jacobsen C, Goldberg J, Buchwald D. Cold pressor pain sensitivity in monozygotic twins discordant for chronic fatigue syndrome. Pain Med 2007; 8: 216-222.
38. Deale A, Husain K, Chalder T, Wessely, S. Long-term outcome of cognitive behaviour therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study. Am J Psychiatry 2001; 158: 2038-2042.
39. Prins JB, Bleijenberg G, van der Meer JWM.. Chronic fatigue syndrome and myalgic encephalomyelitis. Lancet 2002; 359:1699.

40. Hollon SD, DeRubeis RJ, Shelton RC, Amsterdam JD, Salomon RM, O'Reardon JP, et al. Prevention of relapse following cognitive therapy vs medications in moderate to severe depression. Arch Gen Psychiatry 2005; 62: 417-422.
41. Bazelmans E, Prins JB, Lulofs R, van der Meer JWM, Bleijenberg G. Cognitive behaviour group therapy in chronic fatigue syndrome: a wait-list controlled study. Psychother Psychosom 2005; 74: 218-224.
42. Servaes, P. Fatigue in disease-free cancer patients. Thesis. Radboud University Nijmegen, 2003 http://webdoc.ubn.kun.nl/mono/s/servaes_p/fatiindic.pdf
43. Schillings M. Fatigue in neuromuscular disorders and chronic fatigue syndrome. A neurophysiological approach. Thesis. Radboud University Nijmegen, 2005. http://webdoc.ubn.ru.nl/mono/s/schillingsm /fatiinned.pdf
44. Kalkman JS. From prevalence to predictors of fatigue in neuromuscular disorders. The building of a model. Thesis. Radboud University Nijmegen, 2006 http://webdoc.ubn.ru.nl/mono/k/kalkman_j/fromprtop.pdf
45. Gielissen, MFM, Verhagen S, Witjes F, Bleijenberg G. Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: a randomized controlled trial. J Clin Oncol 2006; 24: 4882-7.

2

Is cognitive behaviour therapy for chronic fatigue syndrome also effective for pain symptoms?

Hans Knoop, Maja Stulemeijer, Judith B. Prins, Jos W.M. van der Meer, Gijs Bleijenberg.
Behaviour Research and Therapy 2007; 45: 2034-2043

ABSTRACT

Patients with chronic fatigue syndrome (CFS) frequently report chronic pain symptoms. Cognitive behaviour therapy (CBT) for CFS results in a reduction of fatigue, but is not aimed at pain symptoms. In this study, we tested the hypothesis that a successful treatment of CFS can also lead to a reduction of pain. The second objective was to explore possible mechanisms of changes in pain. The third objective was to assess the predictive value of pain for treatment outcome. Data from two previous CBT studies were used, one of adult CFS patients (n=96) and one of adolescent CFS patients (n=32). Pain severity was assessed with a daily self-observation list at baseline and post-treatment. The location of pain in adults was assessed with the McGill Pain Questionnaire (MPQ). Patients were divided into recovered and non-recovered groups. Recovery was defined as reaching a post-treatment level of fatigue within normal range. Recovered adult and adolescent CFS patients reported a significant reduction of pain severity compared to non-recovered patients. Recovered adult patients also had fewer pain locations following treatment. The decrease in fatigue predicted the change in pain severity. In adult patients, a higher pain severity at baseline was associated with a negative treatment outcome.

INTRODUCTION

Chronic fatigue syndrome (CFS) is characterised by severe fatigue lasting longer than 6 months and leading to functional impairment. CFS is neither the result of an organic disease or ongoing exertion nor alleviated by rest. According to the Centre for Disease Control (CDC) definition of CFS, the patient should have four out of eight additional symptom criteria.[1] Four of these are pain symptoms, i.e. muscle pain, multi-joint pain, headaches and a sore throat. The other four are post-exertional malaise, unrefreshing sleep, concentration and/or memory impairments and sensitive lymph nodes. The frequency of pain symptoms in CFS differs between studies but is usually high.[2 3 4] In the study of Vercoulen et al[2], the frequency of spontaneously reported pain symptoms ranged from 13% (sore throat) to 71% (muscle pain). King and Jason[3] systematically assessed complaints and found much higher frequencies ranging from 60% for a sore throat to 93% for headaches and muscle pain. The chronic pain symptoms in CFS are disabling and compromise physical and social functioning.[4]

The aetiology of CFS is unknown, but cognitions and behaviour can perpetuate CFS.[5 6] A statistically tested model of perpetuating factors in CFS showed that a low sense of control of symptoms and a focus on bodily symptoms had a direct causal effect on fatigue.[7] Furthermore, attributing the symptoms of CFS to a somatic cause produced low levels of physical activity which in turn had a negative causal effect on fatigue. More recently, it was found that a perceived lack of social support can also perpetuate the fatigue.[8]

Several controlled trials have found that cognitive behaviour therapy (CBT) aimed at the perpetuating factors of CFS leads to a reduction of fatigue and disabilities.[9] A recent systematic review showed that of the eight CBT trials for CFS that have been performed, six reported a positive outcome.[10] Most studies used fatigue as an outcome measure.

There are no interventions in the different treatment protocols for CFS that focus on pain symptoms, but it is implicitly assumed that an effective treatment of fatigue will also lead to a reduction of pain. Recently, it was shown that adolescents indeed report a decrease of muscle pain and headache following CBT for CFS.[11] However, the measure used was a four-point Likert scale in which the prevalence of pain had to be evaluated retrospectively over a period of 6 months. This type of pain assessment is easily influenced by situational circumstances and memory biases which can be prevented with the use of a pain diary.[12] To our knowledge, there are no published data pertaining to the effect of CBT for CFS on pain in adult patients.

The first objective of this study was to determine whether an effective treatment of CFS with CBT also leads to a significant reduction of pain symptoms when these symptoms are evaluated with an appropriate assessment method. CBT is considered effective if a patient is recovered, that is reporting a level of fatigue within the range of healthy individuals.[13] In assessing pain symptoms we looked at pain severity and the location of the pain symptoms.

The second objective was to investigate the mechanisms of possible changes in pain severity following CBT. A central feature of CBT for CFS is the gradual increase of physical activity. It is possible that the increased activity levels also leads to a decrease of

pain. CBT for CFS also aims to modify those cognitions and cognitive processes that perpetuate fatigue. The persistent focus on bodily symptoms or body consciousness is one of these cognitive processes.[7] If this focus is lessened as a consequence of therapy, it is likely that this generalises to other symptoms than fatigue, e.g. pain. Finally, CBT for CFS leads to a reduced negative affectivity, which could lead to a diminished report of physical symptoms (i.e. pain).

The third objective was to assess the predictive value of pain severity at baseline on the outcome of the treatment. Although physical activity has a positive effect on chronic pain in the long term[14], increase in activity can have a negative influence on pain symptoms in the short term. Whiteside et al[15] found that CFS patients reported a lower pain threshold following physical activity. In their study, the pain threshold of patients was repeatedly determined after graded exercise. Since graded activity is an important feature of CBT, this could mean that CBT leads to a lower pain threshold. This lower pain threshold might hamper the increase in activity level during therapy and could lead to a less favourable outcome of CBT. We suspected that this was especially true for those patients who already had a high pain severity at the start of the therapy. In determining the predictive value of pain for treatment outcome, we controlled for the relationship between pain and physical activity

METHODS

Subjects To answer our research questions, data from two previous CBT studies with patients with CFS were used. In the first study, the outcome of CBT for CFS in adults was evaluated.[16] The effect of CBT on pain symptoms was not determined in this study. Ninety-six adult patients who met the CDC criteria for CFS participated in the study. They were severely fatigued and functionally impaired. Severe fatigue was defined by a cut-off score of 35 or higher on the subscale fatigue severity of the checklist individual strength (CIS).[2] Functional impairment was assessed with the sickness impact profile (SIP). The SIP consists of eight subscales measuring functional impairments of different domains of functioning. The scores on the subscales were added to provide one weighted score of general disability. A score of 700 or higher was used as a cut-off score.[17] The mean age of the adult patients was 37 years (SD= 11.5). Seventy-three patients were women (76%), and the median duration of the illness was 48 months (range= 264 months).

The second study used was a randomised controlled trial testing the effectiveness of CBT for adolescents with CFS.[11] Patients included in this study were between 10 and 17.2 years old. They met the CDC criteria for CFS. In this study, severe fatigue was defined as having a score of 40 or higher on the CIS subscale fatigue severity. The cut-off score for adolescents is higher than for adults because the mean fatigue severity in healthy adolescents is also higher.[11] Severe functional impairment was operationalised as having a weighted score of 65 or less on the SF-36 Physical Functioning scale. The score on this subscale can range from 0 (maximum physical limitations) to 100 (ability to do vigorous activity). The CBT group consisted of 35 adolescents with a mean age of 15.6 years (SD=

1.3); 31 patients were female (89%) and the median duration of the illness was 16 months (range=44 months). Three patients did not start with the treatment and only the data of the 32 patients who started with CBT after baseline assessment were used for further analysis.

Design All patients were assessed at baseline and post-treatment. Patients were divided in a recovered and non-recovered group based on their post-treatment score on the CIS subscale fatigue severity. The definition of recovery in adult CFS patients was based on a previous randomised controlled trial that tested the effectiveness of CBT for adult CFS patients.[18] In this study, adult patients were considered recovered if their score on the CIS subscale fatigue was lower than 36. This score is within two standard deviations of the mean of a healthy adult control group.[2 19] Using this criterion created a potential overlap with the cut-off score that was used for including patients in the adult study (scoring 35 or higher on the CIS subscale fatigue).[16] However, as no patient in this latter study actually scored lower than 36, we could use scoring lower than 36 as a criterion for recovery for adult patients. The original CBT study with adolescent CFS patients used a criterion of scoring lower than 35.7 on the CIS subscale fatigue.[11] This is a more strict criterion than the one used in adult patients, as a score of 35.7 represents the mean plus one standard deviation of a healthy adolescent control group.[11] We used this cut-off score as a criterion for recovery for adolescent patients.
Sixty three adult patients (66%) had a CIS score lower than 36 at post-treatment and were considered recovered; the remaining 33 patients formed the non-recovered adult group. Of the 32 adolescents, 21 (66%) scored lower than 35.7 and were considered recovered, 11 did not recover. In the analysis, the effect of CBT on pain for recovered and non-recovered patients was compared. For the adolescent study, there were also data available from a waiting list control group. We did an additional analysis in which the effect of CBT on pain symptoms was compared with the waiting list condition.

Assessment
Fatigue The CIS subscale fatigue severity indicates the level of fatigue experienced over the past two weeks. The CIS consists of eight items on a 7-point scale. The score can range between 8 and 56. The CIS has been validated and is reliable.[2 11 19]
Pain Adolescent and adult patients rated their pain on a daily self-observation list four times a day during a period of 12 days, on a scale ranging from 0 (no pain) to 4 (very severe pain). The daily pain score could range between 0 and 16, and the total 12 daily pain scores were averaged into one daily observed pain (DOP) score. The DOP score was compared with the scores of a reference group of 90 healthy people, consisting of 35 men and 55 women (mean age= 37.1, SD= 10.9) who participated as healthy controls in previous studies. Their mean DOP score is 1.0 (SD= 1.3).
Adult patients also completed the McGill Pain Questionnaire (MPQ).[20 21] The MPQ included a whole body outline to indicate the distribution of pain.

To determine the frequency of CDC pain symptoms at baseline, both adolescent and adult patients filled in a questionnaire where they had to report on a four-point scale how often during the last 6 months they had experienced muscle pain, headache, multi-joint pain and sore throat. Scores on each of the four items ranged from 1 to 4 (1= never, 2= several times a month, 3= several times a week, 4= every day).

Physical activity Physical activity level was measured in adolescent and adult patients at baseline with an actometer, a motion-sensing device worn at the ankle that quantifies physical activity. The actometer detects movements of the leg (e.g. during walking or climbing stairs). The actometer was worn 12 consecutive days and nights. A general physical activity score that expressed the mean activity level over this period in the mean number of accelerations per 5-min interval was calculated.[22] Research has shown that the actometer yields highly reliable data and is a valid instrument for measuring physical activity.[23]

Negative affectivity Negative affectivity was operationalised as the level of depressive symptoms. This was assessed only in adults with the subscale depression of the SCL90.[24]

Body consciousness The subscale private body consciousness of the Body Consciousness Questionnaire was used to measure the tendency of adolescent and adult patients to focus on bodily symptoms. This subscale has five items that can be answered on a scale from 0 (extremely uncharacteristic) to 4 (extremely characteristic). It has been used before in studies of CFS patients.[25]

There were two assessments, one at baseline and one directly following termination of the treatment. At each assessment the patient visited the hospital twice in a period of 2 weeks. During the first visit, the patient completed all the questionnaires and received the actometer and daily self-observation list. After 2 weeks, the patient brought the daily self-observation list and actometer back.

Intervention Adult patients received CBT for CFS according to the protocol described by Bleijenberg et al.[26] The treatment consisted of 16 sessions over a period of 6 months and was aimed at changing fatigue-related cognitions and a gradual increase of activities. For adolescents, a protocol was designed that consisted of 10 sessions over a period of 5 months.[11] Adolescents received fewer sessions because experience has found that a positive outcome can be reached quicker.

Statistics T-tests were used to analyse the effect of CBT on pain severity. The change in DOP score from baseline to post-treatment of the recovered groups was compared with the change in DOP score of the non-recovered groups. The differences in the percentage of recovered and non-recovered patients who had a DOP score within normal limits (when compared to healthy controls) were tested with a chi-square test. Within normal limits was defined as having a DOP score of 2.3 or lower (i.e. within the range of the mean plus one standard deviation of the controls). The same analyses with the DOP score were done when the total group of adolescents who received CBT was compared with the group of patients

from the waiting list. The differences in the percentages of recovered and non-recovered adult patients who report pain at the locations identified with the MPQ at baseline and post-treatment were tested with a chi-square test. To determine the possible mechanisms of a change in pain, a stepwise multiple regression was performed with change in DOP score as dependent factor, the change in fatigue severity score, activity level, negative affectivity and body consciousness as predictors and the DOP score at baseline as covariate. For the adolescent group, the same regression was done but without the variable negative affectivity (no data available). For all the predictors, the differences between baseline and post-treatment were first tested with a pairwise t-test. To determine the predictive value of pain symptoms, a multiple regression analysis was performed with the change in CIS-fatigue as dependent variable and the mean DOP score, mean activity level and CIS score at baseline as predictors. Finally, all regression analyses were repeated with residualised instead of raw change scores. Significance in all analyses was assumed at $p< 0.05$. Statistical analysis was performed using SPSS version 12.0.

RESULTS

Pain symptoms at baseline All but one of the adult patients had one or more of the four CDC pain symptoms. All adolescent patients had one or more CDC pain symptoms. Table 1 shows the percentage of patients who reported at baseline that daily or several times a week they experienced muscle pain, headache, multi-joint pain or a sore throat.

The percentage of adult patients with pain at a location identified with the bodily outline of the MPQ is shown in Table 2. Seventy-three patients (78%) reported pain in two or more locations. The MPQ also assesses the duration of pain complaints in five categories: <1 year, 1–2 years, 2–3 years, 3–4 years or >4 years. In 53% of the patients, the pain complaints were present for more than 3 years. At baseline, 37% reported on the MPQ that they used pain medication.

Table 1. Percentage (and number) of CFS patients with pain symptoms daily or several times a week

Symptom	Adults (n=95[a]) with pain	Adolescents (n=32) with pain
Muscle pain	72 % (n=68)	60 % (n=19)
Headache	50 % (n=48)	75 % (n=24)
Multi-joint pain	58 % (n=55)	60 % (n=19)
Sore throat	17 % (n=16)	19 % (n= 6)

[a] for one adult patient there were no data of the pain assessment available

The effect of CBT on pain: comparison of recovered with non-recovered patients In both the adult and the adolescent CFS patients the DOP score decreased from baseline to post-treatment (Fig. 1). The difference in the mean change in DOP score of the recovered adult group (-2.01; 95% CI -2.62 to -1.39) and the non-recovered adults (-0.22; 95% CI -0.85 to 0.41) was statistically significant ($t= 3.74$, $d.f.= 93$, $p< 0.001$). In the adolescent

study, the mean change in DOP score of recovered patients (-3.76; 95% CI -5.69 to -1.84) was also significantly larger than that of non-recovered patients (0.14; 95% CI –0.77 to 1.04; t= 2.96, d.f.= 30, p= 0.006).

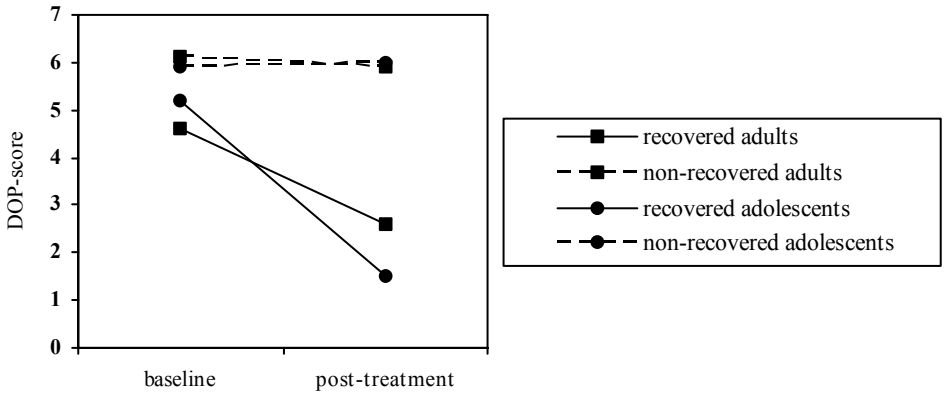

Fig. 1: Mean DOP score of adult and adolescent CFS patients before and after treatment

Fourteen out of the 21 recovered adolescent CFS patients (67%) had a pain level within the range of healthy controls after CBT. In the non-recovered adolescent group, four out of 11 reached this level (36%, χ^2= 2.694, d.f.= 1, p= 0.10). Significantly more recovered adults (36/63; 57%) than non-recovered adults (3/33; 9%) reached a normal pain level (χ^2= 20.73, d.f.= 1, p< 0.001).

Table 2. Percentage (number) of adult patients at baseline with pain on locations identified with the MPQ

Localisation	Adults (n=94[a]) with pain
Head	64% (n=60)
Neck and/or shoulders	61% (n=57)
Legs	56% (n=53)
Arms	48% (n=45)
Low back	34% (n=32)
Stomach	22% (n=21)
Chest	11% (n=10)

[a] for two adult patients there were no data of the MPQ at baseline available

The percentage of adult CFS patients with pain in locations identified with the MPQ at baseline did not differ significantly between recovered and non-recovered adults.

Following treatment, recovered patients reported significantly less pain in neck and/or shoulders, legs, arms and chest compared to non-recovered patients (see Table 3).

Table 3. Percentage of adult patients with pain on a specific location following CBT

Localisation	Recovered adults (%) (n=63)	Non-recovered adults (%) (n=33)	χ^2-value[a]	*p*-value
Head	29%	46%	2.74	0.098
Neck and/or shoulders	22%	55%	10.18	0.001
Legs	22%	52%	8.50	0.004
Arms	16%	46%	9.84	0.002
Low back	22%	30%	0.75	0.385
Stomach	10%	12%	0.16	0.692
Chest	0%	18%	12.22	<0.001

[a] χ^2-test

The effect of CBT on pain compared to a waiting list in the original adolescent study The original adolescent study was a randomised controlled trial in which CBT for CFS was compared with a waiting list condition.[11] We also calculated the DOP scores for all patients of the original study. In case of missing data, the last observation was carried forward. The difference in DOP score in the CBT group (n= 35) between baseline and second assessment was significantly greater than in the waiting list (n= 34) condition (-2.21, SD= 3.85 versus -0.36, SD= 2.19; t= -2.44, d.f.= 67, p= 0.017). Furthermore, at the second assessment there were significantly fewer patients in the waiting list with a pain level within the range of healthy controls (29%) than in the CBT condition (56%; χ^2= 4.38, d.f.= 1, p= 0.04).

Table 4. Change scores in scores of predictors after treatment

	Adults	t-value[a](d.f.)	*p*-value
Δ Fatigue (CIS)	-19.7 (14.1)	-13.6 (95)	<0.001
Δ Physical activity (actometer)	10.4 (21.3)	4.7 (94)	<0.001
Δ Body consciousness (BCS)	-0.7 (1.8)	-4.0 (95)	<0.001
Δ Negative affectivity (SCL-90[b])	-6.2 (8.4)	-7.5 (95)	<0.001
	Adolescents	t-value[a] (d.f.)	*p*-value
Δ Fatigue (CIS)	-24.3 (15.7)	- 8.7 (31)	<0.001
Δ Physical activity (actometer)	10.3 (21.7)	2.5 (27)	0.019
Δ Body consciousness (BCS)	-0.1 (1.8)	-0.5 (28)	0.780

[a]pairwise t-test [b]no data on the SCL90 available in adolescents

The mechanism of changes in pain In both adults and adolescents there was a significant decrease in fatigue and a significant increase in physical activity following treatment (see Table 4). In adults, body consciousness and negative affectivity decreased significantly. In adolescents, the decrease in body consciousness was not significant. A stepwise multiple regression with the baseline DOP score as covariate showed that the change in fatigue severity between baseline and post-treatment was significantly related to the decrease in the DOP score (see Table 5) of both adults and adolescents. The other change scores were not

related to the change in DOP score. We repeated the stepwise multiple regression but now used residualised change scores. This gave the same pattern of results. In adults the residual change score in fatigue was the only significant predictor of the change in pain (β= 0.61, p< 0.001; R^2 adjusted= 0.36). The residual change score in fatigue was also the only significant predictor of the change in pain in adolescents (β= 0.55, p= 0.002; R^2 adjusted= 0.28).

Table 5. Stepwise multiple regression with change in DOP score as dependent variable and baseline DOP score as covariate

	Adults (n=95[a])		Adolescents (n=28[a])	
	B	β	B	β
Constant	-2.59		-4.83	
Baseline DOP score	0.43	0.53**	0.72	0.69**
Δ Fatigue (CIS)	0.07	0.54**	0.13	0.45**
Not in equation				
Δ Physical activity (actometer)				
Δ Negative affectivity (SCL90)[b]				
Δ Body consciousness (BCS)				
R^2 Adjusted	0.46		0.54	

[a] data of one adult and four adolescents missing [b] no data on the SCL90 available in adolescents ** p<0.01

The predictive value of pain symptoms for treatment outcome Multiple regression showed that the DOP score at baseline was a significant predictor of the change in fatigue in adult patients (see Table 6). The regression with the residualised change in fatigue gave the same result (β DOP= –0.26, p= 0.011; R^2= 0.06). In adolescent CFS patients, DOP did not predict outcome (Table 6). This was also true when the residualised change in fatigue was used (β DOP = -0.09, p= 0.612). In all analyses the level of physical activity at baseline was not a predictor of the change in fatigue in both groups.

Table 6. Prediction of change in CIS-fatigue with DOP, CIS-fatigue and physical activity score at baseline

Predictor[a]	Adults (n=95[b])		Adolescents (n=31[b])	
	B	β	B	β
Constant	-17.64		11.62	
DOP	-1.35	-0.28**	-0.34	-0.08
CIS fatigue	0.81	0.30**	0.21	0.05
Physical activity score	0.06	0.09	0.05	0.08
R^2 adjusted	0.09		-0.09	

[a] multiple regression, method enter [b] in both groups the data of one person was missing ** P<0.01

DISCUSSION

The first objective of this study was to determine if an effective treatment of CFS with CBT leads to a reduction of pain symptoms. It was remarkable to find that a treatment aimed at reducing fatigue also had an effect on pain. Patients who recovered following CBT for CFS reported a reduction of pain severity. Furthermore, more recovered than non-recovered adults had a level of pain following treatment that is comparable to healthy controls. The results also showed that most adults report widespread pain before treatment and that after CBT the number of pain locations decreased in the recovered patients.

The second objective of the study was to look at possible mechanisms for the decrease in pain. Changes in physical activity, changes in negative affectivity or changes in body consciousness could not explain the decrease in pain severity. Only a relationship between the decrease in fatigue and the decrease in pain was found. This implies that pain in CFS is part of the syndrome and is directly related to chronic fatigue. It would be interesting to look at other variables that could explain the decrease in pain (and fatigue). Perhaps not focussing on bodily symptoms per se, but the negative labelling of those symptoms might be a more important factor. The role of catastrophising pain symptoms in the perception of pain has been extensively studied.[27] The role of catastrophising fatigue in CFS is largely unknown. It would be interesting to study the relationship between changes in the catastrophising of fatigue and pain in CFS and the reduction of these symptoms following CBT.

The third objective was to investigate the predictive value of pain severity for the outcome of CBT for CFS. Although the amount of variance explained was modest, pain severity at baseline was a significant predictor: a high pain severity at the start of the treatment was associated with a smaller decrease in fatigue. This was not the case in the group of adolescent patients, possibly because of the relatively small group size in the adolescent study, resulting in a lack of statistical power. Alternatively, pain symptoms in adolescents might be different from those in adults. However, the fact that the pattern of results after treatment was the same in both groups speaks against the latter explanation.

How can we understand that pain in CFS can be successfully treated with CBT and closely follows the decrease in fatigue while at the same time recognising that pain is a negative predictor of treatment outcome? A review by Cho et al[28] suggests that there is a possible distinction between CFS and chronic widespread pain (as in fibromyalgia) with only a partial overlap. One could assume that if pain in CFS patients becomes more severe, these patients become more comparable to patients with syndromes in which the chronic widespread pain is the central feature (like fibromyalgia). In those cases, interventions exclusively aimed at the fatigue do not seem sufficient to reach recovery. This would be in accordance with the finding of different alterations in hypothalamic-pituitary-adrenal axis (HPA axis) functioning between CFS, fibromyalgia and patients meeting criteria for both conditions.[28]

The fact that pain severity predicted therapy outcome suggests that a subset of CFS patients could possible benefit from additional interventions aimed at pain symptoms. A gradual

increase of physical activity and the reformulation of pain-related beliefs into more adaptive beliefs can be considered important elements of CBT for chronic pain.[29] Increasing physical activity is already an element of CBT for CFS. Additional interventions should be focused on the reformulation of pain-related cognitions, e.g., the catastrophising of pain or fear of pain.[27]

In this study, we wanted to know if a successful CBT would have an effect on pain symptoms. We only looked at the effect of a successful treatment of fatigue because clinical experience suggested that only then pain symptoms decrease. To generalise our findings to CBT for CFS in general (successful or not), we had to test whether the pain reduction in CBT for CFS is greater than in a control group in a randomised controlled trial. The original adolescent study was a randomised controlled trial and a comparison of the CBT group with the waiting list also showed that the decrease in pain severity following CBT for CFS was larger than in a non-treated control group. This confirmed the positive effect of CBT for CFS on pain symptoms. For adults no data were available of a controlled study with a no-treatment control group.

A weakness of our study is that the role of medication on pain symptoms could not be properly analysed. In the adult study, information about the type of medication and the dosage was missing, and for adolescent CFS patients information about pain medication was lacking entirely.

A second weakness of the study is that we did not correct the significance level for the number of hypotheses tested and/or the number of statistical analyses used to test the hypotheses. This increases the risk for type I errors. We think this is justified, as our study is explorative and one of the first to investigate the effect of CBT for CFS on pain. However, our findings have to be replicated.

The most clinical relevant finding of the present study is that pain symptoms improve following CBT for CFS. A possible clinical implication is that adding interventions aimed at the restructuring of pain-related cognitions, especially in adult CFS patients with higher pain scores, may increase the percentage of patients who benefit from CBT for CFS. Future research will have to show if this hypothesis is correct.

ACKNOWLEDGEMENTS

The authors thank Theo Fiselier for his contribution in the selection of adolescent CFS patients, Lammy Elving for her contribution in the selection of adult patients, and Ria te Winkel for assisting in data collection. Funding for the study of adolescent CFS patients was provided by the Children's Welfare Stamps Netherlands (Stichting Kinderpostzegels Nederland) and the ME Foundation (ME Stichting).

REFERENCES

1. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International chronic fatigue syndrome study group. Ann Intern Med 1994; 121: 953-9.
2. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38: 383-392.
3. King C, Jason LA. Improving the diagnostic criteria and procedures for chronic fatigue syndrome. Biol Psychol 2005; 68: 87-106.
4. Meeus M, Nijs J, De Meirleir K. Chronic musculoskeletal pain in patients with the chronic fatigue syndrome: a systematic review. Eur J Pain 2007; 11: 377-386.
5. Suraway C, Hackmann A, Hawton K, Sharpe M. Chronic fatigue syndrome: a cognitive approach. Behav Res Ther 1995; 33: 535-544.
6. Prins JB, Van der Meer JWM, Bleijenberg G. Chronic fatigue syndrome. Lancet 2006; 376: 346-55.
7. Vercoulen JHMM, Swanink CMA, Galama JMD, Fennis JFM, Jongen PJH, Hommes OR, et al. The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: the development of a model. J Psychosom Res 1998; 45: 507–517.
8. Prins JB, Bos E, Huibers MJ, Servaes P, van der Werf SP, van der Meer JW, et al. Social support and the persistence of complaints in chronic fatigue syndrome. Psychother Psychosom 2004; 73: 174-182.
9. Whiting P, Bagnall AM, Sowden AJ, Cornell JE, Mulrow CD, Ramirez G. Interventions for the treatment and management of chronic fatigue syndrome: a systematic review. J Am Med Assoc 2001; 286: 1360-8.
10. Chambers D, Bagnall A, Hempel S, Forbes C. Interventions for the treatment, management and rehabilitation of patients with chronic fatigue syndrome/myalgic encephalomyelitis: an updated systematic review. J Roy Soc Med 2006; 99: 506-520.
11. Stulemeijer M, de Jong LWAM, Fiselier TJW, Hoogveld SWB, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. Brit Med J 2005; 330: 7481-6.
12. Smith WB, Safer MA. Effects of present pain level on recall of chronic pain and medication use. Pain 1993; 55: 355-361.
13. Prins JB, Bleijenberg G, van der Meer JWM. Chronic fatigue syndrome and myalgic encephalomyelitis. Lancet 2002; 359: 1699.
14. Busch A, Schachter CL, Peloso PM, Bombardier C. Exercise for treating fibromyalgia syndrome. Cochrane Database of Systematic Reviews, Issue 2, 2002, Art. No: CD003786. DOI: 10.1002/14651858.CD003786.
15. Whiteside A, Hansen S, Chauduri A. Exercise lowers pain threshold in chronic fatigue syndrome. Pain 2005; 109: 497-9.
16. Knoop H, Bleijenberg G, Gielissen MFM, van der Meer JWM, White PD. Is a full recovery possible after cognitive behavioural therapy for chronic fatigue syndrome? Psychother Psychosom 2007; 76: 171-6.
17. Van der Werf SP, De Vree B, van der Meer JWM, Bleijenberg G. Natural course and predicting self-reported improvement in patients with a relatively short illness duration. J Psychosom Res 2003; 53: 749-753.
18. Prins JB, Bleijenberg G, Bazelmans E, Elving L, de Boo Th, Severens JL, et al. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. Lancet 2001; 357: 841-7.
19. Vercoulen JHMM, Alberts M, Bleijenberg G. De Checklist Individual Strength (CIS) (The Checklist Individual Strength). Gedragstherapie 1999; 32: 642-9.
20. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975; 1: 277-299.
21. Van der Kloot WA, Oostendorp RA, van der Meij J, van den Heuvel J. De Nederlandse versie van de McGill Pain Questionnaire: een betrouwbare vragenlijst. [The Dutch version of the McGill Pain Questionnaire: a reliable pain questionnaire]. Nederlands Tijdschrift voor Geneeskunde 1995; 139: 669-673.
22. Van der Werf SP, Prins JB, Vercoulen JHMM, van der Meer JWM, Bleijenberg G. Identifying physical activity patterns in chronic fatigue syndrome using actigraphic assessment. J Psychosom Res 2000; 49: 373-9.
23. Vercoulen JHMM, Bazelmans E, Swanink CMA, Fennis JFM, Galama JMD, Jongen PJH, et al. Physical activity in chronic fatigue syndrome: assessment and its role in fatigue. J Psychiat Res 1997; 31:661-3.

24. Arrindell WA, Ettema, H. Dimensional structure, reliability and validity of the Dutch version of the Symptom Checklist (SCL-90): data based on a phobic and "normal" population. Nederlands Tijdschrift voor de Psychologie en haar grensgebieden 1991; 36: 77-108.
25. Van der Werf SP, De Vree B, van der Meer JWM, Bleijenberg, G. (2002). The relationship between body consciousness, somatic symptoms report and information processing speed in chronic fatigue syndrome. Neurol Neuropsychology Behav Neurol 2002; 12: 12-15.
26. Bleijenberg G, Prins J, Bazelmans E. Cognitive behavioral therapies; in Jason LA, Fennell PA, Taylor RR (eds). Handbook of Chronic Fatigue Syndrome. New York, Wiley & Sons, 2003, pp 493-526.
27. Vlaeyen JWS, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain 2000; 85: 317-332.
28. Cho HJ, Skowera A, Cleare A, Wessely S. Chronic fatigue syndrome: an update focusing on phenomenology and pathophysiology. Curr Opin Psychiatr 2006; 19: 67-73.
29. Morley S, Eccleston C, Williams A. Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. Pain 1999; 80: 1-13.

3

The effect of cognitive behaviour therapy for chronic fatigue syndrome on self-reported cognitive impairments and neuropsychological test performance

Hans Knoop, Judith B. Prins, Maja Stulemeijer, Jos W.M. van der Meer, Gijs Bleijenberg.
Journal of Neurology, Neurosurgery and Psychiatry 2007; 78: 434-436

ABSTRACT

Background: Patients with chronic fatigue syndrome (CFS) often have concentration and memory problems. Neuropsychological test performance is impaired in at least a subgroup of patients with CFS. Cognitive behaviour therapy (CBT) for CFS leads to a reduction in fatigue and disabilities.

Aim: To test the hypothesis that CBT results in a reduction of self-reported cognitive impairment and in an improved neuropsychological test performance.

Methods: Data of two previous randomised controlled trials were used. One study compared CBT for adult patients with CFS with two control conditions. The second study compared CBT for adolescent patients with a waiting list condition. Self-reported cognitive impairment was assessed with questionnaires. Information speed was measured with simple and choice reaction time tasks. Adults also completed the symbol digit modalities task, a measure of complex attentional function.

Results: In both studies the level of self-reported cognitive impairment decreased significantly more after CBT than in the control conditions. Neuropsychological test performance did not improve.

Conclusions: CBT leads to a reduction in self-reported cognitive impairment, but not to improved neuropsychological test performance. The findings of this study support the idea that the distorted perception of cognitive processes is more central to CFS than actual cognitive performance.

INTRODUCTION

Chronic fatigue syndrome (CFS) is characterised by severe fatigue, lasting longer than 6 months and leading to functional impairment. The fatigue is not the result of a known organic disease or ongoing exertion, and not alleviated by rest. According to the Centre for Disease Control definition of CFS, impaired concentration and/or memory is an additional symptom criterion.[1] The level of self-reported cognitive impairments in CFS is high[2] and contributes to the social and occupational dysfunctions of patients with CFS.[3]

Studies evaluating neuropsychological functioning in patients with CFS with neuropsychological tests yielded conflicting results.[4] Reduced speed of (complex) information processing is the most consistently found impairment.[3 5 6] However, several studies found no cognitive impairments[7] and other studies identified a subset of patients with defective performance.[8 9]

Fatigue-related cognitions and behaviour can perpetuate CFS.[10] Several controlled trials have shown that cognitive behaviour therapy (CBT) aimed at these perpetuating factors leads to a reduction of fatigue and disabilities.[11]

The first hypothesis tested was that CBT for CFS also results in a reduction of self-reported cognitive impairments. The second hypothesis was that the neuropsychological test performance of patients with CFS improves after CBT. Data of two previous CBT trials[12 13] were used to test the hypotheses.

METHODS

Patients The first study from which data were used compared the effects of CBT for adults with CFS with natural course and support groups[12] in a multi centre randomised controlled trial. Assessments were done at baseline, and at 8 and 14 months. An intention-to-treat analysis showed a reduction in fatigue and functional impairment after CBT. In two of the three participating treatment centres, neuropsychological tests were part of the assessments. Consequently, data from neuropsychological test performance were available for a subset of 233 (78 CBT; 76 natural course; 79 support group) of the total group of 278 patients. The mean (SD) age of this group was 36.8 (10.2) years, 182 (78%) were female and median illness duration was 41 months. The second study was a randomised controlled trial comparing CBT for adolescents with CFS[13] with a waiting list condition. A total of 69 patients were randomly assigned to the conditions. Assessments were done at baseline and at 5 months. The results showed a greater decrease in fatigue and functional impairment in the CBT group. Neuropsychological data of 67 patients were available (33 CBT; 34 waiting list). The mean (SD) age of the group is 15.6 (1.3) years, 59 (88%) were female and median illness duration was 18 months.

Questionnaires assessing self-reported cognitive impairments

Checklist individual strength-concentration (CIS-conc) In both studies, the severity of concentration problems over the past 2 weeks was assessed with the subscale concentration of the checklist individual strength that consists of five items on a seven-point scale. The score can range between 5 and 35.[3 12 13]

Sickness Impact Profile-alertness behaviour (SIP-ab) In adults, the self observed effect of cognitive impairments on daily functioning was assessed with the subscale alertness behaviour of the sickness impact profile.[14] The subscale has 10 items, each item is weighed and the score can range between 0 and 777. No such instrument was available for adolescents.

Self-observation of cognitive impairment (SOCI) In adolescents, the frequency of cognitive impairments was determined with a structured diary. Patients rated both concentration and memory impairment separately on a daily self-observation list four times a day for 12 days (0= no impairment; 1=impaired). The percentage of concentration problems and memory problems (both number of assessments with a problem divided by 48 times 100) were added and then divided by two to calculate the mean percentage of incidents of cognitive impairment.

Neuropsychological tests

Reaction time task The reaction time task consisted of two subtests, simple and choice reaction time tasks. Both are described in detail elsewhere.[8 15] In a previous study, the reaction times of patients with CFS were slower than of healthy controls on both tasks.[8]

Symbol Digit Modalities Task (SDMT) The SDMT[16] was used in the adult study as a measure of complex attention. In previous studies CFS patients scored lower than a matched healthy control group.[8 9]

Statistical analysis Statistical analysis was performed using SPSS V.12.01. Significance was assumed at $p<0.05$. A multivariate analysis of variance was performed with self-reported cognitive impairment and reaction time as dependent variables and treatment as fixed factor. Univariate tests and post hoc analysis are reported if the multivariate test was significant. For the SDMT, a univariate analysis was performed, as data were available for a subset of 174 patients as the SDMT was added later to the test battery. In the adult study, the dependent variables were the change scores at 14 months from baseline and in the adolescent study, it was at 5 months from baseline. Reaction times were transformed by a logarithm transformation. For adults, if data at 14 months were missing and data 8-months post-treatment were available, the second were used. In all other cases, missing data were replaced with estimates derived by single imputation (missing variable analysis regression in SPSS with baseline value as predictor). For significant treatment effects, effect sizes were calculated.

RESULTS

Nineteen adult patients (8%) had missing CIS-conc and SIP-ab post-treatment data. One patient had missing data on both reaction time tasks at baseline, for 44 (19%) patients only baseline data were available and for 30 (17%) patients only a baseline SDMT score was available.

Two adolescent patients had no SOCI scores at baseline. For 4 (6%) patients the CIS-conc and SOCI at second assessment were missing. Two patients had no baseline reaction times and for 13 (20%) adolescents the reaction times at the second assessment were missing.

In both studies, there were more data missing from neuropsychological tests than from questionnaires because some patients were willing to mail the questionnaires, but refused to undergo a second neuropsychological assessment.

Self reported cognitive impairments

Adults The multivariate test (Pillai's trace) showed a significant change in self-reported cognitive impairments ($F_{(4,460)}$= 4.76; p= 0.001). The univariate tests showed a significant effect of treatment on the change in CIS-conc and SIP-ab ($F_{(2,230)}$= 8.94; p< 0.001 and $F_{(2,230)}$= 4.42; p= 0.013). Following CBT, the decrease in CIS was significantly greater than in both the natural course (p< 0.001) and the support group (p= 0.001; see Table 1). There was a significantly greater decrease in SIP-ab score following CBT compared to natural course (p= 0.004). The difference between CBT and support group failed to reach significance (p= 0.055).

Table 1. Estimated treatment effect in change score (95% CI) on the dependent variables

Self-reported cognitive impairments			
Adults	*CBT*	*Natural course*	*Support group*
CIS-conc	-7.4 (-9.1 to -5.7)†	-2.7 (-4.4 to -1.0)**	-3.4 (-5.1 to -1.8)**
SIP-ab	-116 (-156 to -76)‡	-31 (-72 to -10)**	-61 (-100 to -21)
Adolescents	*CBT*	*Waiting list*	
CIS-conc	-6.8 (-10.5 to -3.5)‡	-0.9 (-4.2 to +2.5)*	
SOCI	-7.9 (-12.8 to -2.9)§	0.9 (-4.1 to +6.0)*	
Neuropsychological test performance			
Adults	*CBT*	*Natural course*	*Support group*
Simple reaction time (ms)	9 (-9 to 27)	-5 (-23 to 14)	6 (-12 to 24)
Choice reaction time (ms)	-24 (-51 to 3)	-27 (-54 to 1)	-26 (-53 to 1)
SDMT	2.8 (0.8 to 4.8)	2.3 (0.2 to 4.4)	4 (2 to 6)
Adolescents	*CBT*	*Waiting list*	
Simple reaction time (ms)	-30 (-53 to -8)	-18 (-41 to 4)	
Choice reaction time (ms)	-12 ms (-29 to 6)	-10 (-28 to 8)	

CBT, cognitive behaviour therapy; CIS-conc, checklist individual strength-concentration; SDMT, symbol digit modalities task; SIP-ab, sickness impact profile-alertness behaviour; SOCI, self-observation of cognitive impairment. * significantly different from the CBT condition, p<0.05. **significantly different from the CBT condition, p<0.01. † Cohen's d based on change within treatment condition = 1.3. ‡Cohen's d = 0.6. § Cohen's d = 0.4.

Adolescents The multivariate test showed a significant treatment effect on self-reported cognitive impairments ($F_{(2,62)}$= 5.03; p= 0.009). Univariate tests showed that the decrease in the CIS-conc and SOCI score was significantly larger in the CBT group ($F_{(1,63)}$= 6.4; p= 0.014 and $F_{(1,63)}$= 6.28; p= 0.015).

Neuropsychological test performance

Adults There was no significant effect of treatment on either reaction time task ($F_{(4, 458)}$= 0.44; p= 0.783). There was no significant treatment effect on the SDMT ($F_{(2,171)}$=0.73; p= 0.484).

Adolescents Multivariate tests showed no significant treatment effect on either reaction time task ($F_{(2,62)}$= 0.34; p= 0.714).

DISCUSSION

The hypothesis that self-reported cognitive impairments decrease after CBT in patients with CFS was confirmed. Only one comparison in the adult study, measuring cognitive impairments more indirectly, showed an effect in the expected direction without reaching significance. The results of the original adolescent study[13] already indicated that concentration problems decrease after CBT. In that study, the concentration problems were assessed with a single item evaluating these problems retrospectively over a period of 6 months. This assessment can be easily influenced by situational circumstances and memory biases, which can be prevented by the use of a diary as in the present study. No support could be found for the hypothesis that neuropsychological test performance improves after CBT.

A methodological problem is that in a substantial part of the patients the neuropsychological data of the second assessment were missing. Furthermore, in our analysis we assumed that drop out occurred at random, whereas patients may drop out for non-random reasons. We repeated the analyses, but only on the patients who completed both assessments. Again, there was no significant treatment effect. Our interpretation is that this indicates that improvement in self-reported cognitive impairments after CBT is independent of the change in neuropsychological test performance.

A discrepancy between subjectively reported disabilities versus objectively measured performance is not limited to the current study. Mahurin et al[17] found that the objective cognitive functioning of monozygotic twins discordant for CFS did not differ, whereas the twin with CFS reported more cognitive impairments. Metzger and Denney[18] showed that patients with CFS underestimated their cognitive performance. In the study of Vercoulen et al[8] most patients with CFS reported concentration and memory problems, whereas only a small percentage showed an impaired performance. Given the fact that patients with CFS perceive their cognitive processes as impaired but underestimate their actual performance, one would expect that an effective treatment of CFS would lead to a more accurate perception of one's performance. The results of the present study are consistent with this prediction. CBT resulted in a decreased complaints about cognitive functioning, but not in a

change in performance. This is also in line with the hypothesis that a distorted perception of symptoms and performance is a crucial element of CFS.[10]

ACKNOWLEDGEMENTS

The authors thank Theo Fiselier for contributing to the selection of adolescent patients with CFS, Lammy Elving for contributing to the selection of adult patients and Ria te Winkel and Lida Nabuurs for assisting in data collection.

REFERENCES

1. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994; 121: 953-9.
2. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38: 383-392.
3. Michiel V, Cluydts R. Neuropsychological functioning in chronic fatigue syndrome: a review. Acta Psychiatr Scand 2001; 103: 84-93.
4. Cho HJ, Skowera A, Cleare A, Wessely S. Chronic fatigue syndrome: an update focusing in phenomenology and pathophysiology. Curr Opin Psychiatr 2006; 19: 67-73.
5. Moss-Morris R, Petrie KJ, Large RG, Kydd RR. Neuropsychological deficits in chronic fatigue syndrome: artefact or reality? J Neurol Neurosurg Psychiatry 1996; 60: 474-7.
6. Tiersky LA, Johnson SK, Lange G, Natelson BH, Deluca, J. The neuropsychology of chronic fatigue syndrome: a critical review. J Clin Exp Neuropsych 1997; 19: 560-586.
7. Dipino RK, Kane RL. Neurocognitive functioning in chronic fatigue syndrome. Neuropsychol Rev 1996; 6: 47-60.
8. Vercoulen JH, Bazelmans E, Swanink CM, Galama JM, Fennis JF, van der Meer JW, et al. Evaluating neuropsychological impairment in chronic fatigue syndrome. J Clin. Exp. Neuropsychol 1998; 20: 144-156.
9. Van der Werf SP, Prins JB, Jongen PJ, van der Meer JW, Bleijenberg G. Abnormal neuropsychological findings are not necessarily a sign of cerebral impairment: a matched comparison between chronic fatigue syndrome an multiple sclerosis. Neurol Neuropsychology Behav Neurol 2000; 13: 199-203.
10. Prins JB, Van der Meer JWM, Bleijenberg G. Chronic fatigue syndrome. Lancet 2006; 376: 346-355.
11. Whiting P, Bagnall AM, Sowden AJ, Cornell JE, Mulrow CD, Ramirez G. Interventions for the treatment and management of chronic fatigue syndrome: a systematic review. J Am Med Assoc 2001; 286: 1360-8.
12. Prins JB, Bleijenberg G, Bazelmans E, Elving L, de Boo Th, Severens JL, et al.. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. Lancet 2001; 357: 841-7.
13. Stulemeijer M, de Jong LWAM, Fiselier TJW, Hoogveld SWB, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. Brit Med J 2005; 330: 7481-6.
14. Berger M, Bobbit RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Med Care 1981; 19: 787-805.
15. Jolles J. Maastricht aging study: determinants of cognitive aging. Maastricht, Neuropsychological Publishers, 1995.
16. Stinnissen J, Willems PJ, Coetsier L, Hulsman WLL. Handleiding bij de Nederlandse bewerking van de WAIS [Manual of the Dutch edition of the WAIS.] Amsterdam: Swets and Zeitlinger, 1970.
17. Mahurin RK, Claypoole KH, Goldberg JH, Arguelles L, Ashton S, Buchwald D. Cognitive processing in monozygotic twins discordant for chronic fatigue syndrome. Neuropsychology 2004; 18: 232-9.
18. Metzger FA, Denney DR. Perception of cognitive performance in patients with chronic fatigue syndrome. Ann Behav Med 2002; 24: 106-112.

4

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

Marieke F.M. Gielissen, Hans Knoop, Petra Servaes, Joke S. Kalkman, Marcus J. Huibers, Stans Verhagen, Gijs Bleijenberg. Health and Quality of Life Outcomes 2007; 5: 36

ABSTRACT

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

Methods: 961 participants filled out the FQL (28 adjectives). A component and confirmatory factor analyses were performed and psychometric properties were evaluated. Differences on factor scores between different patients' groups were investigated and pre- and post treatment scores were compared in demonstrating change of perceptions after treatment of fatigue.

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

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

INTRODUCTION

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

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

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

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

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

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

METHODS

Materials

The Fatigue Quality List Researchers and clinicians working at the Expert Centre Chronic Fatigue of the Radboud University Nijmegen Medical Centre made a large list of all possible adjectives that can be used to characterize the feeling of fatigue. The FQL was

developed by asking researchers and health care professionals working with patients with unexplained fatigue complaints to indicate on this large list which of the adjectives best fitted with the experience of the fatigue described by their patients. The final list consisted of 28 adjectives most frequently mentioned by the raters.
In filling out the FQL, subjects are instructed to mark with a cross which of the 28 adjectives fit their experienced fatigue. Multiple answers are possible. In this study the Dutch version of the FQL was used. However, the adjectives were translated into English by a back-translation procedure.
Fatigue severity was measured by a subscale of the checklist individual strength (CIS-fatigue) consisting of 8 items.[14] Each item was scored on a 7-point Likert scale. High scores indicated a high level of fatigue severity. Based on research with CFS patients, a score of 35 or higher on the subscale fatigue severity indicated severe feelings of fatigue. Furthermore, the CIS has excellent psychometric properties.[1 11]

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

- 219 cancer survivors. Hundred-twenty-eight (mean age 44.8, SD= 8.9; female 72%) experienced severe chronic fatigue and 91 (mean age 46.5, SD= 6.3; female 100%) were not fatigued.[3] Forty-one of these cancer survivors were participating in a randomised control trial about the effectiveness of cognitive behaviour therapy (CBT) especially designed to reduce chronic fatigue in cancer survivors.[15] These patients filled out the FQL at pre- and post treatment.
- 160 patients who were diagnosed with CFS, according to the CDC criteria (mean age 38.0, SD= 10.7; female 69%).[4 16] Eighty-two CFS patients who were included in this study were treated for their chronic fatigue complaints with CBT.[4] These patients filled out the FQL two times, at pre- and post treatment.
- 151 employees on sick leave with unexplained fatigue complaints (mean age 44.0, SD= 8.4; female 55%).[17] Sixty-six (44%) of these met research criteria for CFS (mean age 42.9, SD= 8.6; female 61%).
- 276 patients with various neuromuscular disorders. Hundred-sixty-five experienced severe fatigue (mean age 42.2, SD= 10.6; female 48%) and 120 experienced no fatigue complaints (mean age 42.2, SD= 11.3; female 48%).[5 18]
- 77 patients who were diagnosed with pancreatitis. Fifty-three experienced severe fatigue (mean age 49.3, SD= 10.0; female 47%) and 24 were not fatigued (mean age 50.2, SD= 15.5; female 58%).
- 78 healthy persons who experienced no fatigue complaints (mean age 48.2, SD= 6.2; female 100%).[3]

Statistical analysis Data analysis was performed using SPSS (version 12.0.1). The total participant group was randomly divided into two groups. A principal component factor analysis was performed in the first group to identify independent factors. A varimax rotation was used to facilitate the interpretation. Furthermore, factor loadings had to be above .40 with a .10 or greater difference in loadings with the other factors. The scree test and the eigenvalues (above 1) were used to identify the number of factors. The factor model was then tested in the second group by using confirmatory factor analyses / AMOS 5.0 (Comparative Fit Index, Goodness of Fit Index, Adjusted Goodness of Fit Index).[19 20]
The internal consistency reliability for each factor was calculated using Cronbach's alpha. Spearman's rho correlations were used to evaluate psychometric properties of the FQL. To investigate the differences between the groups of patients Kruskal-Wallis tests were performed. When the Kruskal-Wallis test was significant, Mann-Whitney-U tests between the groups followed. The sensitivity to change of the FQL was demonstrated by comparing cancer survivors and CFS patients at pre- and post treatment assessment, using the Wilcoxon Signed Ranks Test of matched pairs. To correct for the multiple comparisons, p-value was set on < 0.01.

RESULTS

Factor solution Three of the 28 adjectives were marked with a cross for less than 10% and therefore excluded from further analyses. Final analyses were done with the remaining 25 adjectives. Table 1 presents the final factor solution in the first group (n= 476). Seven adjectives were excluded of factor analysis because factor loadings were $< .40$ and/or $<.10$ difference in loadings with the other factors. Both the scree test and eigenvalues indicated a 4-factor solution (Table 2). Factor 1 consisted of 5 adjectives, factor 2 of 4 adjectives, factor 3 of 5 adjectives and factor 4 of 4 adjectives, explaining respectively, 24%, 9%, 6%, 5% of the variance prior to rotation. After rotation the four factors explained respectively, 13%, 12%, 10% and 9% of the variance. Factor 1 was labelled as 'Frustrating', Factor 2 as 'Exhausting', Factor 3 as 'Pleasant' and Factor 4 as 'Frightening'. This four factor model was then tested in the second group (n=485) by using confirmatory factor analysis. The fit indices indicated an adequate fit. Chi-square (129, n= 485) = 364.5, $p < 0.001$; Comparative Fit Index = .87; Goodness of Fit Index = .92; Adjusted Goodness of Fit Index = .90.
The four factors were recoded on a 0 to 100 scale, facilitating comparisons between the factors. Higher scores indicate a higher appraisal of the fatigue experience as frustrating, exhausting, pleasant and frightening. The final version of the FQL and the criteria for scoring are presented in appendix A.

Is the FQL a reliable and valid instrument to assess different perceptions of fatigue? For each factor the internal consistency reliability was calculated in the entire sample of 961 participants, which demonstrated moderate to adequate internal consistencies for all four factors, ranging from .57 to .79 (Table 1).

Table 1. Final factor solution: principal-components analysis with varimax-rotation in the first group. Cronbach's Alpha of the four factors

	Frustrating	Exhausting	Pleasant	Frightening
Discouraging	0.735			
Incessant	0.585			
Annoying	0.680			
Persistent	0.559			
Frustrating	0.704			
Exhausting		0.690		
Wearisome		0.537		
Extreme		0.724		
Unbearable		0.509		
Temporary			0.400	
Relaxing			0.661	
Fulfilling			0.713	
Normal			0.522	
Pleasant			0.792	
Upsetting				0.727
Frightening				0.618
Inexplicable				0.490
Insuperable				0.444
Cronbach's Alpha	0.79	0.68	0.61	0.57

Three adjectives were excluded of factor analysis because they were marked with a cross for less than 10%: Protective, Soothing, Threatening. Seven adjectives were excluded of factor analysis because factor loadings <.40 and/or <.10 difference in loadings with the other factors: Demanding, Paralysing, Aggravating, Compelling, Treacherous, Insoluble, Acceptable

Supporting convergent validity we found that all four factors were statistically significant related to fatigue severity (CIS-fatigue) (Table 3).

In calculating general psychometric properties statistically significant intercorrelations between the four factors were found (Table 3). Additionally, low correlations were found between the four factors and age and gender, explaining less than 3% of the variance.

Table 2. Principal-components analysis with varimax-rotation, initial eigenvalues

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

Table 3. Convergent validity of the 4 factors. Spearman's rho correlation in total group (N= 961)

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

* $p < 0.01$

Are the perceptions of fatigue different between several patient groups with and without chronic fatigue complaints and healthy controls? The non-fatigued groups scored significantly lower on Frustrating, Exhausting and Frightening and significantly higher on Pleasant compared with the fatigued groups (Table 4). The following analyses were performed separately in the fatigued groups and the non-fatigued groups.

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

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

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

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

Exhausting The non-fatigued patients with various neuromuscular disorders scored significantly lower on Exhausting than the non-fatigued cancer survivors and the non-fatigued patients with pancreatitis. Between the fatigued groups, CFS patients scored significantly higher on Exhausting than the other groups. Furthermore, fatigued patients with pancreatitis scored significantly lower with respect to fatigued cancer survivors and employees with unexplained fatigue. Additionally, patients with neuromuscular disorders scored significantly lower than employees with unexplained fatigue.
Pleasant In the non-fatigued group patients with various neuromuscular disorders scored significantly lower on Pleasant than non-fatigued cancer survivors and healthy persons. In the fatigued group employees with unexplained fatigue scored significantly lower on Pleasant than the other groups. CFS patients scored significantly lower than cancer survivors and patients with neuromuscular disorders.
Frightening The scores on Frightening in the non-fatigued groups were similar. In the fatigued groups a dichotomy was found between the patients with unexplained fatigue with and without a chronic disease. Fatigued patients without a chronic disease (cancer survivors, CFS patients and employees) scored significantly higher on Frightening than fatigued patients with a chronic disease (patients with a neuromuscular disorder or pancreatitis).

Table 5. Comparison of pre- and post treatment scores on the four factors. Comparison of the post treatment scores with those of healthy individuals

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

CBT = cognitive behaviour therapy * significant difference between pre- and post treatment scores, Wilcoxon signed rank test $p<0.01$ a. significantly different from post treatment scores of group A, Mann-Whitney-U test $p<0.01$ b. significantly different from post treatment scores of group B, Mann-Whitney-U test $p< 0.01$ c. significantly different from post treatment scores of group C, Mann-Whitney-U test $p< 0.01$ d. significantly different from post treatment scores of group D, Mann-Whitney-U test $p< 0.01$

Do perceptions of fatigue change in patients who recover after treatment for fatigue?
Forty-one fatigued cancer survivors and eighty-two CFS patients were treated for their fatigue complaints with CBT at our department and filled out the FQL at pre- and post

treatment. Sensitivity to change of the FQL was demonstrated by dividing the CFS patients and the cancer survivors into two groups: patients who were completely recovered after CBT (CIS-fatigue < 35) and patients who remained fatigued after CBT (CIS-fatigue >=35). Baseline scores on the four factors were not significantly different between patients who recovered and patients who remained fatigued. The scores on the four factors at pre- and post treatment were compared. Additionally, we compared the post treatment scores on the four factors with the scores of healthy individuals (Table 5). Cancer survivors who were completely recovered after CBT (n= 27) showed a significant decrease on the factors Frustrating, Exhausting and Frightening and a significant increase on the factor Pleasant. The post-treatment scores were not significantly different from those of healthy individuals. In contrast, the cancer survivors who still remained fatigued after CBT (n=14) did not show a change in the scores on the four factors from pre- to post treatment. Furthermore, their scores at post treatment were significantly different from the scores of healthy individuals. In investigating CFS patients who recovered after CBT (n= 47) the same pattern was found. They also decreased significantly on the factors Frustrating, Exhausting and Frightening and increased significantly on the factor Pleasant. The scores at post treatment were not significantly different from those of healthy individuals. CFS patients who were not recovered after CBT (n= 35) showed no change between pre- and post treatment scores on the factors Frustrating, Exhausting and Pleasant. Although a significant decrease was seen on the factor Frightening, the post treatment scores of the four factors were significantly different form those of healthy individuals.

DISCUSSION

The present study shows that the FQL provides a self report instrument that assesses the perceptions of fatigue. The FQL consists of four coherent factors, namely Frustrating, Exhausting, Pleasant and Frightening. The stable pattern of these factors was indicated with a confirmatory factor analyses, revealing an invariant internal structure in a second group of patients. Furthermore, the data of this study show that the FQL has adequate psychometric properties. Both the intercorrelations and the correlations of the four factors with the subscale CIS-fatigue were not to the extent that the factors could be seen as a parallel test, thus supporting the relative uniqueness of each factor.

The assumption that fatigue is experienced differently by everybody is confirmed with the data of this study. Severely fatigued patients had different perceptions of fatigue compared to healthy individuals. The healthy persons described fatigue as temporary, relaxing, fulfilling, normal and pleasant. None of these adjectives were chosen by 70% of the severely fatigued patients. Even patients with similar fatigue severity, appreciated fatigued differently. Different patterns were seen on the four factors of the FQL between the different populations of patients experiencing fatigue. CFS patients and severely fatigued employees had the highest score on the factors Frustrating, Exhausting and Frightening and also the lowest score on the factor Pleasant in contrast with the other fatigued groups. Until now the underlying aetiology of CFS still remains unclear.[21 22] Because the patients can not

attribute their fatigue to a distinct cause, it's possible that they are more focussed on their fatigue and perceive their fatigue in a more negative way than the other groups. In agreement with this finding, Moss-Morris et al[23] found that CFS patients had a more negative view about their symptoms than patients with Rheumatoid arthritis (RA). Additionally, Taillefer et al[24] found higher levels of illness worry in CFS patients than MS patients who were fatigued. Results of the FQL also showed that patients with a current chronic disease experience their fatigue as less frightening than patients with no current or a past disease. It is possible that these patients attribute their fatigue to their illness and therefore perceive it as less frightening. Cancer survivors may experience fatigue as highly anxiety provoking because they can see fatigue as a symptom for disease-recurrence. Therefore fatigue can be labelled as frightening.[25] Future research is necessary to examine if the FQL is applicable for individual assessment and furthermore investigate what the effect of these different perceptions is on the management of fatigue complaints in the clinical practice.

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

REFERENCES

1. Vercoulen JHHM, Swanink CMA, Fennis JFM, Galama JMD, van der Meer JWM, Bleijenberg G. Dimensional assessment of Chronic Fatigue Syndrome. J Psychosom Res 1994; 38: 383-392.
2. Vercoulen JHMM, Hommes OR, Swanink CMA, Jongen PJH, Fennis JFM, Galama JMD, et al. The measurement of fatigue in multiple sclerosis: a comparison with patients with chronic fatigue syndrome and healthy subjects. Arch Neurol 1996; 53: 642-9.
3. Servaes P,Verhagen C, Bleijenberg G. Determinants of chronic fatigue in disease-free breast cancer patients, a cross-sectional study. Ann Onco 2002; 13: 589-598.
4. Prins JB, Bleijenberg G, Bazelmans E, Elving L, de Boo Th, Severens JL, et al. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. Lancet 2001; 357: 841-7.
5. Kalkman JS, Schillings ML, van der Werf SP, Zwarts MJ, van Engelen BGM, Bleijenberg G. Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I. J Neurol Neurosurg Psychiatry 2005; 76: 1406-9.
6. van der Werf SP, van den Broek H, Anten H, Bleijenberg G. The experience of severe fatigue long after stroke and its relation with depressive symptoms and disease characteristics. Eur Neurol 2001; 45:6-12.
7. Servaes P, Prins J, Verhagen C, Bleijenberg G. Fatigue after breast cancer and in chronic fatigue syndrome:

similarities and differences. J Psychosom Res 2002; 52: 451-7.
8. Cooper L. Myalgic. Encephalomyelitis and the medical encounter. Sociol Health Ill 1997, 19: 17-37.
9. Fitzgibbon EJ, Murphy EJ, O'Shea K, Kelleher C. Chronic debilitating fatigue in Irish general practice: A survey of general practitioners experience. Brit J Gen Pract 1997; 47: 618-622.
10. Deale A, Wessely S. Patient's perceptions of medical care in chronic fatigue syndrome. Soc Sci Med 2001; 52: 1859-1864.
11. Dittner AJ, Wessely SW, Brown RG. The assessment of fatigue. A practical guide for clinicians and researchers. J Psychosomatic Res 2004 ; 56: 157-170.
12. Melzack R, Torgerson WS. On the language of pain. Anesthesiology 1971; 34: 50-9.
13. Melzack R. The McGill Pain Questionnaire: from description to measurement. Anesthesiology 2005; 103: 199-202.
14. Vercoulen JHMM, Alberts M, Bleijenberg G. De Checklist Individual Strength (CIS). Gedragstherapie 1999; 32:131-6.
15. Gielissen MFM, Verhagen C, Witjes JA, Bleijenberg G. Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: a randomized controlled trial. J Clin Oncol 2006; 23: 4882-7.
16. Brouwers FM, van der Werf S, Bleijenberg G, van der Zee L, van der Meer JWM. The effect of a polynutrient supplement on fatigue and physical activity of patients with chronic fatigue syndrome-a double blind randomized controlled trial. Q J Med 2002; 95: 677-683.
17. Huibers MJH, Beurskens AJHM., van Schayck CP, Bazelmans E, Metsemakers JFM, Knottnerus JA, et al. Efficacy of cognitive-behavioural therapy by general practitioners for unexplained fatigue among employees: randomised controlled trial. Br J Psychiatry 2004; 184: 240-6.
18. Van der Werf SP, van Engelen B, Kalkman J, Schillings M, Jongen P, Zwarts M, et al. Fatigue in neuromuscular diseases, a comparison with multiple sclerosis. In: Van der Werf SP, Determinants and consequences of experienced fatigue in chronic fatigue syndrome and neurological conditions. Dissertation KUN, February 2003. http://webdoc.ubn.kun.nl/mono/w/werf_s_van_der/deteancoo.pdf
19. Arbuckle JL. Amos 4.0. User's guide. Chicago, IL: SmallWaters Corporation, 1994.
20. Masedo AI, Esteve R. Some empirical evidence regarding the validity of the Spanish Version of the McGill Pain Questionnaire (MPQ-SV). Pain 2000; 85: 451-6.
21. Prins JB, van der Meer JWM, Bleijenberg G. Review: Chronic fatigue syndrome. Lancet 2006; 367: 346-355.
22. Cho HJ, Skowera A, Cleare A, Wessely S. Chronic fatigue syndrome: an update focusing on phenomenology and pathophysiology. Curr Opin Psychiatry 2006; 19: 67-73.
23. Moss-Morris R, Chalder T. Illness perceptions and levels of disability in patients with chronic fatigue syndrome and rheumatoid arthritis. J Psychosom Res 2003; 54: 331-7.
24. Taillefer SS, Kirmayer LJ, Robbines JM, Lasry JC. Correlates of illness worry in chronic fatigue syndrome. J Psychosom Res 2003; 55:305-8.
25. Gil KM, Mishel MH, Belyea M, Germino B, Porter LS, LaNey IC, et al. Triggers of uncertainty about recurrence and long-term treatment side effects in older African American and Caucasian breast cancer survivors. Onco Nurs Forum 2004; 31: 633-9.
26. Knoop H, Bleijenberg G, Gielissen MFM, Van der Meer JWM, White PD. Is a full recovery possible after cognitive behavioural therapy for chronic fatigue syndrome? Psychother Psychosom 2007; 76: 171-6.

Appendix A

FATIGUE QUALITY LIST - FQL

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

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

Upsetting	Persistent
Discouraging	Frustrating
Temporary	Relaxing
Exhausting	Inexplicable
Incessant	Fulfilling
Wearisome	insuperable
Frightening	Unbearable
Annoying	Normal
Extreme	Pleasant

Scoring FQL

The scoring for the adjectives is:

20	25
Discouraging	Upsetting
Temporary	Exhausting
Incessant	Wearisome
Annoying	Frightening
Persistent	Extreme
Frustrating	Inexplicable
Relaxing	Insuperable
Fulfilling	Unbearable
Normal	
Pleasant	

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

Factor 1: Frustrating	adjectives: discouraging, incessant, annoying, persistent, frustrating
Factor 2: Exhausting	adjectives: exhausting, wearisome, extreme, unbearable
Factor 3: Pleasant	adjectives: temporary, relaxing, fulfilling, normal, pleasant
Factor 4: Frightening	adjectives: upsetting, frightening, inexplicable, insuperable

5

Is a full recovery possible after cognitive behavioural therapy for chronic fatigue syndrome?

Hans Knoop, Gijs Bleijenberg, Marieke F.M. Gielissen, Jos W.M. van der Meer, Peter D. White. Psychotherapy and Psychosomatics 2007; 76: 171-176

ABSTRACT

Background: Cognitive behaviour therapy (CBT) for chronic fatigue syndrome (CFS) leads to a decrease in symptoms and disabilities. There is controversy about the nature of the change following treatment; some suggest that patients improve by learning to adapt to a chronic condition, others think that recovery is possible. The objective of this study was to find out whether recovery from CFS is possible after CBT.

Methods: The outcome of a cohort of 96 patients treated for CFS with CBT was studied. The definition of recovery was based on the absence of the criteria for CFS set up by the Center for Disease Control (CDC), but also took into account the perception of the patients' fatigue and their own health. Data from healthy population norms were used in calculating conservative thresholds for recovery.

Results: After treatment, 69% of the patients no longer met the CDC criteria for CFS. The percentage of recovered patients depended on the criteria used for recovery. Using the most comprehensive definition of recovery, 23% of the patients fully recovered. Fewer patients with a co-morbid medical condition recovered.

Conclusion: Significant improvement following CBT is probable and a full recovery is possible. Sharing this information with patients can raise the expectations of the treatment, which may enhance outcomes without raising false hopes.

INTRODUCTION

Between 50 and 70% of the patients show a significant reduction of symptoms and disabilities after cognitive behaviour therapy (CBT) for chronic fatigue syndrome (CFS).[1 2] The nature of this improvement is uncertain. Some suggest that patients improve by adapting better to a chronic condition, while others think that recovery is possible.[3] This debate shows some similarities to the issue of recovery from mood disorders.[4 5]

The attitude of the therapist towards the treatment goals will affect the expectations and perceptions of the patient. If learning to cope with CFS is the jointly agreed maximal goal of treatment, patients will engage with treatment accordingly. If the therapist suggests that recovery is possible, the patient expectations are raised, which in turn may lead to a change in the perception of symptoms as well as disability. This is also the essence of the placebo response. The placebo response of CFS patients to psychological interventions is lower than that related to biomedical interventions and lower than that expected in other medical conditions[6], suggesting that CFS patients are sceptical of psychological interventions. Since the communication of the aim of a treatment is an intervention that can facilitate change[7], the controversy about the nature of improvement is clinically important.

To find out the tenable goal of therapy – adaptation or recovery – a definition of recovery is needed that can be operationalized and measured. We propose that a definition is used that closely follows the Center for Disease Control (CDC) criteria for CFS.[8] Two key elements of the CDC criteria are that a patient is severely fatigued and disabled. Recovery then implies that the patient's level of fatigue is within the range of healthy controls. We propose operationalizing this criterion as scoring *within the range of the mean plus (or minus) 1 standard deviation (SD)* of the healthy population.

A second aspect of recovery is that a patient will no longer be disabled. This means that patients have no physical disabilities – an often used criterion in CFS – and no disabilities in any other domains of functioning. Again, we propose scoring within the range of the mean plus 1 SD of the healthy population as the criterion for recovery. Although patients who are no longer abnormally fatigued *or* disabled do not meet the CDC criteria for CFS, having a 'normal' level of fatigue *and* not being disabled is a more satisfactory definition of recovery.

For complete recovery the perception of the patient also has to change. The patient has to perceive his fatigue and functioning as both normal and comparable to healthy people. Finally, a comprehensive definition combines changes in fatigue, disability and perception.

The objective of this study was to find out whether recovery is possible after CBT. For this, we collected data from a cohort of patients treated with CBT. For comparison we used healthy population norms. By doing this, we assumed that CFS was the only health problem of the patients. However, it is possible that the patient had another medical condition beside CFS, causing disability. Therefore, we measured the confounding effect of co-morbid medical conditions on the outcome.

METHODS

Subjects All consecutive patients with CFS that were treated with CBT at the Radboud University Nijmegen Medical Centre between September 2003 and May 2005 were eligible for the study if they met the following inclusion criteria:

1. CDC criteria for CFS[8];
2. severely fatigued and functionally impaired, defined by a cut-off score of 35 or higher on the fatigue severity subscale of the Checklist Individual Strength (CIS-fatigue)[9] and a weighted score of 700 or higher on the Sickness Impact Profile (SIP) scale[10];
3. completed the pre- and post-treatment assessment.

If a medical co-morbidity was present which could not explain the fatigue, it was registered for further analyses.

Intervention All patients received CBT for CFS according to a protocol described elsewhere.[11]

Assessment The assessment was part of the clinical routine and performed by research assistants not involved in the treatment.

Self-Reported Improvement Self-rated improvement was measured after treatment by one question: patients indicated whether they had no symptoms, significantly fewer symptoms, the same complaints or whether the symptoms had become worse.[12]

Fatigue The different definitions of recovery are summarized in Table 1. The CIS-fatigue indicates the level of experienced fatigue over the past 2-week period and consists of 8 items on a 7-point scale. The score can range between 8 and 56.[9] A normal group of 53 healthy adults with a mean age of 37.1 (SD= 11.5) has a mean score on the CIS-fatigue of 17.3 (SD= 10.1). Using this as a reference for the CBT group, there resulted a threshold score of 27, the mean plus 1 SD.[13]

Disabilities Physical disabilities were measured with the 'physical functioning' subscale of the Medical Outcomes Survey Short Form-36 (SF-36).[14] [15] The scores range from 0 (maximum physical limitations) to 100 (ability to do vigorous activity). Healthy adults without a chronic condition[16] were used as a norm group, with a mean score of 93.1 (SD= 11.7). A patient had to score 80 or higher to be considered as recovered.

Social functioning was measured with the subscale 'social functioning' of the SF-36, ranging between 0 (no social activities) and 100 (normal participation in social activities). Using the same criterion and reference group as above resulted in a threshold score for recovery of 75 or higher.

The SIP measures functional disability in ambulation, home management, mobility, alertness behaviour, sleep/rest, work limitations, social interactions, recreation and pastimes. The eight subscales were added to provide one weighted score of disability (SIP8 total). The mean SIP8 total score of a healthy group of 78 women is 65.5 (SD= 137.8).[17]

Recovery was defined as scoring the same or lower than the mean plus 1 SD of this reference group, i.e. scoring 203 or lower.

Combining Fatigue and Disabilities This definition of recovery was operationalized by combining cut-off scores on SF-36 physical functioning and the CIS-fatigue.

Perception of Health and Fatigue Health perception was assessed with the scale 'general health perception' of the SF-36. This scale measures the evaluation of the health status by a patient, with scores ranging between 0 and 100. The mean in the reference group was 80 (SD= 14.5) resulting in a cut-off score of 65.[16]

The perception of fatigue was assessed with the Fatigue Quality List (FQL). The FQL consists of 18 adjectives and patients pick which adjectives best fit their experience of fatigue. Factor analysis showed a 4-factor solution; 3 of the 4 factors have negative connotations of fatigue: 'frustrating', 'exhausting' and 'frightening'. About 97% of the untreated CFS patients scored on 1 or more of the 3 factors [Gielissen et al, unpubl. data]. Recovery was defined as no longer scoring on any of the 3 negative factors.

Combining Fatigue, Disabilities and Perception This comprehensive definition of recovery was operationalized by combining the cut-off scores on the CIS-fatigue, the SF-36 scales of physical functioning and social disabilities, the general health perception and the FQL.

Table 1. Operationalization of the different definitions of recovery

Definition of recovery	Measure	Criterion used	Cut-off
Level of fatigue comparable to healthy people	CIS-fatigue	Mean + 1 SD	≤27
No physical disability	SF-36 physical	Mean – 1 SD	≥80
No social disability	SF-36 social	Mean – 1 SD	≥75
No disabilities in all domains	SIP8 total	Mean + 1 SD	≤203
Normal fatigue and no physical disability	CIS-fatigue/SF-36 physical	Mean + 1 SD/– 1 SD	≤27, ≥80
Normal health perception	SF-36 general health	Mean – 1 SD	≥65
No negative perception of fatigue	FQL	Factor score neg.= 0	
Combining criteria of			
Fatigue	CIS-fatigue	Mean + 1 SD	≤27
Physical and social disabilities	SF-36 physical and social	Mean – 1 SD	≥80, ≥75
Perception of health	SF-36 general health	Mean – 1 SD	≥65
Perception of fatigue	FQL	Factor score neg.= 0	

Mean = Mean of healthy norm group.

RESULTS

Baseline data Of the 112 CFS patients with a pre-treatment assessment, 3 (3%) did not start with CBT. There were 13 drop-outs (11% of the patients starting with therapy) during treatment, so 96 patients completed the pre- and post-treatment assessment. The mean age of this group was 37.0 years (SD= 11.5). Seventy-three patients were women (76%). The mean duration of the illness was 70.8 months (range= 12–276 months, SD= 52.8).

Treatment results Table 2 shows the scores of the patients before and after treatment. Following treatment, 73 (77%) of the 95 patients, who rated their improvement (data were missing for 1 patient), reported that they had no or significantly fewer symptoms. There was a significant decrease in CIS-fatigue and patients also reported significantly fewer disabilities on the SF-36 subscale physical functioning and the SIP8. In total, 66 patients (69%) no longer met the inclusion criteria for fatigue severity and the level of disabilities (SIP8 ≥700).

Table 2. Pre- and post-treatment scores of CIS-fatigue, SF-36 physical and SIP8 (n= 96)

	Pre-treatment mean	Post-treatment mean	Treatment effect	95% CI	t value	d.f.	*p*-value
Self-rated improvement		77%					
CIS-fatigue	50.0 ± 5.2	30.3 ± 14.0	–19.7	–16.8 to –22.6	–13.6	95	<0.001
SF-36 physical	51.8 ± 19.1	76.3 ± 23.0	24.5	19.1 to 29.8	9.1	94	<0.001
SIP8 total	1,448 ± 510	682 ± 619	–766	–631 to – 900	–11.3	95	<0.001

t values assessed by pairwise t test.

Full recovery as outcome The percentage of recovered patients was determined for all criteria and ranged between 23 and 59% (Table 3).

Table 3. Percentage of patients (n= 96) who meet the definitions of recovery following CBT

Definition of recovery	Criterion reached, %
Level of fatigue comparable to healthy people	48
No physical disability	59
No social disability	55
No disabilities in all domains	26
Normal level of fatigue *and* no physical disability	44
Normal health perception	54
No negative perception of fatigue	37
Combining criteria of fatigue, disabilities and perception of health and fatigue	23

The effect of medical co-morbidity Twenty-two of the 96 patients (23%) had a medical co-morbid condition beside CFS. Fifteen patients had one medical co-morbidity: treated hyperthyroidism, gonadal dysgenesis with normal karyotype, menorrhagia, controlled diabetes mellitus, quiescent ulcerative colitis, nephrotic syndrome, controlled asthma, allergy (2), recurrent sinusitis, epilepsy, migraine, periodic leg movement disorder, multiple traumas, intramedullary haemangioma on medication. Seven patients had two co-morbidities: treated hyperthyroidism and epilepsy, controlled diabetes mellitus and Forestier's disease, controlled asthma and chronic low back pain (2), allergy and treated sleep apnoea, single transient ischaemic attack and cervical arthrosis, chronic headache and treated high blood pressure. After CBT, patients with medical co-morbidity had a mean CIS-fatigue score of 35.8 (SD= 13.7) compared to a mean CIS-fatigue score of 28.6 (SD= 14.0) for the group without (t= 2.15, d.f.= 94, p= 0.034). The group with medical co-morbidity also had more SIP disabilities following CBT, compared to the group without co-morbidity (t= 2.22, d.f.= 94, p= 0.029). The SIP8 total mean scores were 934 (SD= 563) and 607 (SD= 739), respectively. The SF-36 physical functioning following treatment was lower in the group with co-morbidity (mean of 66 (SD= 27.9) and 80 (SD= 20.4), respectively; t= 2.46, d.f.= 94, p= 0.016). Fewer patients with medical co-morbidity recovered (Table 4). For social disability, the perception of fatigue, and the combination of all criteria for recovery, the difference in the proportions of recovered patients failed to reach statistical significance.

Table 4. Percentage of recovered patients following CBT with (n= 22) and without (n= 74) medical co-morbidity

Definition of recovery	No co-morbidity %	Co-morbidity %	Z value	*p*-value
Level of fatigue comparable to healthy people	55	23	–2.68	0.007
No physical disability	65	41	–2.00	0.046
No social disability	59	50	–0.56	0.578
No disabilities in all domains	31	19	–2.05	0.040
Normal level of fatigue *and* no physical disability	50	23	–2.25	0.024
Normal health perception	58	41	–1.41	0.157
No negative perception of fatigue	41	23	–1.52	0.129
Combining criteria of fatigue, disabilities and perception of health and fatigue	29	12	–1.17	0.241

Z values determined by the Mann-Whitney U test.

DISCUSSION

More than 70% of the CFS patients reported significantly fewer symptoms following treatment with CBT and roughly 70% no longer met the CDC criteria for CFS. This favourable outcome is consistent with the results of earlier controlled studies.[1 2]

Improvement and not meeting research criteria for an illness are different from recovering.[18 19] To examine if recovery was possible we used different definitions of

recovery that encompassed three elements: no longer being severely fatigued, being able to resume all activities, and a perception of health and fatigue that is similar to the perception of healthy persons. Depending on the definition used, up to 59% of the patients recovered. Even if we used the most conservative definition of recovery, 23% fully recovered. We therefore conclude that recovery from CFS following CBT is possible.

In the absence of a control treatment group, it is difficult to attribute this effect to treatment with certainty. A comparison with the natural course of CFS provides some useful information. In a review[20] that used less stringent criteria for recovery, the median recovery rate without treatment was 5% of the patients meeting operational criteria for CFS. As expected, the recovery rates following CBT found in this study were substantially higher. Our study was only concerned with the short-term effects of treatment. The only controlled study investigating the long-term efficacy of CBT for CFS showed lasting benefits 5 years after treatment.[21]

Some may argue that it is not possible to recover from CFS and that our recovered patients were misdiagnosed. We found no evidence to support this, with all patients meeting CDC criteria for CFS. Ninety-one of our 96 patients complained of post-exertional malaise, which some suggest is the main characteristic feature of CFS.[22]

The criteria for recovery were based on healthy norms. Patients had to score within the range of the mean plus or minus 1 SD. The norm groups were selected for their good health. Assuming a normal distribution, this means that 15% of the healthy subjects (scoring between 1 and 2 SD beyond the mean) had a score that would be considered as deviant from the norm in the present study. One could say that a patient meeting these criteria not only recovered from CFS, but is also more healthy than a substantial part of the healthy general public. Thus, the effect of CBT may be underestimated.

In determining the threshold scores for recovery we assumed a normal distribution of scores. However, in the healthy population the SIP and SF-36 scores were not normally distributed. Therefore one could argue that recovery according to the SIP8 has to be defined as scoring the same or lower than the 85th percentile of the healthy reference group. In that case, the recovery rate using the definition of having no disabilities in all domains (i.e. scoring the same or lower than the 85th percentile on the SIP8) would decrease from 26 to 20%. As we do not know the exact distribution of the SF-36 scores, we cannot control for the effects of violation of the assumption of normality.

Patients with medical co-morbidities had significantly higher levels of disabilities after treatment. This implies that less stringent criteria for recovery should be used that incorporate the effect of the co-morbidity. Using healthy adults as a reference group will lead to an underestimation of the effect of CBT in those with medical co-morbid conditions.

The fact that fatigue, disability and health can return to a ‘normal’ level following treatment is a promising finding. Keeping in mind that most patients suffered several years of ill health, it is remarkable that such a change in perception can take place. These results suggest that recovery after CBT may be possible when it is applied to other related disorders for which CBT has been found to be helpful, such as fibromyalgia.[23]

The first clinical implication of the present study is that a therapist delivering CBT can tell the patient that substantial improvement is likely to occur and that full recovery is possible. By communicating this, the therapist can counterbalance factors that lower the expectations of the patient. Examples of such factors are a negative attitude of certain patient advocacy groups towards behavioural interventions or an oversolicitous attitude of significant others in response to CFS.[24] There is empirical evidence that lower expectations of patients have a negative influence on therapy outcome.[25]

The second clinical implication of the present study is that recovery is a construction. The percentage of recovered patients differed depending on the definition of recovery used. It is possible that a patient has another concept of recovery than the therapist. It is important that they jointly (re)formulate a definition which forms the objective of the treatment.

REFERENCES

1. Whiting P, Bagnall AM, Sowden AJ, Cornell JE, Mulrow CD, Ramirez G. Interventions for the treatment and management of chronic fatigue syndrome: a systematic review. J Am Med Assoc 2001; 286: 1360-8.
2. Stulemeijer M, de Jong LWAM, Fiselier TJW, Hoogveld SWB, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. Br Med J 2005; 330: 7481-6.
3. Prins JB, Bleijenberg G, de Boo TM, van der Meer JWM. Cognitive behaviour therapy for chronic fatigue syndrome: correspondence, authors reply. Lancet 2001; 358: 240-1.
4. Fava GA: The concept of recovery in affective disorders. Psychother Psychosom 1996; 65: 2-13.
5. Andrews G. Should depression be managed as a chronic disease? Br Med J 2001; 322: 419-421.
6. Cho HJ, Hotopf M, Wessely S. The placebo response in the treatment of chronic fatigue syndrome: a systematic review and meta-analysis. Psychosom Med 2005; 67: 301-313.
7. Di Blasi Z, Harkness E, Ernst E, Georgiou A, Kleijne J. Influence of context effects on health outcomes: a systematic review. Lancet 2001; 357: 757-762.
8. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994; 121: 953-9.
9. Vercoulen JHMM, Swanink CMA, Fennis JFM, Galama, JMD, van der Meer JWM, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38: 383-392.
10. Van der Werf SP, De Vree B, van der Meer JWM, Bleijenberg G. Natural course and predicting self-reported improvement in patients with a relatively short illness duration. J Psychosom Res 2003; 53: 749-753.
11. Bleijenberg G, Prins J, Bazelmans E. Cognitive behavioral therapies; in Jason LA, Fennell PA, Taylor RR (eds). Handbook of Chronic Fatigue Syndrome. New York, Wiley & Sons, 2003, pp 493-526.
12. Prins JB, Bleijenberg G, Bazelmans E, Elving L, de Boo TM, Severens JL, et al. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. Lancet 2001; 357: 841-7.
13. Vercoulen JHMM, Alberts M, Bleijenberg G. De Checklist Individual Strength (CIS) (The Checklist Individual Strength). Gedragstherapie 1999; 32: 642-9.
14. Stewart A, Hays R, Ware J. The MOS short form general health survey: reliability and validity in a patient population. Med Care 1988; 26: 724-732.
15. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30: 473-483.
16. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease population. J Clin Epidemiol 1998; 51: 1055-1068.
17. Servaes P, Verhagen C, Bleijenberg G. Determinants of chronic fatigue in disease-free breast cancer patients, a cross-sectional study. Ann Oncol 2002; 13: 589-598.

18. Pasquali R. The biological balance between psychological well-being and distress: a clinician's point of view. Psychother Psychosom 2006; 75: 69-71.
19. Ryff CD, Dienberg Love G, Urry HL, Muller D, Rosenkranz MA, Friedman EM, et al. Psychological well-being and ill-being: do they have distinct or mirrored biological correlates? Psychother Psychosom 2006; 75: 85-95.
20. Cairns R, Hotoph M. A systematic review describing the prognosis of chronic fatigue syndrome. Occup Med C 2005; 55: 20-31.
21. Deale A, Husain K, Chalder T, Wessely S. Long-term outcome of cognitive behaviour therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study. Am J Psychiatry 2001; 158: 2038-2042.
22. White PD, Thomas JM, Amess J, Grover SA, Kangro HO, Clare AW. The existence of a fatigue syndrome after glandular fever. Psychol Med 1995; 25: 907-916.
23. van Houdenhove B, Egle UT. Fibromyalgia: a stress disorder? Psychother Psychosom 2004; 73: 267-275.
24. Prins JB, Bos E, Huibers MJ, Servaes P, van der Werf SP, van der Meer JW, et al. Social support and the persistence of complaints in chronic fatigue syndrome. Psychother Psychosom 2004; 73: 174-182.
25. Bentall RP, Powell P, Nye FJ, Edwards RH. Predictors of response to treatment for chronic fatigue syndrome. Br J Psychiatry 2002; 181: 248-252.

6

Efficacy of cognitive behavioral therapy for adolescents with chronic fatigue syndrome: long-term follow-up of a randomized, controlled trial

---

Hans Knoop, Maja Stulemeijer, Lieke W.A.M. de Jong, Theo J.W. Fiselier, Gijs Bleijenberg. Pediatrics, in press

ABSTRACT

Objectives: The purpose of this work was to assess the long-term outcome of adolescents with chronic fatigue syndrome who received cognitive behavioral therapy and to determine the predictive value of fatigue severity and physical impairments of the adolescent and the fatigue severity of the mother at baseline for the outcome of the treatment at follow-up.

Patients and methods: Sixty-six adolescent patients with chronic fatigue syndrome who previously participated in a randomized, controlled trial that showed that cognitive behavioral therapy was more effective than a waiting-list condition in reducing fatigue and improving physical functioning were contacted for a follow-up assessment. Fifty participants of the follow-up study had received cognitive behavioural therapy for chronic fatigue syndrome (32 formed the cognitive behavioral therapy group in the original trial, and 18 patients received cognitive behavioral therapy after the waiting period). The remaining 16 patients had refused cognitive behavioural therapy after the waiting period. The main outcome measures were fatigue severity (Checklist Individual Strength), physical functioning (Short-Form General Health Survey), and school attendance.

Results: Data were complete for 61 patients at follow-up (cognitive behavioral therapy group: 47 patients; no-treatment group: 14 patients). The mean follow-up time was 2.1 years. There was no significant change in fatigue severity between posttreatment and follow-up in the cognitive behavioral therapy group. There was a significant further increase in physical functioning and school attendance (10% increase). The adolescents in the cognitive behavioral therapy group were significantly less fatigued and significantly less functionally impaired and had higher school attendance at follow-up than those in the no-treatment group. Fatigue severity of the mother was a significant predictor of treatment outcome.

Conclusions: The positive effects of cognitive behavioral therapy in adolescents with chronic fatigue syndrome are sustained after cognitive behavioral therapy. Higher fatigue severity of the mother predicts lower treatment outcome.

INTRODUCTION

Chronic fatigue syndrome (CFS) is characterized by severe fatigue, lasting > 6 months, and leading to functional impairments. CFS is not the result of an organic disease or ongoing exertion and is not alleviated by rest.[1] Several controlled trials have shown that cognitive behaviour therapy (CBT) leads to a reduction of fatigue and disabilities in adults with CFS.[2] CBT is aimed at changing fatigue related cognitions and a gradual resumption of activities. We published the first and until now only randomized, controlled trial that tested the effectiveness of CBT for adolescent patients with CFS.[3] The effects of CBT (10 sessions over a period of 5 months) were compared with a waiting-list condition. The adolescent patients who received CBT reported a greater reduction in fatigue and a larger improvement in physical functioning directly after treatment than patients from the waiting list. The school attendance of the CBT group also increased more than in the waiting list. The main objective of the present study to determine whether the positive effects of CBT of the previous study were sustained over a longer period. Secondly, using an explorative analysis, we determined the predictive value of fatigue severity and physical functioning of the adolescent at baseline for the outcome of the treatment at the time of follow-up. In addition, we also looked at the predictive value of the fatigue severity of the mother of the adolescent patient with CFS for treatment outcome at follow-up. The parents of the adolescent patient with CFS are involved in the treatment.[3] This is most often the mother, because she is generally more involved in the daily care of the child. During the treatment, she acts as a coach for younger adolescents. The parent supports older adolescent patients with CFS as they try to increase activity and change fatigue-related cognitions. We presume on the basis of our clinical experience that the ability of the mother to be effectively involved in the treatment is, to some extent, dependent on her own fatigue-related cognitions and level of fatigue. A recent study[4] showed that the level of fatigue of the mother and that of the adolescent with CFS are related. In the current study, we wanted to determine whether such a relationship also existed between the level of fatigue of the mother and the treatment outcome of the adolescent patient with CFS.

PATIENTS AND METHODS

Patients Sixty-nine consecutively referred adolescent patients were included in the original trial. They were randomly assigned to the CBT condition (n= 35) or waiting-list condition (n= 34).[3] All of the patients met the CFS criteria of the US Centers for Disease Control and Prevention[1] and were between 10.0 and 17.2 years of age.

Following the guidelines of the human ethics committee of the Radboud University Nijmegen Medical Centre evaluating the original research protocol, patients who were assigned to the waiting list were offered CBT directly after the postwaiting-list assessment. Of the 34 patients, 16 did not want CBT and 18 were treated according to the same protocol as in the original study.[3]

At the start of the study, patients were informed that they could be contacted for a follow-up assessment. In total, 66 patients were contacted for the follow-up. Fifty of them had

received CBT (32 patients from the original CBT condition and 18 patients who received CBT after the waiting-list period). Because the main objective of the present study was to determine whether the positive effects of CBT are sustained over time, the 3 patients from the original CBT condition who never started with therapy were not contacted for the follow-up.

Design and procedures The 18 patients who received CBT after the waiting period were assessed 5 months later, immediately after CBT, for a posttreatment assessment. Most patients were contacted by mail for the follow-up assessment. Some were contacted by telephone, and if they agreed to cooperate, a set of questionnaires was sent to them. If patients did not send the questionnaires back within 2 weeks, a reminder was sent to them by mail. This was repeated if the patient did not respond to the reminder within 3 weeks. The time interval between follow-up and the posttreatment or post–waiting-list assessment varied. This was because patients entered the study and started treatment at different times, whereas the follow-up moments were fixed because of the limited availability of the participating researchers.

Outcome variables Fatigue was measured in the same way as in the original trial, with the subscale "fatigue severity" of the Checklist Individual Strength (CIS). It consists of 8 items on a 7-point scale, with scores ranging from 8 (no fatigue) to 56 (severely fatigued). The CIS is a reliable and valid instrument.[3 5] Functional impairment was measured with the subscale "physical functioning" of the Short-Form General Health Survey (SF-36).[6] Scores range between 0 (maximal physical limitation) to 100 (ability to do vigorous activity). The SF-36 is reliable and valid[6] and was also used in the previous study.[3] Patients had to score >= 40 on the fatigue severity scale of the CIS and <= 65 on the SF-36 physical functioning subscale to participate in the original trial. School attendance was established as the percentage of regular school hours attended in the previous week.[3] If a patient worked at the time of follow-up, the percentage of work attendance was calculated in the same way.

Predictors of treatment outcome We determined the predictive value of fatigue severity and physical functioning at baseline for treatment outcome at follow-up. The mother of the adolescent patient completed the fatigue severity subscale of the CIS at baseline.

Analysis Statistical analysis was performed using SPSS 12.01 (SPSS Inc, Chicago, IL). Significance was assumed at a P value of < 0.05. The effect of CBT for the patients from the
waiting list was determined with a pairwise t test comparing pretreatment with the posttreatment assessment. In case of missing observations, the last value was carried forward. With a t test for independent groups, it was tested if the posttreatment scores of the patients treated after the waiting period were different from the scores of the CBT group from the original study. If data at follow-up were missing, they were replaced with

estimates derived from single imputation (missing variable analysis, regression with baseline value as predictor). The relationship between time to follow-up (varied) and change in the outcome measures was determined with a Pearson correlation. Comparing the scores at follow-up with those at posttreatment with pairwise t tests helped to determine whether the effects of CBT were sustained. This was also done for the no-treatment group to get an indication of the course of CFS without CBT. We defined patients as showing clinical significant improvement[3] at follow-up if they had a reliable change index of > 1.96 and a score of < 35.7 (1 SD above the mean for 420 healthy adolescents) on the fatigue severity subscale, had an increase of > 50 or an end score of $>= 75$ for on the physical functioning subscale of the SF-36,[7] and were fully attending work and/or school at follow-up. A χ^2 test was used to assess the difference between the percentage of clinical significant improvement between the last assessment and follow-up. Furthermore, the scores on the outcome measures and the percentages of clinical significant change at follow-up of the CBT group were compared, using t tests and χ^2 tests with the group who did not receive treatment. The predictive value of the selected variables on treatment outcome (fatigue) was determined with the use of multiple regression.

RESULTS

Effect of CBT after the waiting list condition Of the patients who received CBT after the waiting-list condition, 15 completed the treatment and the posttreatment assessment, and 3 patients (16%) withdrew from therapy. Their posttreatment data were missing. In those cases, the last observation was carried forward.

Table 1. Effect of CBT for patients (n=18) who received treatment after the waiting list condition

	Post-waiting list	Post-treatment	Treatment effect (95% CI)	t –value (d.f.= 17)	*p*-value
	Mean score (sd)				
Fatigue severity[1]	46.2 (12.8)	29.6 (15.0)	16.6 (8.3 to 24.8)	4.2	0.001
Physical functioning[2]	54.2 (18.1)	72.2 (20.5)	18.1 (8.5 to 27.6)	4.0	0.001
% School attendance	72.6 (34.0)	80.6 (28.7)	7.9 (-13.5 to 29.4)	0.8	0.447

[1] CIS fatigue severity subscale.[2] SF-36 physical functioning subscale

Patients showed a significant decrease in fatigue severity and an increase in physical functioning (Table 1). School attendance was already high at the start of the treatment and was not significantly different at posttreatment assessment. The posttreatment scores of the patients who received CBT after the waiting-list condition were compared with the posttreatment scores of the 32 patients from the treatment condition in the original study. The posttreatment fatigue score of the treated patients from the original study was 28.2 (SD: 16.1) and was not significantly different from the posttreatment score of the patients who received CBT after the waiting list (mean= 29.6, SD= 15.0; t= -0.3; d.f.= 48; P= 0.765). The level of physical functioning (72.0, SD= 28.9) and the school attendance (75%,

SD= 38.9%) of the patients treated with CBT in the original study were also not significantly different from those of the patients treated after the waiting list (mean physical functioning= 72.2, SD= 20.5; t= -0.03; d.f.= 48; P = 0.979; mean school attendance= 81.0%, SD= 28.7%; t= 0.6; d.f. 48; P= 0.581).

Change in outcome variables between final assessment and follow-up Five patients did not complete the follow-up assessment. Three of them were from the CBT group (6%): 2 did not send the questionnaires back and 1 patient had moved without leaving an address. All 3 of the patients had withdrawn from therapy without completing posttreatment assessments. Of the 16 patients on the waiting list who did not want treatment, 2 (12.5%) did not send the follow-up questionnaires back. The 5 patients who did not complete the follow-up assessment did not significantly differ in fatigue severity, physical functioning, and school attendance at baseline from the other patients. The mean time passed between the last assessment and follow-up was 2.1 years (range: 3 months to 6 years and 8 months). There was no significant correlation between time elapsed since the final assessment and the changein fatigue severity (r= -.02; P= 0.892), physical functioning (r= -.15; P= 0.240), and school and/or work attendance (r= -.05; P= 0.739) between follow-up and posttreatment or postwaiting-list assessment. The mean age at follow-up was 18.6 years (SD= 1.7 years; range= 14.8–22.7 years).

Table 2. Change in mean fatigue severity, physical functioning and school attendance between final assessment and follow-up

Group[1]	Final assessment	Follow-up	Change score (95% CI)	-value[5]	*p*-value
	Mean score (sd)				
Fatigue severity [2]					
CBT	28.7 (15.6)	27.9 (14.4)	-0.8 (-4.5 to 6.1)	-0.3	0.764
No treatment	41.6 (14.0)	39.2 (15.3)	-2.4 (-10.7 to 5.8)	-0.6	0.539
Physical functioning[3]					
CBT	72.1 (24.5)	83.3 (20.6)	11.2 (4.8 to 17.7)	3.5	0.001
No treatment	57.8 (23.7)	69.8 (26.7)	12.0 (1.3 to 22.6)	2.4	0.030
% School/work attendance[4]					
CBT	79.0 (33.7)	92.2 (14.2)	13.2 (1.1 to 25.3)	2.2	0.033
No treatment	64.9 (33.3)	68.8 (38.8)	3.9 (-27.9 to 35.7)	0.3	0.793

[1]CBT n=50; no treatment=16; [2] CIS fatigue severity subscale; [3]SF-36 physical functioning subscale; [4]Number of patients reporting that they worked or attended school: n=42 for CBT, n=12 no treatment; [5]Fatigue severity/physical functioning d.f. CBT=49, no treatment=15; schoolwork attendance d.f. CBT=41, no treatment=11

Follow-up of patients treated with CBT After CBT there was no significant difference in fatigue between posttreatment assessment and follow-up. There was a significant further increase in physical functioning. At follow-up, 34 patients attended school and 8 worked. The school and/or work attendance was significantly higher at follow-up (see Table 2).
The percentages of patients who had received CBT and who showed clinical significant improvement in fatigue severity and physical functioning did not significantly change

between posttreatment and follow-up. The percentage of patients with a full school and/or work attendance had significantly increased at the time of follow-up (Table 3).

Table 3: Change in the number of patients (%) with a clinical significant improvement between final assessment and follow-up

Group[1]	Final assessment	Follow-up	Change score (95% CI)	$\chi 2$ (d.f.=1)	*p*-value
	No (%) improved[2]				
Fatigue severity					
CBT	30/50 (60)	32/50 (64)	0.04 (-0.14 to 0.22)	1.2	0.279
No treatment	5/16 (31)	5/16 (31)	0.0 (-0.28 to 0.28)	2.8	0.094
Physical functioning					
CBT	31/50 (62)	37/50 (74)	0.12 (-0.05 to 0.29)	1.9	0.171
No treatment	5/16 (31)	8/16 (50)	0.19 (-0.03 tot 0.40)	7.3	0.007
School/work attendance[3]					
CBT	29/50 (58)	29/42 (69)	0.10 (-0.15 to 0.34)	4.9	0.027
No treatment	4/16 (25)	5/12 (42)	0.17 (-0.29 to 0.62)	0.1	0.735

[1] CBT n=50; no treatment=16; [2] Definition of clinical significant improvement: a reliable change index of >1.96 and a score of <35.7 on the CIS fatigue severity; increase of >50 or an end score of >= 75 on the SF-36 physical functioning; full work/school attendance; [3] number of patients reporting that they worked or attended school: n=42 for CBT n=12 no treatment.

Follow-up of patients who did not receive CBT In the group who did not receive CBT, there was an improvement in physical functioning at follow-up. There was no significant change in fatigue severity. At the time of follow-up, 9 patients attended school and 3 worked. Their school and/or work attendance did not significantly change between post–waiting-list assessment and follow-up (Table 2).

Significantly more patients had a clinically significant change in physical functioning at follow-up assessment when compared with the post–waiting-list assessment. There was no difference in the number of patients a clinically significant improvement in fatigue and a full school and/or work attendance at the time of follow-up (Table 3).

Difference in outcome at follow-up between CBT group and the group who did not receive CBT Patients from the CBT group were significantly less fatigued (mean difference in fatigue severity= -11.3; 95% confidence interval (CI) of the difference: -2.9 to -19.7; t= -2.7; d.f.= 64; P= 0.009), had a higher physical functioning score (mean difference physical functioning= 13.5; 95% CI: 0.8 to 26.2; t= 2.1; d.f.= 64; P= 0.037), and a higher school and/or work attendance (mean difference attendance= 23%; 95% CI: 9.1% to 37.8%; t= 3.3; d.f.= 52; P= 0.002) at the time of the follow-up assessment than the patients who had not received treatment.

More patients from the CBT group showed a clinically significant change in fatigue severity (mean difference= 33%; 95% CI: 5% to 60%; χ^2= 5.3; d.f.= 1; P= 0.02). The difference between the percentage of clinically significant improvement in physical functioning (mean difference= 24%: 95% CI: -6% to 54%; χ^2= 3.2; d.f.= 1; P= 0.073) and school/work attendance (mean difference= 27%; 95% CI: -4% to 58%; χ^2= 3.0; d.f.= 1: P=

0.083) between the patients from the CBT group and the patients who did not receive treatment failed to reach statistical significance.

Prediction of treatment outcome Fatigue severity and the level of physical functioning of the adolescents at baseline did not predict fatigue severity at follow-up for the patients who received CBT (Table 4). The more fatigued the mother of the adolescent patient was, the more negative the treatment outcome of the adolescent. Twenty-eight percent of the mothers who filled the fatigue severity subscale of the CIS in at baseline (11 of 40) were extremely fatigued (score of > 35[8]).

Table 4. Prediction of the level of fatigue at follow-up of patients who received CBT

Predictor at baseline[1]	Unstandardized coefficients	Standardized coefficients
Constant	6.32	
Fatigue severity	0.38	0.10
Physical functioning	-0.16	-0.17
Fatigue severity Mother	0.40	0.35*
R^2 adjusted	0.15	

* $p<0.05$ [1] n=40, for 10 patients data on the fatigue severity of mother were lacking

DISCUSSION

The positive effects of CBT for adolescent patients with CFS were sustained over a period of about 2 years after termination of the treatment. The level of fatigue did not change, whereas the physical functioning and the school and/or work attendance of patients who had received CBT improved further over time. The percentage of patients with a clinically significant improvement in fatigue and physical functioning after CBT remained high at follow-up. The percentage of patients with full school and/or work attendance after CBT showed a further increase from posttreatment to follow-up. These favorable results are comparable or superior to the known long-term effects of CBT for adult patients with CFS. Several randomized, controlled trials confirm that the positive effects of CBT in adult patients with CFS are sustained over a period of 6 to 8 months after the treatment.[9 10] One study that investigated the efficacy of CBT over a 5-year follow-up period also showed that CBT for CFS produced lasting benefits in adults.[10]

In the original trial, 2 treatment protocols were used: 1 for patients with a passive physical activity pattern and 1 for relatively active patients.[3] The physical activity pattern of the adolescent patient with CFS was measured with an actometer, a motion-sensing device attached to the ankle. Directly after treatment, passive and active patients showed equal improvements on all of the primary outcome variables.[3] We also compared the change scores between the postintervention assessment and follow-up for passive and relative active patients. The results of this analysis (data not shown) showed that there were no significant differences in the changes in fatigue severity, physical functioning, and school/work attendance between passive and active patients with CFS.

The level of fatigue of the mother was a significant predictor of the fatigue of the treated patient at follow-up. The finding that the level of symptoms of 1 of the parents and their children with CFS are related is not new.[4 11 12] What is new is that the fatigue of the mother was also related to the response to CBT. Of the fathers, a high proportion (8 of 36 [22%]) was also severely fatigued at baseline. However, there was no significant correlation between the fatigue of the father at baseline and the fatigue of the adolescent at follow-up (r= -.05; P= 0.757). This is in correspondence with the study of van de Putte et al,[4] who also found that the level of fatigue of the father was not related to that of the adolescent patient with CFS. The fact that the fatigue of the mother is related to treatment outcome of the adolescent patient with CFS could implicate that additional interventions aimed at the mother will facilitate the response of the adolescent to CBT, especially when the mother has a level of fatigue that is within the range of adult patients with CFS (28% in our sample[8]). Other research has shown that adults with CFS can also be effectively treated with CBT.[2] Future research has to determine whether the outcome of adolescent patients with CFS after CBT can be improved by individually treating the severely fatigued mother simultaneous with individual treatment of the child.

Existing literature indicates that the prognosis for CFS in adolescents (without and after treatment) is more favorable[12–16] than in adults.[17] A recent community study showed that chronic fatigue and CFS in adolescents has a relatively good prognosis.[12] However, as the authors of this study point out, the prognosis of adolescent patients with CFS who are referred to tertiary care seems less favorable, and those adolescents remain disabled for long periods of time.[13] Our results confirm this. The group of patients who did not receive treatment showed substantially less clinically significant change at follow-up (31%–50%) than patients who received CBT (64%–74%). A majority of the untreated adolescent patients with CFS remained severely fatigued and functionally impaired. The substantial differences between the untreated patients with CFS and the patients with CFS who did receive CBT suggest that the outcome of adolescents with CFS is more favorable after treatment with CBT. We recommend that future research pay close attention to the reasons of adolescent patients with CFS for declining the offered CBT. One could use this information to develop strategies to motivate patients for CBT. It is also important to investigate the possible determinants of the lack of a positive response to CBT in a subgroup of adolescent patients.

One could argue that nonspecific effects, like having had regular contact with health care staff rather than the specific intervention, could explain the difference in outcome between the adolescents who received CBT and the patients in the waiting-list condition. There are 2 studies with adult patients with CFS that compared the effect of CBT for CFS with a "placebo" or nonspecific condition. Both showed a superior effect of CBT on fatigue and the level of disabilities.[9 18] Furthermore, a recent review showed that the placebo response of patients with CFS to psychological interventions is lower than in other medical conditions.[19]

To assess the long-term effects of CBT, we sent questionnaires to the patients by mail. A patient can be more easily influenced by others when filling in the questionnaire at home than at the treatment center, as was done in the earlier assessments. We cannot rule out that patients might have been influenced by others during the assessment and that this might have had an effect on the results of the follow-up assessment.

The mean follow-up time was 2 years, with a wide variation between patients in the time period between the postintervention assessment and follow-up. One could argue that this introduced a bias in the study, because the long-term effect of the treatment could change over time. We think that this is unlikely, because the results showed no statistically significant relationship between time passed since the postintervention assessment and the change scores of the outcome measures.

Data on the type of activities of patients at the time of the follow-up assessment were not available for all of the patients. Some patients only indicated on the questionnaires that they did not study and did not work. We decided not to impute these missing values, because more detailed information about their activities were lacking. This could have introduced a bias when determining the long-term effects of CBT on work and/or school attendance. An example of such a bias would be that these patients are less active and function at a lower level than the patients who indicated that they worked or attended school, which, in turn, might have led to an overestimation of the effect of CBT.

In assessing the predictive value of the fatigue of the mother on treatment outcome, data on the fatigue severity of a substantial number of mothers were lacking. We can only conclude that the relationship between the fatigue of the mother and the treatment outcome of the adolescent patients existed in the subgroup of patients where the fatigue severity of the mother was assessed. Furthermore, an alternative explanation for the association between the fatigue of the mother and that of the adolescent could be the negative influence of a child being sick on the functioning of the mother. However, it is our clinical experience that if the mother of the adolescent patient with CFS is severely fatigued, her fatigue exists longer than (and, thus, precedes) that of the child.

In comparing the long-term outcome of patients treated with CFS and the patients who did not want CBT, it must be noted that it is possible that the patients with untreated CFS form a subgroup of the total group of patients with CFS who were referred for treatment. This subgroup could have some specific characteristics. These characteristics and not the fact that they did not receive CBT could have negatively influenced their level of fatigue and disabilities at follow-up. Lastly, it must be noted that the group of untreated patients in this study was small, which limits the scope of the conclusions that can be drawn from this sample. We suggest that the results of the current study can only be generalized to those adolescent patients with CFS who do want to be treated with CBT.

CONCLUSIONS

The original trial showed that CBT significantly reduced the symptoms of CFS in adolescents in 10 sessions. The current study showed that these results were not only

sustained over a time span of 2 years but that some aspects of CFS symptoms and disabilities had decreased even further after CBT. It is important that this effective treatment becomes available to more adolescent patients with CFS.

ACKNOWLEDGEMENTS

This work was supported by the Foundation for Children's Welfare Stamps Netherlands (Stichting Kinderpostzegels Nederland) and the ME Foundation (ME Stichting).

We thank all of the participants and their parents, and we thank Maaike van Kuijk and Ester Meijer for carrying out the therapy of the patients from the waiting list.

REFERENCES

1. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International chronic fatigue syndrome study group. Ann Intern Med 1994; 121: 953-9.
2. Chambers D, Bagnall A, Hempel S, Forbes C. Interventions for the treatment, management and rehabilitation of patients with chronic fatigue syndrome/myalgic encephalomyelitis: an updated systematic review. J Roy Soc Med 2006; 99: 506-520.
3. Stulemeijer M, de Jong LWAM, Fiselier TJW, Hoogveld SWB, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomized controlled trial. Brit Med J 2005; 330: 7481-6.
4. van de Putte EM, van Doornen LJP, Engelbert RHH, Kuis WM, Kimpen JLL, Uiterwaal CSPM. Mirrored symptoms in mother and child with chronic fatigue syndrome. Pediatrics 2006; 117: 2074-9.
5. Vercoulen JHMM, Swanink CMA, Fennis JFM, Galama, JMD, van der Meer JWM, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38: 383-92.
6. Stewart AL, Hays RD, Ware JE. The MOS short form general health survey: reliability and validity in a patient population. Med Care 1988; 26: 724-732.
7. Powell P, Bentall RP, Nye FJ, Edwards RH. Randomised controlled trial of patient education to encourage graded exercise in chronic fatigue syndrome. Brit Med J 2001; 322: 387-390.
8. Knoop, H, Bleijenberg G, Gielissen MFM, van der Meer JWM, White PD. Is a full recovery possible after cognitive behavioural therapy for chronic fatigue syndrome? Psychother Psychosom 2007; 76:171-6.
9. Prins JB, Bleijenberg G, Bazelmans E, Elving L, de Boo Th, Severens JL, et al. Cognitive behaviour therapy for chronic fatigue syndrome: A multicentre randomized controlled trial. Lancet 2001 357; 841-7.
10. Deale A, Husain K, Chalder T, Wessely, S. Long-term outcome of cognitive behaviour therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow up study. Am J Psychiatry 2001; 158: 2038-2042.
11. Rangel L, Garralda ME, Jeffs J, Rose G. Family health and characteristics in chronic fatigue syndrome, juvenile rheumatoid arthritis, and emotional disorders of childhood. J Am Acad Child Adolesc Psychiatry 2005; 44:150-8.
12. Rimes KA, Goodman R, Hotoph M, Wessely S. Incidence, prognosis, and risk factors for fatigue and chronic fatigue syndrome in adolescents: a prospective community study. Pediatrics 2007; 119:603-9.
13. Rangel I, Garralda ME, Levin M, Roberts H. The course of severe chronic fatigue syndrome in childhood. J R Soc Med 2000; 93:129-134.
14. Bell DS, Jordan K. Robinson M. Thirteen-year follow up of children and adolescents with chronic fatigue syndrome. Pediatrics 2001; 107: 994-8.
15. Patel MX, Smith DG, Chalder T, Wessely S. Chronic fatigue syndrome in children: a cross sectional survey. Arch Dis Child 2003; 88: 884-898.
16. Gill AC, Dosen A, Ziegler JB. Chronic fatigue syndrome in adolescents. Arch Pediatr Adolesc Med 2004; 158: 225-9.

17. Cairns R, Hotoph M: A systematic review describing the prognosis of chronic fatigue syndrome. Occup Med-C 2005; 55: 20-31.
18. Deale A, Chalder T, Marks I, Wessely S. Cognitive behavior therapy for chronic fatigue syndrome: a randomized controlled trial. Am J Psychiatry 1998; 155: 1461-2.
19. Cho HJ, Hotopf M, Wessely S. The placebo response in the treatment of chronic fatigue syndrome: a systematic review and meta-analysis. Psychosom Med 2005; 67: 301-313.

7

Efficacy of guided self-instructions in the treatment of patients with chronic fatigue syndrome: a randomised controlled trial

---

Hans Knoop, Jos W.M. van der Meer, Gijs Bleijenberg, submitted

ABSTRACT

Background: A minimal intervention for Chronic fatigue syndrome (CFS), consisting of self-instructions combined with email contact, was developed from the protocol for cognitive behavioural therapy.

Aims: 1) test if guided self-instructions lead to a reduction of fatigue and disabilities; 2) predict for which patients this minimal intervention suffices.

Method: In a randomised controlled trial the effects of the intervention were compared to a waiting list condition. Patients met CDC criteria for CFS. Main outcome measures (fatigue severity and disabilities) were determined at baseline and after the intervention or waiting period.

Results: 85 patients were allocated to the treatment condition, 86 to the waiting list. An intention to treat analysis showed that fatigue and disabilities decreased significantly more after guided self-instructions. Fatigue severity and disabilities were negatively related with treatment outcome.

Conclusion: Guided self-instructions are an effective treatment for relatively less severely disabled and fatigued CFS patients.

INTRODUCTION

Chronic fatigue syndrome (CFS) is characterised by severe fatigue, lasting longer than six months and leading to disabilities.[1] Cognitive behaviour therapy (CBT), aimed at the cognitions and behaviours that perpetuate the fatigue leads to a decrease of fatigue and disabilities.[2 3] CBT for CFS is an intensive treatment, requiring thirteen to sixteen sessions depending on the protocol used.[4-6] It is likely that for a subgroup of patients a less intensive intervention suffices. We developed a minimal intervention based on the CBT protocol for CFS[7] consisting of self-instructions combined with email contact. The first objective of this study was to determine if self-instructions were an effective treatment for CFS. For this, the effects of the guided self-instructions on fatigue severity and level of disabilities were compared to a waiting list condition in a randomised controlled trial. Secondly, the predictive value of indices of severity of CFS and of the perpetuating factors of CFS for treatment outcome were investigated in an explorative analysis to determine which patients benefited from a minimal intervention. Furthermore, cut-off scores on the predictors of treatment outcome were determined to be able in the future to select those patients at baseline who have the largest chance on a favourable outcome with the minimal intervention.

METHOD

Patients All consecutive patients referred for CBT to the Expert Centre Chronic Fatigue of the Radboud University Nijmegen Medical Centre were eligible to enter the study if they met the following inclusion criteria:

- Being 18 years or older;
- Being able to speak and read Dutch;
- The 1994 research criteria for CFS as formulated by the US Center for Disease Control; [1 8]
- Being severely fatigued, operationalised as reaching a score of 35 or more on the subscale Fatigue Severity of the Checklist Individual Strength (CIS);[9]
- Being severely disabled, operationalised as having a total score on the Sickness Impact Profile (SIP total score) of 700 or higher;[10]
- Given written consent for participation in the study.

Patients were excluded if they were engaged in a legal procedure concerning disability related financial benefits. This was done because a previous intervention study had shown that being engaged in a legal procedure predicted a negative treatment outcome.[11] Patients could still be included in the study after the legal procedure was ended. The local ethics committee approved the study.

Design and procedures All referred patients received a baseline assessment as a part of clinical routine. Patients that met the inclusion criteria of the study were offered CBT and were told that they were placed on a waiting list for the treatment. The waiting period was 6 to 12 months and was caused by a limited treatment capacity. If a patient had agreed with

placement on the waiting list for CBT he or she was given detailed information about the study. Patients were told that they could participate in a study that tested the efficacy of guided self-instructions while he or she waited for individual therapy. Participation in the study would not lead to a longer waiting period than usual to the start of the individual CBT. If the patient had given informed consent for participation in the study he or she was randomly assigned to either the intervention condition (guided self-instructions) or a waiting list condition. Allocation to group was carried out by the therapist using cards in consecutive numbered and sealed envelopes that were opened in the presence of the patient. A statistical advisor independent of the study prepared the envelopes by coding them according to a computer-generated list of random numbers. Randomisation was performed in blocks of 8. Patients in both conditions were assessed two times, at baseline and directly following the waiting period or intervention. This period could vary between 6 to 12 months depending on the available treatment capacity.

Intervention The self-instructions were derived from the protocol for CBT that was developed on the basis of a model of perpetuating factors of CFS.[12] It has been tested in several studies[6 10 13] and is aimed at changing fatigue related cognitions and a gradual increase of activities. There are two treatment protocols, depending on the pattern of physical activity of the patient.[7] This activity pattern is assessed with an actometer, a motion sensing device that can quantify physical activity. A relatively active and a passive pattern is distinguished. The relatively active physical activity pattern is characterised by bursts of activity followed by periods of rest. Relatively active patients first have to attain a base level of activity where they divide their activities more evenly during the day. Subsequently they gradually increase their activity level and resume work and other activities. Patients with a passive activity pattern are characterised by an extremely low physical activity level and start immediately with a graded activity program. The two treatment protocols were also used in the self-instructions. Patients received a self-instruction booklet that consisted of information about CFS and assignments. The assignments were given per week, the total program took at least 16 weeks, but would more often take more time in order for the patient to reach goals as resumption of work. The booklet was given to the patient by the therapist who also invited the patient to email once every two weeks to report on his or her progress and ask questions about the self-instructions. If a patient did not use email, the therapist proposed that the patient phoned at least once every two weeks. Patients were told that they were free to email (or phone if they did not email) more often if they wanted. If patients did not email or phoned every two weeks a reminder was send by the therapists by mail or patients were contacted by telephone. The intervention was carried out by 6 cognitive-behavioural therapists trained in the treatment of CFS patients with CBT. They received group supervision once a week over the interventions carried out in the guided self-instruction condition.

Primary outcome measures Primary outcome variables were fatigue severity and level of disabilities. Fatigue severity was measured with the subscale 'fatigue severity' of the Checklist Individual Strength (CIS). It indicates the level of experienced fatigue over the past 2-week period and consists of eight items on a seven point scale. Scores range from 8 (no fatigue) tot 56 (severely fatigued). The CIS is a reliable and valid instrument.[9] The level of disabilities were measured in two ways. The Sickness Impact Profile was used to measure functional disability in ambulation, home management, mobility, alertness behaviour, sleep/rest, work limitations, social interactions, recreation and pastimes. The eight subscales were added to provide one weighted score of disability (SIP total score). The SIP was used in several intervention studies with CFS patients.[6 10] Physical disabilities were measured with the 'physical functioning' subscale of the Medical Outcomes Survey Short Form-36. Scores range from 0 (maximum physical limitations) to 100 (ability to do vigorous activity). The SF-36 is reliable and valid.[14]

Secondary outcome measure Psychological distress was the secondary outcome measure. This was measured with the total score of the Symptom Checklist 90 (SCL90). The SCL90 consists of 90 items scored on a 5-point scale. Scores range from 90 to 450. A low total score reflects high psychological well-being. The SCL-90 is a reliable and valid instrument.[15]

Clinical significant improvement To determine if the changes in fatigue severity and level of disabilities were clinical meaningful, cut-off scores for a clinical significant improvement were used. Clinical significant improvement was defined in two ways. First, as a reliable change index of 1.96[16] and scoring lower than 35 on the subscale fatigue severity of the CIS at the second assessment. This score is within two standard deviations of the mean of healthy adults.[17] Secondly, improvement was defined as having a clinical significant improvement in fatigue and a total score of less than 700 on the SIP.

Assessment of predictors of treatment outcome The fatigue severity score on the CIS, the SIP total score and the number of CDC additional symptom criteria present at baseline were seen as indices of the severity of CFS. To determine the number of additional symptom criteria the patients filled in a questionnaire where they had to indicate if they experienced the symptoms muscle pain, headache, multi-joint pain, sore throat, post-exertional malaise, unrefreshing sleep, concentration and/or memory impairment, and sensitive lymph nodes. Scores could range from 4 to 8.
Vercoulen et al[12] showed that there are several factors that perpetuate the CFS symptoms. These factors are physical inactivity, a low self-efficacy, strong somatic attributions of symptoms and a focus on bodily symptoms. All these factors were assessed at baseline in the present study. The physical activity level was measured with an actometer, a motion-sensing device worn at the ankle that quantifies physical activity. The actometer was worn 12 consecutive days and nights. A general physical activity score that expressed the mean

activity level over this period in the mean number of accelerations per 5-minute interval was calculated. Patients were classified in relative active and passive by comparing their activity pattern with reference scores.[18] On the basis of this typology they received a different type of treatment. For the analysis of the predictive value of the physical activity for treatment outcome the mean activity level was used.

The self-efficacy scale, consisting of seven questions, measured the sense of control in relation to CFS complaints. The seven items were scored on a 4-point Likert scale, scores ranged between 7 and 28.[19]

Somatic attributions with respect to the CFS symptoms were measured by the causal attribution list consisting of five questions scored on a 5-point likert scale. Scores range from 5 to 20, a higher score indicating stronger somatic attributions.[6]

Focusing on bodily symptoms was measured with the subscale somatisation of the SCL90. This subscale consist of 12 items scored on a 5-point Likert scale, scores range from 12 to 60.[6]

Sample size and data analysis The sample size was determined on the basis of the change in the primary outcome measure fatigue severity. A score of lower than 35 on the CIS (scoring within two standard deviations of the mean of healthy controls) at second assessment would reflect an acceptable change in fatigue. We assumed that in the waiting list 10% of the patients would have a fatigue score of lower than 35. A power calculation showed that 98 patients in each condition were needed to detect a difference of 15% in the proportion of patients with a fatigue score within normal limits (10% in the waiting list versus 25% in the guided self-instructions condition) assuming a significance of 5%, power of 90% and a drop-out rate of 20%.

Data analyses were performed using SPSS, version 14.0. Significance was assumed at $p< 0.05$ in all analyses. Independent samples t-tests and χ^2 tests were used to determine if there were differences at baseline between the two conditions in patient characteristics. To test if there was a difference in scores between the two conditions on the primary and secondary outcome measures ANCOVA was used[20] with the score on the second assessment as dependent variable, the baseline score as covariate and condition as fixed factor (2 levels). Differences between the two conditions in the proportion of patients with a clinical significant improvement were tested with χ^2 tests. All comparisons between the two conditions were performed on the basis of an intention to treat, in case of missing data the last observation was carried forward. For the patients in the guided self-instructions who completed the second assessment pearson correlations were calculated between CIS fatigue severity at the second assessment and the scores on the (potential) predictors of treatment outcome at baseline. Fatigue severity at second assessment was chosen as a measure of treatment outcome and not the SIP total score and SF-36 physical functioning to reduce the risk on a type I error by calculating many different correlations. The variables that correlated significantly with fatigue severity were subsequently used as predictors in a multiple regression (method enter) with post-intervention fatigue severity as dependent

variable. For the predictors that were significant in the multiple regression, optimal cut-off scores were determined that correctly identified the largest proportion of patients that did and did not profit from the minimal intervention.

RESULTS

In the course of the study it became clear that the number of patients lost at the second assessment was much lower than expected (about 5% instead of the expected 20%). The same power analysis was repeated but now using an estimated drop-out rate of 5%. The results indicated that a sample size of 85 in each condition sufficed and it was decided to stop with the inclusion of patients when this sample size was reached. There were 184 consecutively referred CFS patients eligible to enter the study (Figure 1).

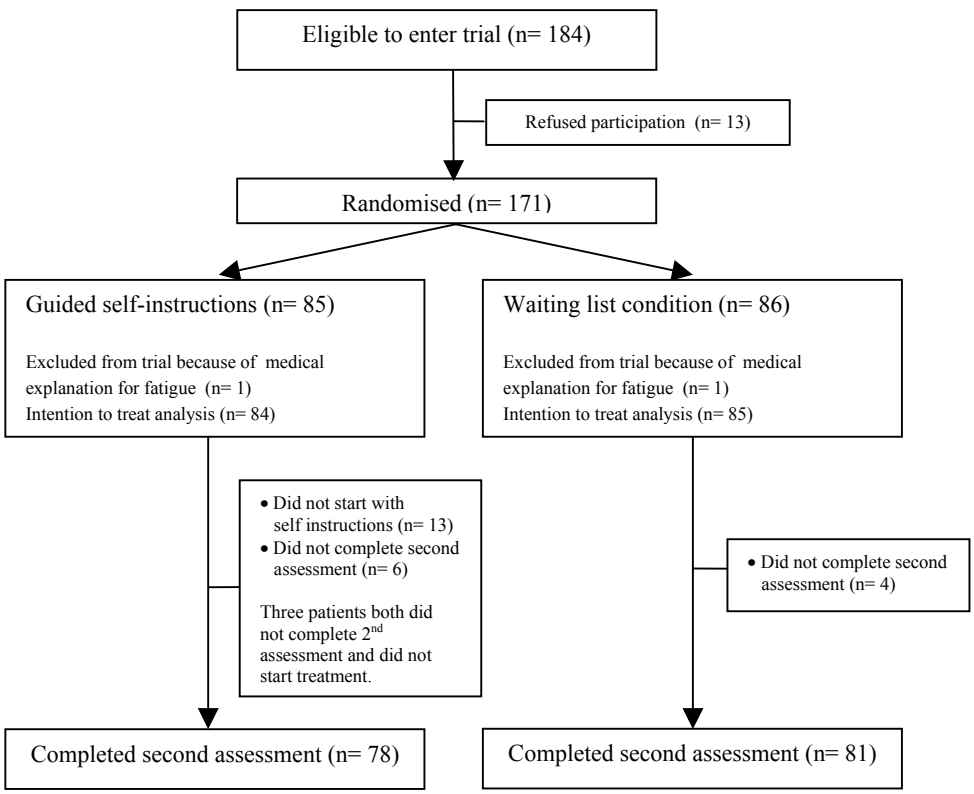

Fig. 1: Trial profile

Thirteen patients refused participation, 8 because they preferred a face to face contact with a therapist, of the remaining 5 the reasons for refusing were unknown. The remaining 171 patients were randomly assigned to either the guided self-instructions condition or the

waiting list. Of the total group of patients, 85 patients entered the self-instructions condition and 86 patients remained on the waiting list. Two patients were excluded from the study because another medical condition that could explain the fatigue was diagnosed after randomisation. In the treatment condition one patient was excluded after a constriction of the coronary arteries was diagnosed that subsequently was treated with surgery. In the waiting list one patient was excluded after Hashimoto's Thyroiditis was diagnosed. In the intention to treat analysis 84 patients of the self-instruction condition were compared with 85 patients of the waiting list. Thirteen patients (15%) did not start with the self-instructions, six patients (7%) did not complete the second assessment (three of them also had not started with the treatment). Of the 13 patients that did not start with the self-instruction, 6 indicated that they preferred a face to face contact with a therapist, from the others the reasons for not starting were unknown. In the waiting condition four patients (5%) did not complete the second assessment. There were 78 patients (93%) in the intervention condition with complete data, in the waiting list condition 81 patients (95%) had complete data.

Baseline characteristics In Table 1 the baseline characteristics of the patients from the two conditions are described. There were no significant differences between the self-instructions condition and the waiting list in the scores on the outcomes measures at baseline.

Table 1. Baseline characteristics of the patients from the two conditions

	Self-instructions (n=84)	Waiting list (n=85)	t-value[2]	*p*-value
	Mean score (SD)			
Demography				
Age (yrs)	37.6 (10.0)	38.5 (10.6)	-0.55	0.582
Duration of complaints (months)[1]	72 (12,420)	96 (12,420)	-1.22	0.225
Male/Female	15/69	20/65	χ^2=0.83	0.363
Outcome measures				
CIS fatigue severity	49.1 (5.2)	49.9 (5.6)	-0.96	0.336
SIP total score	1659 (648)	1515(545)	1.56	0.120
SF-36 physical functioning	52.3 (20.4)	54.1 (21.1)	-0.56	0.575
SCL-90 total score	167.3 (40.5)	168.6 (39.3)	-0.21	0.834
Indices of severity				
Number of CDC symptoms	7.1 (1.6)	7.3 (1.6)	-0.58	0.566
Perpetuating factors				
Activity pattern (passive/active)	24/60	20/65	χ^2=0.56	0.455
Self efficacy	17.4 (3.2)	17.9 (2.8)	-0.99	0.326
Somatic attributions	12.4 (2.9)	12.0 (3.2)	0.86	0.392
Focusing on bodily symptoms	28.7 (8.1)	29.6 (8.3)	-0.68	0.496

[1] median (min, max) [2] d.f.= 167

The effects of guided self-instructions The mean time passed between baseline and second assessment was 10.5 months (SD= 4.0) for the guided self-instruction condition and 9.7 (SD= 3.6) for the waiting list. This difference in time passed was not statistically significant (t= 1.34, d.f.= 157, p= 0.182).

Of the 84 patients in the self-instructions condition 55 (66%) emailed with the therapist, 5 (6%) exclusively used the telephone and 10 (12%) used both email and telephone. The remaining 14 (17%) patients had not contacted the therapist, 13 of them did not start with the self-instructions and 1 completed the program without assistance of a therapist. The mean number of emails send by the patients was 11 (SD= 7.0) with a mean number of 285 words (SD= 194). The mean time passed between the first and last mail send by the patients was 32 weeks (SD = 19). There were no reliable data collected on the number of telephone calls of the patients or the number of emails send by the patients who combined email and telephone.

There was a statistically significant difference on all primary outcome measures between the guided self-instructions condition and the waiting list (Table 2). Patients from the intervention condition were significantly less fatigued, reported less disabilities on the SIP and scored significantly higher on the SF-36 physical functioning.

Table 2. Change in outcome measures between baseline and second assessment

	Self-instruction (n=84)[1]	Waiting list (n=85)[1]	$F_{(1,166)}$	*p*-value
Primary outcome measures				
CIS fatigue severity	-10.1 (-12.7 to -7.6)	-3.5 (-5.2 to -1.7)	20.61	<0.001
SIP total score	-579 (-690 to –469)	-195 (-312 to -79)	19.77	<0.001
SF-36 physical functioning	13.6 (9.4 to 17.8)	6.1 (2.3 to 9.9)	6.56	0.011
Secondary outcome measures				
SCL-90 total score	-20.4 (-27.9 to -12.9)	-10.6 (-16.6 to -4.6)	5.86	0.017

[1] mean difference between second assessment and baseline (95% confidence interval)

After guided self-instructions patients also reported significantly less psychological distress at the second assessment than patients from the waiting list (Table 2).

After guided self-instructions 27% of the patients showed a clinical significant improvement in fatigue which was significantly more than the 7% from the waiting list (Table 3). More patients from the intervention condition also showed a clinical significant reduction of fatigue and disabilities at second assessment (21% versus 2%).

Table 3. Proportion of patients with a clinical significant improvement at the second assessment

	Self-instructions (n=84)		Waiting list (n=85)		χ^2 (d.f. =1)	*p*-value
	No	% (95% CI)	No	% (95% CI)		
CIS fatigue severity < 35[1]	23/61	27 (18 to 37)	6/79	7 (2 to 13)	12.27	<0.001
CIS <35[1] and SIP total score <700	18/66	21 (12 to 30)	2/83	2 (0 to 6)	14.73	<0.001

[1] and a reliable change index of 1.96

The prediction of the response to guided self-instructions Of the variables that were selected as indices of the severity of CFS, fatigue and the level of disabilities on the SIP at baseline were significantly correlated with the treatment outcome of the patients who completed the second assessment. The pearson correlations with the fatigue severity at the second assessment were respectively .32 (p= 0.004) with baseline CIS fatigue severity and 0.37 (p=0.001) with the SIP total score. The number of CDC symptoms reported at baseline were not correlated with outcome (r = .19; p= 0.10).

The perpetuating factors physical activity (r= -.20; p= 0.081), somatic attributions (r= .19; p= 0.092) and self-efficacy (r= .11; p=0.325) showed no statistical significant association with treatment outcome. The correlation between focusing on bodily symptoms and the fatigue severity following the intervention was significant (r= .35; p= 0.002).

Table 4 shows the results of a multiple regression with the variables that correlated significantly with treatment outcome as predictors. This regression showed that fatigue severity and the level of disabilities at baseline predicted treatment outcome.

Table 4. Prediction of the level of fatigue after guided self-instructions

Predictor at baseline[1]	Unstandardized coefficients	Standardized coefficients
Constant	-6.32	
CIS Fatigue severity	0.56	0.24*
SIP total score	0.60	0.31**
Focusing on bodily symptoms	0.27	0.18
R^2 *adjusted*	0.22	

* p<.05; **p<.01 [1] n=78 patients from the treatment condition who completed the second assessment

Cut-off points were calculated, using the SIP total score and CIS fatigue severity subscale score, that correctly predicted the largest proportion of patients who did not profit from the intervention. From the eleven patients that had a CIS fatigue severity score of 51 or higher and a SIP total score of 2250 or higher none reported a clinical significant change in fatigue at second assessment. From the 73 patients that scored lower on the CIS and SIP, 23 patients (32%) showed a clinical significant improvement. This difference in proportion (0% versus 32%) clinical significant improvement between the group who had an extremely high score on CIS and SIP and the group who scored lower on these measures was statistical significant (χ^2= 4.77, d.f.= 1, p= 0.029).

DISCUSSION

The main objective of this study was to test the efficacy of guided self-instructions for the treatment of CFS. The self-instructions were based on the protocol for CBT for CFS. The results showed that the minimal intervention led to a significant decrease of fatigue severity, disabilities and psychological distress compared to a waiting list condition. Also, after the self-instructions more patients showed a clinical significant improvement in fatigue and disabilities. It was already known that 'face to face' CBT is an effective treatment for CFS[3], the current study showed that a less intensive intervention based on the same principles suffices for a subgroup of CFS patients. Although, as far as we know, this is the first randomised controlled trial testing the effects of a minimal intervention based on CBT in CFS patients, the present findings are in line with previous research. A randomised controlled study with patients with chronic fatigue showed that a self-help manual based on CBT combined with support from a nurse was more effective than no treatment.[21] However, in this study only a small minority of the included patients suffered from CFS. Burgess and Chalder[22] found in an uncontrolled study with nine CFS patients that a self-help manual based on CBT combined with telephone contact with a therapist had a positive effect on fatigue and disabilities.

Powell et al[23] also performed a randomised controlled trial with a minimal intervention for CFS patients but this intervention was based on graded exercise therapy, another evidenced based behavioural intervention for CFS.[2 3] In this study psycho-education and a graded activity program in the form of a self-help manual were combined with telephone contact with a therapist. It was found that the fatigue and disabilities of patients in the treatment condition decreased more than in a control condition and that these positive effects were maintained at follow-up.[24] Direct comparisons of the magnitude of the effects from the two studies is difficult, but the results of the trial of Powell et al[23] are impressive and seem larger than the effects of the minimal intervention reported here. It could be that graded exercise therapy lends itself better for adaptation to a minimal intervention than CBT as it focuses more on behaviour change and less on the restructuring of cognitions. An alternative explanation would be that the therapist that delivered the intervention (there was only one therapist in the study of Powell et al[23]) was highly effective, thereby limiting the possibility to generalize the findings of this study. In our study six therapists delivered the intervention and although the number of patients is too small to statistically analyse the effect of the therapist, the percentages of patients with a clinical significant improvement vary from therapist to therapist. We suggest that in the future more attention is paid to the role of therapist characteristics on the outcome, not only in this minimal intervention but also in 'face to face' CBT for CFS.

All patients in the current study were severely fatigued and disabled. A subgroup of patients who reported extremely high levels of fatigue and disabilities profited less from the minimal intervention. This indicates that guided self-instructions should preferably be offered to those CFS patients who, although being severely fatigued and disabled, do not report extremely high levels of fatigue and disabilities. This group of patients has a better

chance on a favourable response to this minimal intervention. For these patients, guided self-instructions could form a first step in a model of stepped care for CFS. If they do not profit from the minimal intervention, they could subsequently be offered individual CBT. Patients with the most severe fatigue and an extremely high level of disabilities could perhaps best directly be referred for individual 'face to face' CBT. By using the self-instructions in this way, the available treatment capacity for CFS can be used more effectively and probably also more economically. Furthermore, a substantial subset of patients will not be required to visit a treatment facility regularly to effectively reduce their complaints.

We assumed that self-instructions would be an effective treatment for a subgroup of patients but on the whole would be less effective than the individual 'face tot face' CBT. This assumption was confirmed in a comparison of the outcome of patients receiving self-instructions with the outcome of a cohort of 96 CFS patients receiving individual CBT in the same treatment facility and delivered by the same therapists.[10] After the self-instructions 21% of the patients had a clinical significant improvement in fatigue and disabilities. In the group receiving individual CBT, 53% of the patients reached this criterion using the same instruments and definition of clinical significant improvement. The fact that individual CBT is more effective does not form a problem in using self-instructions as long as individual CBT is available for those patients who do not profit from the minimal intervention. The difference in effectiveness would become problematic if the chances on a favourable response to CBT for CFS are lessened if it is preceded by a minimal intervention that was unsuccessful. If this would be the case, one withholds a CFS patient a possible more favourable outcome by first offering a less effective treatment. Data about the outcome of patients treated with CBT after an unsuccessful minimal intervention are needed to rule out this potential negative effect of the minimal intervention. These data are not yet available.

Limitations of this study As we did not use a placebo or non-specific intervention as control condition but a waiting list we can not be sure that the specific elements in the minimal intervention condition were responsible for the reduction in fatigue and disabilities in the CFS patients. There are two randomised controlled trials that compared the effect of CBT for CFS with a 'placebo' or non-specific condition. Both showed a superior effect of CBT on fatigue and the level of disabilities.[6 25] Furthermore, a review of Cho et al[26] investigating the placebo response of CFS patients, showed that the placebo response of CFS patients to psychological interventions is lower than in other medical conditions.

In the intention to treat analysis we carried the last observation forward in the case of missing data. By doing this we assumed that the symptoms and disabilities would not increase from baseline to second assessment. This does not have to be the case and by assuming this we could have introduced a bias in our analysis. We tried to correct this by repeating the analysis but now missing data on the outcome measures were replaced with estimates derived by single imputation (missing variable analysis regression with the

baseline value as predictor). The pattern of results on the main outcome measured stayed the same.

With the design used in the study we do not know if a combination of self-instructions and contact with a therapist by email or telephone is necessary for the positive effect on fatigue and disabilities. We found no significant correlations between the number of emails sent by the patients, number of words of the emails, time passed between first and last email, or number of emails sent by the therapist and the fatigue severity or level of disabilities at second assessment. Those aspects of the contact with the therapist do not seem related to treatment outcome. However, we did not analyse the content of emails which perhaps shows a relation with the outcome of the intervention.

In this trial we also did not study differences in the effects of email alone, email combined with telephone contact, or contact by telephone. This was mainly because of the small number of patients who did not use email contact but we also failed to collect data about the number and durations of phone calls. It could be that having a telephone conversation with a therapist has a different effect on the patient than receiving an email often a couple of days after the patient had sent a message. The two previous studies testing the effectiveness of forms of self-help for CFS used the telephone as only mean of communication between patient and therapist.[22 23] It would be worthwhile to investigate possible differences in effect of the self-help intervention using email or the telephone. It could be that contact by phone is more effective that an email contact. The two intervention modes also differ in their use of therapist time. Email can be used more flexible by the therapist than the telephone, but it could be that a telephone consult is less time consuming. It is important to look more closely at these aspects of the intervention because they determine the time a therapist has to invest in the treatment. This will have an effect on the treatment capacity for CFS and the cost-effectiveness of the minimal intervention.

In the study of Chalder et al[21] the self-help manual was combined with a consult with a research nurse. In our study qualified cognitive-behavioural therapists, all psychologists, delivered the intervention. If other health care professionals, e.g. psychiatric nurses with less psychotherapeutic qualifications would be able to effectively guide CFS patients in using the self-instructions, this would probably further add to the cost-effectiveness of the intervention.

ACKNOWLEDGEMENTS

We thank the patients who participated in the study. We thank Thea Berends, Annemarie Gerritsen, Gerrie van de Heijdt, Henriette Vermeer and Hein Voskamp for treating the patients in the guided self- instruction condition, and Carel Kruip, Tiny Fasotti and Lianne Vermeer for their assistance in data collection.

REFERENCES

1. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994; 121: 953-9.
2. Whiting P, Bagnall AM, Sowden AJ, Cornell JE, Mulrow CD, Ramirez G. Interventions for the treatment and management of chronic fatigue syndrome: a systematic review. J Am Med Assoc 2001; 286: 1360-8.
3. Chambers D, Bagnall A, Hempel S, Forbes C. Interventions for the treatment, management and rehabilitation of patients with chronic fatigue syndrome/myalgic encephalomyelitis: an updated systematic review. J Roy Soc Med 2006; 99: 506-520.
4. Quarmby L, Rimes KA, Deale A, Wessely S, Chalder T. Cognitive-behaviour therapy for chronic fatigue syndrome: comparison of outcomes within and outside the confines of a randomised controlled trial. Behav Res Ther 2007; 45: 1085-1094.
5. Sharpe M, Hawton K, Simkin S, Surawy C, Hackmann A, Klimes I et al. Cognitive behaviour therapy for the chronic fatigue syndrome: a randomised controlled trial. Br Med J 1996; 312: 22-6.
6. Prins JB, Bleijenberg G, Bazelmans E, Elving L, de Boo TM, Severens JL, et al. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. Lancet 2001; 357: 841-7.
7. Bleijenberg G, Prins J, Bazelmans E. Cognitive behavioral therapies; in Jason LA, Fennell PA, Taylor RR (eds). Handbook of Chronic Fatigue Syndrome. New York, Wiley & Sons 2003: 493-526.
8. Reeves WCC, Lloyd A, Vernon SD, Klimas N, Jason LA, Bleijenberg G, et al. Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. BMC Health Serv Res 2003; 31:25.
9. Vercoulen JHMM, Swanink CMA, Fennis JFM, Galama, JMD, van der Meer JWM, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38: 383-392.
10. Knoop, H, Bleijenberg G, Gielissen MFM, van der Meer JWM, White PD. Is a full recovery possible after cognitive behavioural therapy for chronic fatigue syndrome? Psychother Psychosom 2007; 76:171-6.
11. Prins JB, Bazelmans E, van der Werf S, van der Meer JWM, Bleijenberg G. Cognitive behaviour therapy for chronic fatigue syndrome: predictors of outcome. In: Sivik T, Byrne D, Lipsitt DR, Cristodoulou GN, Dienstfrey H (eds). Psycho-neuro-endocrino-immunology, a common language for the human body. Elsevier 2002: 131-135.
12. Vercoulen JHMM., Swanink CMA, Galama JMD, Fennis JFM, Jongen PJH, Hommes OR, et al. The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: the development of a model. J Psychosom Res 1998; 45: 507–517.
13. Stulemeijer M, de Jong LWAM, Fiselier TJW, Hoogveld SWB, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. Br Med J 2005; 330: 7481-6.
14. Stewart A, Hays R, Ware J. The MOS short form general health survey: reliability and validity in a patient population. Med Care 1988; 26: 724-732.
15. Derrogatis LR. SCL-90-R: Administration, scoring and procedures, manual (3rd edn). Minneapolis, MN, National Computer Systems 1994.
16. Jacobsen NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy. J Consult Clin Psychol 1991; 59: 12-19.
17. Vercoulen JHMM, Alberts M, Bleijenberg G. De Checklist Individual Strength (CIS) (The Checklist Individual Strength). Gedragstherapie (Behavioural Therapy) 1999; 32: 642-9.
18. Van der Werf SP, Prins JB, Vercoulen JHMM, van der Meer JWM, Bleijenberg G. Identifying physical activity patterns in chronic fatigue syndrome using actigraphic assessment. J Psychosom Res 2000; 49: 373-9.
19. Gielissen MF, Verhagen CA, Bleijenberg G. Cognitive behaviour therapy for fatigued cancer survivors: long-term follow-up. British Journal of Cancer 2007: doi:10.1038/sj.bjc.6603899.
20. Van Breukelen GJP. Ancova versus change from baseline: more power in randomized studies, more bias in nonrandomized studies. Journal of Clinical Epidemiology 2006; 59: 920-5.
21. Chalder T, Wallace P, Wessely S. Self-help treatment of chronic fatigue in the community: a randomized controlled trial. British journal of health psychology 1997; 2: 189-198.

22. Burgess M, Chalder T. Telephone cognitive behaviour therapy for chronic fatigue syndrome in secondary care: a case series. Behav Cogn Psychoth 2001; 29: 447-455.
23. Powell P, Bentall RP, Nye FJ, Edwards RHT. Randomised controlled trial of patient education to encourage graded exercise in chronic fatigue syndrome. Brit Med J 2001; 322: 1-5.
24. Powell P, Bentall RP, Nye FJ, Edward RHT. Patient education to encourage graded exercise in chronic fatigue syndrome: 2 year follow-up of a randomised controlled trial. Br J Psychiatry, 2004 184, 142-146.
25. Deale A, Chalder T, Marks I, Wessely S. Cognitive behaviour therapy for chronic fatigue syndrome: a randomised controlled trial. Am J Psychiatry 1997 154; 408-414.
26. Cho HJ, Hotopf M, Wessely S. The placebo response in the treatment of chronic fatigue syndrome: a systematic review and meta-analysis. Psychosom Med 2005; 67: 301-313.

8

General discussion

In this final chapter the results of the studies reported on in this dissertation will be discussed in light of the literature on cognitive behaviour therapy (CBT) for chronic fatigue syndrome (CFS). Furthermore, implications of our findings for the treatment of CFS patients will be formulated as well as possible directions for future research. This chapter is divided into three parts; the effects of CBT for CFS, the development of a model of stepped care for CFS, and future directions for research of CBT for CFS.

The effects of CBT for CFS

There is agreement in the scientific literature that the existing evidence shows that CBT leads to a reduction of self-reported symptoms and disabilities.[1] Yet uncertainty exists about the nature and scope of the changes brought on by CBT. Here, it will be discussed what the studies described in this dissertation have added to our knowledge about the effects of CBT for CFS. First, the possibility to recover from CFS after CBT will be discussed; then what the effects of CBT are on symptoms other than fatigue; how CBT can change the experience of fatigue and lastly; what the long-term effects of CBT are. The clinical implications of these findings and unresolved issues surrounding these effects of CBT will also be mentioned.

Recovery of CFS

In chapter 5, the possibility to recover from CFS after CBT was investigated. The literature shows different views on this matter. Some authors state that the goal of CBT for CFS is to help patients improve activity levels and quality of life, rather than to overcome symptoms.[2] They find empirical support for this point of view in the fact that CFS patients continue to experience more fatigue than healthy controls after successful treatment with CBT, that only a minority of treated patients meet the criteria of full recovery and that some patients with a positive outcome directly following treatment relapse in the long term.[2] Others think that recovery following CBT is not possible because CBT does not treat the causes of the syndrome. They often entail hypothetical pathophysiological models of CFS which are not easy to combine with the cognitive-behavioural model of CFS used in CBT.[3-5] There are also authors that think that recovery from CFS is possible.[6] In chapter 5, we empirically tested the controversy about the nature of change following treatment by defining recovery in constructs that can be assessed more or less objectively and that closely follow the CDC criteria for CFS. This seemed to us more fruitful than discussing hypothetical models of CFS or exchanging ideological viewpoints. It is important to note that the question was (and is) *whether* recovery is possible, not how many patients actually recover. Therefore, the aforementioned findings, e.g. that CFS patients as a group are more fatigued than healthy people after treatment, are not essential to answer this question. We think, on the basis of the study reported in chapter 5, that full recovery of CFS following CBT is possible. However, full recovery is only achieved by a subgroup of patients. The characteristics of this group of patients are unknown, aside from the finding reported in chapter 5 that patients without a co-morbid medical illness have a better chance of

recovery. For the further development of CBT, it is crucial that our findings are replicated and that more is known about which patients do and which do not recover following treatment. Knowing the characteristics of these categories of patients could help in the development of new interventions that may increase the proportion of patients that recover. It could also lead to the conclusion that there is a subgroup of patients for whom recovery is not a tenable goal. For them, acceptance of a chronic condition should be seen as the aim of treatment.[7]

In chapter 5, we reported that about half of the patients had a level of fatigue after CBT within the range of healthy controls. Only about one third of the patients no longer experienced fatigue as something negative. The fact that less patients reach the latter criterion of recovery, suggests that a 'normalisation' of the experience of fatigue is more difficult to establish in CFS patients with CBT than a reduction of the severity of the fatigue. It also seems that a return to normal physical functioning is more common than healthy functioning in other domains of living. This warrants further investigation and the development of strategies that better influence these aspects of CFS.

In chapter 5, we did not look at the physical activity level of patients after CBT but mostly relied on self-reported change in symptoms and behaviour. As an increase of physical activity is seen as an important element of CBT, it would be interesting to look at the change in the scores on the actometer, a motion sensing device that reliably measures the actual level of physical activity of a patient.[8] Re-examination of the available data of the 96 patients in the recovery study (chapter 5) showed that after CBT and when measured with the actometer, 59 patients (62%) had a level of physical activity that was within the mean minus one standard deviation of healthy controls.[8] At baseline, before treatment, 35% of the patients had an activity level within normal limits. The increase in the proportion of patients with an activity level within normal limits is statistically significant (χ^2-test). Chapter 3 showed that the level of physical activity measured with the actometer also significantly increased in adolescent CFS patients after a successful CBT. Is the increase in physical activity necessary to recover from CFS? The available data suggest that it is not. Again, we revisited the data of the cohort of patients from chapter 5. There was no significant correlation between the decrease of fatigue severity and increase of physical activity (pearson r= -.06, p= 0.552). After CBT, there was also no significant association between the level of fatigue and the physical activity level (pearson r= -.18). Thirteen of the 46 patients that had a level of fatigue within the mean plus one standard deviation of healthy controls after CBT, being a very strict criterion for recovery, still had a physical activity level *below* that of healthy controls. The activity level of these 13 patients (13/46= 28%) was, even after CBT, more than one standard deviation below the mean of healthy controls. This means that it is possible to recover from CFS without reaching a physical activity level that is within normal limits. As most CBT protocols for CFS emphasize the importance of increasing the patient's physical activity level to reduce fatigue and disabilities,[6] it is remarkable to find that the relationship between an increase in physical activity and a decrease of fatigue is weak. We conclude from this, that rather than the increase in physical

activity, changes in cognitions play a crucial role in reaching recovery. Increasing activity levels is important because it facilitates the change in the cognitions about fatigue and disabilities, yet it is not the main mechanism of change in CBT for CFS. The role of physical activity and cognitions (and their interplay) in reaching recovery needs further research. To this end, an analysis of the process of change that takes place in a successful CBT for CFS is needed (see further).

The most important clinical implication of our outcome study is the need to communicate to patients that recovery is possible, but in no way a certain cure. Installing hope can motivate patients to change illness-related cognitions and behaviour and thus, increase the chance of a positive outcome of CBT for CFS.

The effect of CBT on pain and cognitive impairments in CFS

Most intervention studies use fatigue severity and level of disability as outcome measures. In this dissertation, we looked at the effects of CBT on pain and impairments in concentration and memory. Pain symptoms and cognitive impairments together form five of the eight additional CFS symptom criteria formulated by the Center for Disease Control (CDC). The majority of CFS patients report these symptoms. We studied the effect of CBT on these symptoms and found that pain and self-reported cognitive impairments decrease after successful treatment. This suggests that both symptoms are part of the syndrome of chronic fatigue and closely linked to the main symptom fatigue.

It is important that these positive effects of CBT, which were not reported before by other research groups, are communicated to patients and clinicians who deliver care to CFS patients. There is no empirical support for often used alternative interventions for pain symptoms of CFS patients, like pain medication or physiotherapy. On the basis of existing evidence, CBT for CFS is the preferred treatment for pain symptoms of CFS patients. At the start of the treatment, the therapist asks the patients to stop all other treatments for CFS-related symptoms. This is done to ensure that patients can attribute the reduction of symptoms and disabilities to changes in his or her cognitions and behaviour. This will help to increase the self-efficacy of patients. The cessation of other treatments also includes the use of medication for CFS-related pain symptoms. The results of the study on pain symptoms in this thesis are in accordance with this intervention.

Although pain severity decreases after CBT, patients with a very high pain level benefit less from CBT for CFS. We already suggested in chapter 2 that CFS patients with a high pain level are more like patients with syndromes in which the chronic widespread pain is a central feature (e.g. fibromyalgia). There is evidence that the biological correlates of CFS and these chronic pain syndromes differ.[9] Furthermore, the subjective experience of severe pain is different from that of severe fatigue. Pain is an inherently negative sensation that is perceived as a possible signal of physical damage. Fatigue is a less alarming sensation that, for most healthy people, has, rather than negative, neutral or pleasant connotations (see chapter 4). In CFS patients, the fatigue gets negative connotations because of the negative consequences for the functioning of the person. Accordingly, one would expect that

patients with chronic fatigue have different symptom-related cognitions than patients with severe chronic pain. In chronic pain syndromes, catastrophising of pain symptoms plays a crucial role. It is an important predictor of the level of pain and disability of the patient, medication usage and psychological distress.[10] Petrie et al[11] found a tendency for catastrophising of fatigue in one third of the CFS patients. Those patients reported higher levels of fatigue and disabilities. There are several studies from one research group who also found a significant association between fatigue severity and catastrophising in patients receiving treatment for cancer and in cancer survivors.[12-14] However, for these patients, fatigue is probably a far more threatening symptom than for CFS patients. In a large, multicentre study performed by our research group in cooperation with Belgium researchers from the university of Gent we found that catastrophising occurred less often in CFS patients compared to patients with severe chronic pain [Vermeer et al, unpublished data]. Furthermore, the relationship between catastrophising, fatigue severity and level of disabilities was weak. On the basis of this research we concluded that catastrophising is not a common clinical phenomenon in CFS. This could explain why CFS patients with severe pain (who perhaps do catastrophise) do not respond well to CBT. For this subgroup of patients, specific interventions aimed at the catastrophising of pain (and fatigue) could help to increase the effectiveness of CBT. Further research is necessary to test if these conclusions and assumptions are correct.

The role of cognitive impairments in CFS

In chapter 3, we found a decrease of self-reported cognitive impairments following CBT without a positive effect on neuropsychological test performance. This discrepancy between subjectively reported disabilities versus objectively measured performance is an important characteristic of CFS. With this in mind, one would expect that an effective treatment of CFS would lead to a more accurate perception by CFS patients of their performance. This is exactly what was found: CBT resulted in a decrease of complaints about cognitive functioning but not in a change in cognitive performance.

One could argue against this interpretation that an improvement in neuropsychological test performance after treatment can only be expected for the sub-group of CFS patients with a defective performance at baseline. Recent research showed that the subgroup of CFS patients who report (retrospectively) a sudden onset of symptoms perform worse on neuropsychological tests compared to their monozygotic twin discordant for CFS.[15] It is unclear how we must interpret these findings. Are the neuropsychological deficits just epiphenomena of some patients with CFS or is there an identifiable subgroup of CFS patients that differs from other patients on certain characteristics? And if so, what is the relevance of these characteristics for the treatment of CFS?

In an attempt to find some preliminary answers to these questions we reanalysed the data of chapter 3 for those adult and adolescent CFS patients whose neuropsychological test performance at baseline is significantly worse than that of healthy controls. We compared the reaction times of CFS patients with the reaction times of healthy controls on the simple

and choice reaction time task. Reaction times were considered deviant if they were slower than the mean plus one standard deviation of healthy controls (21 males and 59 females with a mean age of 37.8, SD= 11.7). There were 94 adult (41%) and 20 adolescent patients (31%) with a deviant simple reaction time at baseline. In the choice reaction time task 126 adults (54%) and 12 adolescents (18%) had a deviant performance. We tested the performance of both adolescents and adults with deviant baseline reaction times to see if their performance on the reaction time tasks improved after CBT. The results showed that patients with an 'objective' impairment in speed of information processing did not show an improvement in neuropsychological test performance following treatment. On the basis of these data, one could still conclude that the cognitive impairments remain after treatment but that patients learn to better cope with them, which results in a reduction of complaints. This would be an alternative explanation for the results of the study reported in chapter 3, namely for the sub-group of patients with a deviant neuropsychological test performance. We further examined this possibility by analysing the test performance on the reaction time tasks but now from the cohort of patients from the recovery study reported in chapter 5. We used this cohort and not the cohort from chapter 3 because the latter is much smaller, which lessens the statistical power. In the cohort of 96 adult CFS patients, 44% had a 'normal' level of fatigue and no physical disabilities following treatment. The recovery rate of patients with a deviant simple reaction time at baseline (again mean plus one standard deviation of healthy controls) did not significantly differ from patients with a normal reaction time (46% versus 43%, χ^2= 0.03, d.f. 1, p= 0.854). The recovery rate of patients with a deviant choice reaction time was also not significantly different from the recovery rate of patients without an impaired choice reaction time (64% versus 41%, χ^2= 2.00, d.f. 1, p= 0.158). These results suggest that reaching recovery of CFS following CBT is independent of neuropsychological test performance. This would implicate that having a deviant score or not is irrelevant for the treatment of CFS with CBT. We see an analogy: the lack of connection between neuropsychological test performance and complaints about mental functioning is very similar to the lack of connection between changes in physical activity and the reduction of fatigue. The improvement in fatigue severity or self-reported cognitive impairments is not related to changes in objective test performance or physical activity. We consider this evidence for the central role of perception and cognitions in CFS.
During CBT, patients who complain about mental functioning follow a graded activity program where they systemically increase their mental activity (e.g. reading or surfing the internet). We assume that during this graded activity program they change their cognitions about their mental functioning (e.g. increase their self-efficacy), while no change occurs in their objective mental functioning.
Smith and Sullivan[16] showed that the beliefs of CFS patients about their cognitive functioning negatively influenced their actual test performance. In a study of Van der Werf et al[17] more than 20 % of the CFS patients had a submaximal performance on a symptom validity test. We used the same symptom validity test in the study reported in chapter 3 but did not report the data in the final paper. As in previous studies, we found that a substantial

proportion of CFS patients (19% of the adult and 18% of the adolescent CFS patients) performed submaximally on a symptom validity task.[17 18] Further analysis showed that this submaximal performance was associated with a significantly lower neuropsychological test performance on the reaction times tasks and the Symbol-Digit Modality Test. This implies that in order to be able to interpret the neuropsychological test performance of CFS patients in research and clinical practice, one needs a symptom validity test. The fact that most studies do not use symptom validity tests seriously hampers the interpretation of the findings of these studies. We strongly feel that that without the use of symptom validity tests, it is not possible to come to valid conclusions about the reasons why a subgroup of CFS patients perform worse on neuropsychological tests than matched healthy controls.

The experience of fatigue in CFS

As far as we know, the studies described in chapter 4 and 5 were the first to show a change in the experience of fatigue following CBT for CFS. The fact that fatigue no longer has a negative connotation in a group of patients who have suffered several years from chronic fatigue is remarkable. Although this is a positive finding, only a subgroup of patients reaches this point, implying that it is not easy to change the experience of fatigue. The fact that more patients report a reduction of fatigue severity and disabilities than a change in the experience of fatigue suggests that there is room for improvement. How could the perception or experience of fatigue be addressed more successfully in therapy? One could try -more than is being done in the current protocol- to normalise the experience of fatigue after patients report that they are no longer chronically fatigued but still have moments of severe fatigue. Knowing that fatigue does not have to have negative consequences for the patient's functioning (as was the case before), can reduce the negative connotations of fatigue. During therapy this is made explicit. Articulating this change in experience can further lessen the negative connotations of fatigue. These kinds of interventions can influence the attentional and attributional processes that are, in most likelihood, at the core of the perpetuation of CFS.[19]

It would be interesting to see if, some time after the completion of CBT, the negative connotations surrounding fatigue decrease further in those patients who no longer are severely fatigued. Perhaps time is necessary to get rid of the negative associations with fatigue that were established over a long period of being disabled by the fatigue. It would also be worthwhile to test whether a change in the experience of fatigue after successful CBT, more specifically whether fatigue has once again become a normal or even pleasant experience, protects a patient from future relapses in the future. Although the follow-up studies performed so far have shown that the treatment effects are sustained over time in both adult and adolescent CFS patients (see chapter 6), relapse does occur.[2] One could assume that continuing to experience fatigue as something negative after (an otherwise successful) CBT will make patients more vulnerable for a recurrence of CFS.

Long-term outcome of CBT for CFS

Several randomized controlled trials in adults confirmed that the positive effects of CBT in CFS patients are sustained over a period of 6 to 8 months following the treatment.[2 20] One study investigating the efficacy of CBT over a 5 year follow-up period also showed that CBT for CFS produced lasting benefits in adults.[2] On the basis of the follow-up study reported in chapter 6 of this thesis, the conclusion that the treatment effects sustain over time can be extended to adolescent CFS patients treated with CBT. However, relapses occur after CBT.[2] In our study we found that the percentage of patients with a clinical significant improvement in fatigue slightly increased from post-treatment to follow up (from 60% to 64%). However, further analysis showed that from the 30 patients that improved at post-treatment, 9 patients relapsed at follow-up (31%). While this was compensated by the number of patients who improved after the treatment, it shows that relapse is also a clinically relevant problem in adolescent CFS patients. We think that more attention should be paid to relapse after CBT. This can be investigated by doing repeated assessments over a longer period after termination of CBT in cohorts of patients who were successfully treated. In this way the characteristics of patients that show a relapse can be studied, which can aid in the development of interventions that prevent the recurrence of CFS.

Towards a model of stepped care for CFS

Minimal intervention for CFS

It is estimated that there are between 30.000 to 40.000 patients with CFS in the Netherlands.[21] The capacity to treat these patients with CBT is lacking and it is unlikely that enough trained therapists will be available in the near future. We have developed a minimal intervention requiring less time of a therapist to deliver, and we have tested its effectiveness. The results reported in chapter 7 show that guided self-instructions based on the protocol for CBT for CFS is an effective treatment for a subgroup of patients. For this group, a minimal intervention suffices. This intervention could form a first step in a model of stepped care for CFS patients.

How effective are self-instructions compared to individual CBT? Scheeres et al[22] calculated the mean (within treatment) effect size for fatigue severity and disabilities of CBT for CFS derived from four randomised controlled trials testing the effectiveness of this treatment. The mean effect size (cohen's d) for fatigue was 1.44 (95% CI: 0.97 tot 1.89) and for disabilities it was 1.04 (95% CI =0.63 tot 1.44). The effect sizes of the guided self-instructions was for fatigue severity 1.1 and for the level of disabilities (which was measured with the Sickness Impact Profile; SIP) it was 0.8, both within the confidence interval of the statistical benchmark. For physical functioning, the effect size was 0.6, outside the confidence interval of the benchmark for disabilities. On the basis of this comparison it can be concluded that, aside from the outcome with respect to physical functioning, the effect-sizes of self-instructions are not different from those of 'face to face' individual therapy. However, the patients in the trials were not always treated by

experienced therapists[20] and the protocol of CBT has been improved on the basis of the outcome of the trials testing the effectiveness of CBT for CFS.[23] We calculated the effect sizes of the cohort of 96 CFS patients from chapter 5 who received individual CBT in the same treatment facility as in the randomised controlled trial testing the effectiveness of guided self-instructions (see chapter 6). Nearly all patients were treated by therapists who also participated in the study reported in chapter 6. The effect sizes were 1.9 for fatigue severity, 1.4 for level of disabilities measured with the SIP and 1.2 for the increase in physical functioning. The effect size of CBT in this cohort treated by experienced therapists is higher for fatigue severity than the statistical benchmark and reached the upper limit of the confidence interval of the benchmark for the measures of the disabilities. We also calculated the effect sizes at follow-up of the 'face to face' CBT in adolescent CFS patients from chapter 6. For fatigue severity the effect size was 1.9, which is again higher than the statistical benchmark. For the increase in physical functioning the effect size was 1.4, again near the upper limit of the confidence interval. On the basis of these data we conclude that individual treatment has become more effective and is superior, providing it is delivered by experienced therapists in a specialized treatment facility, to guided self-instructions. This does not mean that there is no place for self-instructions in the care for CFS patients. As long as patients have access to individual treatment when the minimal intervention does not succeed, self-instructions are an efficient treatment form.

Currently, our group is engaged in two studies that further investigate the effects of guided self-instructions. In the first study, psychiatric nurses deliver the treatment instead of fully trained cognitive behavioural therapists. A second difference is that the self-instructions are offered to CFS patients diagnosed in primary care instead of CFS patients referred to a tertiary, specialised CFS clinic. In this study, the effects of the guided self-instructions are also compared to a waiting list condition. If this trial can replicate the findings of the original study described in chapter 7, the treatment capacity for CFS can be increased rapidly because the training of psychiatric nurses for this specific intervention requires less time than the training program for cognitive-behavioural therapists. Furthermore, by offering self-instructions in primary care CFS patients can enter treatment earlier. This is important, as the mean symptom duration of patients in our specialised CFS clinic is more than 6 years. Reduction of the time passed before the start of CBT will reduce the suffering of patients and will also reduce the medical and societal costs of CFS. The second study on self-instructions is a follow-up of the original trial reported in chapter 7. The effectiveness of individual therapy for patients who still desire individual treatment after completion of the self-instructions, is compared with the effects of the same treatment that patients receive after the waiting list. This will help us determine whether the chance of a positive outcome after 'face to face' individual CBT is smaller if one has had an unsatisfactorily response to the self-instructions. Data on this issue are necessary to make an informed decision about implementation of self-instructions in a model of stepped care.

Future directions in the development of interventions for a model of stepped care

In a model of stepped care, specific interventions should also be available for patients who do not profit from individual CBT for CFS. A substantial subgroup drops out from CBT or does not have a positive outcome. They remain severely fatigued and disabled. Perhaps for this group a form of treatment has to be developed that learns patients to manage symptoms that are chronic and disabling. There are some exploratory studies that show promising results of such treatment forms. Surawy et al[24] found that mindfulness training (which aims to facilitate non-judgmental attention to present moment experience through the practice of meditation) in CFS patients waiting for CBT resulted in a significant reduction of anxiety and fatigue and in an increase of quality of life and physical functioning. Treatment gains were modest compared to those following CBT but mindfulness training could be helpful for those patients who do not profit from CBT.

Another subgroup where interventions have to be developed and tested with regard to their effectiveness, is that of patients that are too severely disabled for CBT delivered in an out-patient clinic. Patients who are continuously bedridden, depend on a wheelchair or have extremely severe complaints, could perhaps best be treated in an in-patient setting. There have been some studies testing the effectiveness of behavioural interventions in an in-patient setting.[1 25] Two of them reported positive treatment effects. However, it is not clear to what extent the patients in these studies were more severely disabled. The studies also have methodological flaws and the interventions offered seem to differ from the CBT protocol. One uncontrolled case study found a positive effect of CBT for CFS in an outpatient setting for two patients who depended on a wheelchair.[26] The patients had a large number of contacts (55-60) with the therapists, some face to face, some by telephone. It is probable that the protocol for CBT for CFS has to be adjusted in order to effectively treat the subgroup of patients who are homebound. They show a persistent low physical activity level, are at risk for developing physical deconditioning and more often have had depressive episodes in the past. Motivating these patients for behavioural intervention will probably be very difficult as they tend to have stronger somatic attributions of CFS symptoms.[27] Controlled studies testing the effectiveness of interventions based on CBT for these groups of CFS patients (homebound, dependent on wheelchair) are lacking and badly needed, but will be difficult to perform.

Future directions in the research of CBT for CFS

Mechanisms of change in CBT for CFS: the role of physical activity and perception

CBT is an effective treatment for CFS, but the mechanisms by which the changes in symptoms and disabilities are reached is unknown. Some postulate that CFS is associated with a physical deconditioning and that by systematically increasing the level of physical activity, this is reversed and followed by a reduction of symptoms.[28] However, research has shown that physical deconditioning is not a perpetuating factor in CFS, at least not in the majority of CFS patients.[29] Also, the improvement in symptoms and functioning in CFS patients is not associated with increased fitness after a graded exercise program but with a

change of illness-related cognitions.[30] Furthermore, we did not find an association between a change in the level of physical activity and a reduction of fatigue severity after CBT. Recovery of CFS was possible, even if the physical activity level of the patient remained low. If there are no direct connections between the level of physical activity and/or fitness of CFS patients and the response to therapy what could be the role of graded physical activity in CFS? Some suggest that by gradually becoming more active, the fear and avoidance of activity decreases and activity impeding cognitions are restructured.[31] The gradual increase of physical activity can then be seen as a form of exposure therapy. This could well apply to patients with an extremely low physical activity pattern where activity-impeding cognitions play an important role.[6] However, the majority of CFS patients have a fluctuating activity pattern, in which bursts of activity leading to an increase of symptoms are followed by periods of inactivity.[8] They are not characterised by activity-impeding cognitions. For those patients, the gradual increase of physical activity could reinforce the belief that they can increase their activity, at a slower pace, without becoming extremely fatigued. This change in cognitions could, in turn, help to reduce disabilities. Seen in this way, the precise level of physical activity reached is less relevant. The graded activity has a function in changing the perception and to elicit positive feedback that patients receive when they increase their level of activity (from others and from the evaluation of one's own behaviour). The change in perception and elicited feedback will also lead to an increased self-efficacy and a decreased focus on bodily symptoms, both factors that perpetuate the fatigue.[5] This would explain how fatigue severity can decrease as a consequence of the graded activity program. Finally, being physically active could be an inherently positive experience to some CFS patients, as is regularly reported by patients during therapy. Examples of this are feelings of 'healthy' fatigue or of being less exhausted after the walks that are part of the graded activity program. This could add to the restructuring of dysfunctional cognitions about the negative consequences of activity on fatigue. This is in accordance with the evidence that physical activity of moderate intensity has positive effects on affect, activation and relaxation.[32]

The aforementioned hypothetical mechanisms of change in CBT would imply that the central disorder in CFS is one of perception of bodily symptoms and one's own performance and activity in relation to the symptoms. This would be in accordance with the already mentioned findings of others concerning the discrepancy between subjective complaints and objective performance of CFS patients.[33-36] It would also be in line with recent research using F-MRI in which not the actual performance but the interpretation and affective labelling of the errors made during a task of CFS patients differ from healthy controls.[37] A recent review describing a model of medically unexplained symptoms referring to different research findings also emphasized the role of attention and attribution in the maintaining of symptoms.[19]

However, it must be noted that solid data about the possible mechanisms of change in CBT for CFS are still lacking. These data are crucial to better understand CFS and to further improve CBT for CFS. Our research group will start a study to find out which variables

during the therapy process contribute to recovery or predict an unsuccessful outcome of CBT for CFS. We chose variables that are related to the specific interventions in CBT and variables that are known perpetuating factors of CFS.[5 6] Examples of the process variables of interest are self-efficacy, pain, social support, level of physical activity, expectations from the patients of the therapy, the focus on bodily symptoms and catastrophising of pain and fatigue. By studying the process of change in these variables and its relation to changes in fatigue and disabilities, more will be known about the specific mechanisms of change and how they interact in a successful treatment of CFS. This will also provide more insight into the role of physical activity and perception in reaching recovery.

Another way of investigating the role of physical activity is to compare the difference in the effects of a graded activity program that is aimed at increasing mental activity (using the computer, doing work that requires mental effort, increasing social contacts) with a physical activity program (e.g. walking). If physical activity is crucial for the positive effects of CBT, one would expect that the patients who increase their physical activity will show a larger reduction in fatigue and disabilities.

Currently, a study investigating the response of CFS patients to virtual physical activity is in preparation. The use of virtual reality in CBT is not new, especially as an alternative to exposure in vivo.[38] With this technique patients can be exposed to virtual physical activity and assess the effects of the activity on cognitions and symptoms. Repeating this assessment in different phases of the therapy may facilitate a better understanding of the relationship between fatigue, cognitions and physical activity.

Finally, evidence is mounting that CFS patients show neurobiological abnormalities.[37 39] Structural and functional MRI before and after therapy could help us to better understand the biological correlates of CFS and the mechanisms of change in CBT. Similar research in affective disorders has proven to be fruitful.[40 41]

Prediction of the response to CBT

Several studies have looked for variables that predict the response to CBT. Membership of a self-help group, being dysphoric, receiving sickness benefits, being involved in a legal procedure concerning a disability claim, having a low self-efficacy, being strongly focused on bodily symptoms and having an extremely low physical activity pattern were all predictors of a poor response to therapy.[2 42 43] The fact that certain characteristics of a patient, his or her environment, or a symptom belonging to the syndrome predicts the response to treatment could be seen as an indication that during the treatment the influence of the specific predictor has not been adequately addressed. The finding that a low physical activity was a predictor of treatment outcome led to an adjustment of the protocol of CBT for CFS.[44] After this adjustment, the activity pattern no longer predicted treatment outcome.[23] The predictive value of certain patient characteristics for treatment outcome can also lead to the exclusion of patients because CBT is not effective in their situation. An example of this is being involved in a legal procedure concerning a disability claim what in the current protocol leads to (temporarily) exclusion from treatment. In this way,

knowledge about what predicts the response to treatment can help to make CBT more effective and efficient.

In this dissertation, some new predictors of the response to treatment were found. The role of pain as predictor of treatment outcome has already been discussed earlier in this chapter. The study discussed in chapter 5 showed that somatic co-morbidity is associated with a lower response to CBT. There are two possible explanations for this effect of co-morbidity. The first would be that the symptoms and disabilities that remain are caused by somatic co-morbidity and do not reflect the effect of CFS. If this is true then other criteria for recovery from CFS have to be used that incorporate the effect of the co-morbidity on symptoms and disabilities. In other words, the treatment goal is different for this subgroup of patients. An alternative explanation would be that having a somatic disorder hampers the treatment of CFS because it strengthens the perception of patients that they are ill and therefore cannot recover. When the latter is true, then it is important to direct more attention to the restructuring of the attributions of the fatigue in such a way that the patients can influence the fatigue and reduce the fatigue-related disabilities. Replication of our findings and further investigations into the difference between patients with and without somatic co-morbidity with respect to their fatigue related cognitions is warranted. In chapter 5 only the effect of somatic co-morbidity was analysed. Prins et al[45] diagnosed a current psychiatric disorder in 32% of the CFS patients participating in a randomised controlled study testing the effect of CBT for CFS. That percentage was significantly higher than the percentage of psychiatric illness in the general population. There was no difference in treatment outcome (fatigue severity and disabilities) between patients with and without a psychiatric diagnosis.

In the adolescent study, an interesting finding was that the fatigue of the mother of the adolescent CFS patient was related to treatment outcome of the adolescent. The clinical implication of this finding was already discussed in chapter 6. The question is whether this relationship has a parallel in adult CFS patients. It would be interesting to look at the relationship between the response to CBT and the fatigue of the partner or other proxy. Perhaps if such a person is seriously fatigued, this also hampers, like in adolescents, the treatment of the adult with CFS. If so, this could also have clinical implications of the interventions carried out.

For future research it is important to test the predictive value of variables for the treatment response in larger cohorts of patients because the studies performed so far were probably under-powered.

Incorporating new developments in CBT in the treatment of CFS

In studying CBT for CFS we can learn from the new developments in CBT, already applied to some other disorders. Three developments could be relevant for CFS. The first is the concept of metacognitions in the perpetuation of dysfunctional beliefs that produce symptoms. Metacognitions can be seen as appraisals of the consequences of choosing to adopt a particular belief or style of thought.[46] Matthews and Wells[46] use the example of patients with health anxiety to illustrate the role of metacognition. A subgroup of patients

with health anxiety, believes that worrying is desirable because it is perceived to be a way to detect problems at an early stage, before it is too late. This metacognition will keep a patient worrying, even if it leads to negative consequences like anxiety or fatigue for which the patient seeks help. There have been a few uncontrolled studies in anxiety disorders testing the effectiveness of interventions aimed at the modification of metacognitions instead of the conventional treatment aimed at the restructuring of symptom related beliefs. The studies showed remarkable large positive effects of this intervention strategy.[47 48] We consider it possible that metacognitions play an important role in the focusing on bodily symptoms which is a perpetuating cognitive process in CFS. If this is true, this could lead to alternative treatment strategies for this perpetuating factor.

The focus on bodily symptoms is also an important characteristic of patients with social phobia with fear of blushing, trembling and sweating. Task concentration training aimed at redirecting the attention away from the bodily symptoms to the social task is an effective treatment.[49] It would be worthwhile to test the effectiveness of this type of intervention incorporated in the protocol of CBT in CFS patients.

According to some, a 'third generation' of cognitive behavioural therapies has emerged. These therapies see the modification of dysfunctional cognitions as unnecessary to induce change. Instead, the role of behavioural change, constructivism and attentional control is emphasized.[50] Examples of such therapies are Acceptance and Commitment Therapy (ACT) and mindfulness based cognitive therapy. The study of Surawy[25], investigating the effects of mindfulness training is an example of the use of these new therapies in CFS. There are two studies that investigated specifically the role of acceptance in CFS.[7 51] According to some, CBT for CFS focuses exclusively on gaining control over the fatigue, while acceptance of CFS could also have a positive effect on the symptoms. Acceptance is defined as a willingness to live with fatigue without reactance, disapproval or attempts to reduce or avoid it. In chronic pain patients' acceptance is associated with less disabilities, symptom reduction (or less attention to symptoms) and less medical consumption. In an experimental study in CFS patients it was shown that that hostile rejection towards in contrast to acceptance of CFS or relaxation triggered more symptoms.[51] The CBT protocol used in the studies reported in this dissertation also contains elements of acceptance: patients who are relatively active learn to accept the fact that they are currently severely fatigued in order to prevent bursts of activity that worsen symptoms. Given that CFS patients tend to perceive a lack of social support and a lack of acknowledgement of symptoms, we emphasize acceptance of the current situation and the social responses to this situation to be able to focus on reaching recovery in the future. However, it is conceivable that a more systematic use of elements from coping strategies aimed at the acceptance of CFS in those situations could help patients to deal better with their current situation. This seems especially true for the subgroup of patients who do not profit (enough) from CBT. We believe that the new developments in CBT could help to further improve the treatment of CFS patients and deserve to be tested on their effectiveness.

REFERENCES

1. Chambers D, Bagnall A, Hempel S, Forbes C. Interventions for the treatment, management and rehabilitation of patients with chronic fatigue syndrome/myalgic encephalomyelitis: an updated systematic review. J Roy Soc Med 2006; 99: 506-20.
2. Deale A, Husain K, Chalder T, Wessely, S. Long-term outcome of cognitive behaviour therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow up study. Am J Psychiatry 2001; 158: 2038-2042.
3. Van Houdenhove B. What is the aim of cognitive behaviour therapy in patients with chronic fatigue syndrome? Psychother Psychosom. 2006; 75: 396-7.
4. Suraway C, Hackmann A, Hawton K, Sharpe M. Chronic fatigue syndrome: a cognitive approach. Behav Res Ther 1995; 33: 535-544.
5. Vercoulen JHMM, Swanink CMA, Galama JMD, Fennis JFM, Jongen PJH, Hommes OR, et al. The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: the development of a model. J Psychosom Res 1998; 45: 507–517.
6. Bleijenberg G, Prins J, Bazelmans E. Cognitive behavioral therapies; in Jason LA, Fennell PA, Taylor RR (eds). Handbook of Chronic Fatigue Syndrome. New York, Wiley & Sons, 2003: 493-526.
7. Van Damme S, Crombez G, Van Houdenhove B, Mariman A, Michielsen W. Well-being in patients with chronic fatigue syndrome: the role of acceptance. J Psychosom Res 2006; 61:595-9.
8. Van der Werf SP, Prins JB, Vercoulen JHMM, van der Meer JWM, Bleijenberg G. Identifying physical activity patterns in chronic fatigue syndrome using actigraphic assessment. J Psychosom Res 2000; 49: 373-9.
9. Cho HJ, Skowera A, Cleare A, Wessely S. Chronic fatigue syndrome: an update focusing on phenomenology and pathophysiology. Curr Opin Psychiatr 2006; 19: 67-73.
10. Keefe FJ, Rumble ME, Scipio CD, Giordano LA, Perri LM. Psychological aspects of persistent pain: current state of the science. J Pain 2004; 5: 195-211.
11. Petrie K, Moss-Morris R, Weinman J. The impact of catastrophic beliefs on functioning in chronic fatigue syndrome. Psychosom Res 1995; 39: 31-7.
12. Broeckel JA, Jacobson PB, Horton J, Balducci L, Lyman GH. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. J Clin Oncol 1998; 16: 1689-1696.
13. Jacobson PB, Azzarello LM, Hann DM. Relationship of catastrophizing to fatigue severity in women with breast cancer. Cancer Research Therapy and Control 1999; 8: 155-164.
14. Jacobsen PB, Andrykowski MA, Thors CL. Relationship of catastrophizing to fatigue among women receiving treatment for breast cancer. J Consult Clin Psychol 2004; 72:355-361.
15. Claypoole KH, Noonan C, Mahurin RK, Goldberg J, Erickson T, Buchwald D. A twin study of cognitive function in chronic fatigue syndrome: the effects of sudden illness onset. Neuropsychology 2007; 21: 507-13.
16. Smith S, Sullivan, K. Examining the influence of biological and psychological factors on cognitive performance in chronic fatigue syndrome: a randomized, double blind, placebo-controlled, crossover study. Int J Behav Med 2003; 10: 162-173.
17. Van der Werf SO, De Vree B, Van der Meer JWM, Bleijenberg G. The relationship between body consciousness, somatic symptoms report and information processing speed in chronic fatigue syndrome. Neurol Neuropsychology Behav Neurol 2002; 12: 12-15.
18. Van der Werf S, Prins JB, Jongen P et al. Abnormal neuropsychological findings are not necessarily a sign of cerebral impairment: a matched comparison between chronic fatigue syndrome an multiple sclerosis. Neurol Neuropsychology Behav Neurol 2000; 13:199-203.
19. Deary V, Chalder T, Sharpe M. The cognitive behavioural model of medically unexplained symptoms: A theoretical and empirical review. Clin Psychol Rev 2007; 27:781-97.
20. Prins JB, Bleijenberg G, Bazelmans E, Elving L, de Boo Th, Severens JL, et al. Cognitive behaviour therapy for chronic fatigue syndrome: A multicentre randomised controlled trial. Lancet 2001 357; 841-7.
21. Gezondheidsraad. Het chronische-vermoeidheidssyndroom [Health council. Chronic fatigue syndrome]. Den Haag: gezondheidsraad, 2005, publicatie nr 2005/02.

22. Scheeres K, Wensing M, Knoop H, Bleijenberg G. Implementing cognitive behavioral therapy for chronic fatigue syndrome to a mental health centre: a benchmarking evaluation. J Consult Clin Psychol, accepted for publication.
23. Stulemeijer M, de Jong LWAM, Fiselier TJW, Hoogveld SWB, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. Brit Med J 2005; 330: 7481-6.
24. Surawy C, Roberts J, Silver A. The effect of mindfulness training on mood and measures of fatigue activity and quality of life in patients with chronic fatigue syndrome on a hospital waiting list: A series of exploratory studies. Behav Cogn Psychoth 2005; 33: 103-9.
25. Lim A, Lubitz L. Chronic fatigue syndrome: successful outcome of an intensive inpatient programme. J Pediatr Child Health 2002; 38: 295-9.
26. Powell P, Edwards RHT, Bentall RP. The treatment of wheelchair-bound chronic fatigue syndrome patients: two case studies of a pragmatic rehabilitation approach. Behav Cogn Psychoth 1999; 27: 249-260.
27. Van der Werf SP, Prins J, Klein-Rouweler E, Alberts M, Van der Meer J, Bleijenberg G. Homebound chronic fatigue syndrome patients. In: Van der Werf SP, Determinants and consequences of experienced fatigue in chronic fatigue syndrome and neurological conditions. Dissertation KUN, February 2003. http://webdoc.ubn.kun.nl/mono/w/-werf_s_van_der/deteancoo.pdfan.
28. Clark LV, White PD. The role of deconditioning and therapeutic exercise in chronic fatigue syndrome. Journal of Mental Health 2005; 14: 237-252.
29. Bazelmans E, Bleijenberg G, Van der Meer JWM, Folgering, H. Is physical deconditioning a perpetuating factor in chronic fatigue syndrome? A controlled study on maximal performance with fatigue, impairment and physical activity. Psychol Med 2001; 31: 107-114.
30. Moss-Morris R, Sharon C, Tobin R, Baldi JC. A randomized controlled graded exercise trial for chronic fatigue syndrome: outcomes and mechanisms of change. Health Psychol 2005; 10: 245-59.
31. Deale A, Chalder T, Wessely S. Commentary on: randomised, double-blind, placebo-controlled trial on fluoxetine and graded excercise for chronic fatigue syndrome. Br J Psychiat 1998; 172: 491-2.
32. Ekkekakis P, Hall EE, VanLanduyt LM, Petruzzello SJ. Walking in (affective) circles: can short walks enhance affect? J Behav Med 2000; 23: 245-75.
33. Mahurin RK, Claypoole KH, Goldberg JH, Arguelles L, Ashton S, Buchwald D. Cognitive processing in monozygotic twins discordant for chronic fatigue syndrome. Neuropsychol 2004; 18: 232-39.
34. Watson NF, Jacobsen C, Goldberg J, Kapur V, Buchwald D. Subjective and objective sleepiness in monozygotic twins discordant for chronic fatigue syndrome. Sleep 2004; 27: 973 –7.
35. Ullrich PM, Afari N, Jacobsen C, Goldberg J, Buchwald D. Cold pressor pain sensitivity in monozygotic twins discordant for chronic fatigue syndrome. Pain Med. 2007; 8:216-222.
36. Vercoulen JH, Bazelmans E, Swanink CM, Galama JM, Fennis JF, van der Meer JW, et al. Evaluating neuropsychological impairment in chronic fatigue syndrome. J Clin. Exp. Neuropsychol 1998; 20: 144-156.
37. de Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Werf SP, van der Meer JWM, Toni I. Neural correlates of the chronic fatigue syndrome- an fMRI study. Brain 2004; 127: 1979-1992.
38. Krijn M, Emmelkamp PM, Olafsson RP, Biemond R. Virtual reality exposure therapy of anxiety disorders: a review. Clin Psychol Rev 2004; 24: 259-81.
39. Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JWM, Toni I. Gray matter volume reduction in the chronic fatigue syndrome. NeuroImage 2005; 26: 777-781.
40. Kennedy SH, Konarski JZ, Segal ZV, Lau MA, Bieling PJ, McIntyre RS, et al. Differences in brain glucose metabolism between responders to CBT and Venalaxafine in a 16-week randomized controlled trial. Am J Psychiatry 2007; 164: 778-788.
41. Siegle GJ, Carter CS, Thase ME. Use of F-MRI to predict recovery from unipolar depression with cognitive behaviour therapy. Am J Psychiatry 2007; 163: 735-8.
42. Prins JB, Van der Meer JWM, Bleijenberg G. Chronic fatigue syndrome. Lancet 2006; 376: 346-355.
43. Bentall RP, Powell P, Nye FJ, Edwards RH. Predictors of response to treatment for chronic fatigue syndrome. Br J Psychiatry 2002; 181: 248-352.

44. Bazelmans E, Prins JB, Bleijenberg G. Cognitive behaviour therapy for relative active and for passive chronic fatigue syndrome patients. Cogn Behav Pract 2006; 13: 157-166.
45. Prins J, Bleijenberg G, Rouweler EK, van der Meer J. Effect of psychiatric disorders on outcome of cognitive-behavioural therapy for chronic fatigue. Br J Psychiatry 2005; 187: 184-5.
46. Matthews G, Wells A. Attention, automaticity and affective disorder. Behav Modif 2002; 24: 69-93.
47. Wells A, King P. Metacognitive therapy for generalized anxiety disorder: an open trial. J Behav Ther Exp Psychiat 2006; 37: 206-212.
48. Fischer PL, Wells A. Experimental modification of beliefs in obsessive-compulsive disorder; a test of the metacognitive model. Behav Res Ther 2005; 43: 821-829.
49. Bogels SM. Task concentration training versus applied relaxation, in combination with cognitive therapy, for social phobia patients with fear of blushing, trembling, and sweating. Behav Res Ther 2006; 44: 1199-1210.
50. Longmore RJ, Worell M. Do we need to challenge thoughts in cognitive behavior therapy? Clin Psychol Rev 2007; 27: 173-187.
51. Bogaerts K, Hubin M, Van Diest I, De Peuter S, Van Houdenhove B, Van Wambeke P, Crombez G, Van den Bergh O. Hyperventilation in patients with chronic fatigue syndrome: the role of coping strategies. Behav Res Ther 2007; 45: 2679-90.

Summary

This dissertation reports on six studies that investigate different aspects of the treatment of patients with chronic fatigue syndrome (CFS). CFS is characterized by severe fatigue lasting longer than six months and leading to a substantial reduction of activities. A somatic explanation for the fatigue is lacking. Cognitive behaviour therapy (CBT) is an evidence based treatment for CFS that leads to a reduction of fatigue and disabilities. CBT is aimed at changing cognitions and behaviours that perpetuate the fatigue. Although there is substantial evidence that CBT leads to a decrease of symptoms, there are concerns about the effectiveness and scope of CBT. This thesis aims to not only address some of the unresolved issues surrounding CBT, but also to test the effectiveness of a minimal intervention based on the protocol of CBT for CFS.

In *chapter 1* the outline of this thesis is presented.

Patients with CFS frequently report chronic pain symptoms. CBT for CFS is not aimed at pain symptoms. The study reported in *chapter 2* had three objectives. First, to test the hypothesis that successful treatment of CFS can also lead to a reduction of pain. CBT was considered successful if a patient reached a post-treatment level of fatigue within normal range. The second objective was to explore the possible mechanisms of changes in pain. The third objective was to assess the predictive value of pain for treatment outcome. Data from two CBT studies were used, one of adult CFS patients and one of adolescent CFS patients. The results showed that adult and adolescent CFS patients reported a significant reduction of pain severity after a successful CBT. Adult patients also had fewer pain locations following successful treatment. The decrease in fatigue predicted the change in pain severity. In adult patients, a higher pain severity at baseline was associated with a negative treatment outcome.

CFS patients often have concentration and memory problems. Neuropsychological test performance is impaired in at least a subgroup of patients with CFS. In the study, described in *chapter 3* we tested the hypothesis that CBT results in a reduction of self-reported cognitive impairment and in an improved neuropsychological test performance. We used the data of two randomised controlled trials; one of adult CFS patients and one of adolescent patients. In both studies the level of self-reported cognitive impairment decreased significantly more after CBT than in the control conditions. Neuropsychological test performance did not improve. The findings of this study support the idea that the distorted perception of cognitive processes is more central to CFS than actual cognitive performance.

In *chapter 4* the change in the experience of fatigue following CBT was investigated. For this, an adjective checklist, the Fatigue Quality List (FQL) was developed. The FQL aims to assess different perceptions of fatigue. The psychometric properties of the list were evaluated and component and confirmatory factor analyses were performed. Different

perceptions of fatigue were found in different patients' groups. CFS patients were characterised by strong negative connotations of fatigue. CFS patients who recovered after CBT did no longer differ in their experience of the fatigue from healthy controls.

There is controversy about the nature of the changes following treatment of CFS with CBT; some suggest that patients improve by learning to adapt to a chronic condition, others think that recovery is possible. The objective of the study presented in *chapter 5* was to find out whether recovery from CFS is possible after CBT. The outcome of a cohort of 96 patients treated with CBT was studied. The definition of recovery was based on the absence of the criteria for CFS set up by the Center for Disease Control (CDC), but also took into account the perception of the patients' fatigue and their own health. Data from healthy population norms were used in calculating conservative thresholds for recovery. After treatment, 69% of the patients no longer met the CDC criteria for CFS. The percentage of recovered patients depended on the criteria used for recovery. Using the most strict definition of recovery, 23% of the patients fully recovered. Fewer patients with a co-morbid medical condition recovered. It was concluded that significant improvement following CBT is probable and that full recovery is possible. Sharing this information with patients can raise the expectations of the treatment, which may enhance outcomes.

In *chapter 6* the long term outcome of adolescents with CFS who received CBT was investigated. Also, the predictive value of fatigue severity and physical impairments of the adolescent, and the fatigue severity of the mother at baseline for the outcome of the treatment at follow-up was determined. Adolescent CFS patients who previously participated in a randomized controlled trial were contacted for a follow-up. The original study showed that CBT was more effective than a waiting list condition in reducing fatigue and improving physical functioning. In this particular study, the mean follow-up time was 2.1 years. There was no significant change in fatigue severity between post treatment and follow-up in the patients who had received CBT. There was a significant further increase in physical functioning and school attendance. A group of patients who did not receive treatment were more fatigued, more functionally impaired, and had a lower school attendance at follow-up than patients treated with CBT. Higher fatigue severity of the mother predicted lower treatment outcome in adolescent patients. We concluded that the positive effects of CBT in adolescents with CFS are sustained after CBT.

The capacity to treat CFS patients with CBT is lacking and it is unlikely that enough trained therapists will be available in the near future. We developed a minimal intervention for CFS consisting of self-instructions combined with email contact based on the protocol for CBT. We tested if the guided self-instructions led to reduction of fatigue and disabilities and tried to predict for which patients this minimal intervention suffices. In a randomised controlled trial the effects of the intervention were compared to a waiting list condition. The main outcome measures, fatigue severity and level of disabilities, were determined at baseline

and after the intervention or waiting period. The trial is described in *chapter 7*. In total 85 patients were allocated to the treatment condition, 86 to the waiting list. An intention to treat analysis showed that fatigue and disabilities decreased significantly after guided self-instructions. Fatigue severity and disabilities were negatively related with treatment outcome. We concluded that guided self-instructions are an effective treatment for relatively less severely disabled and fatigued CFS patients.

Finally, in *chapter 8,* the findings of the six studies were discussed in light of the literature on CBT for CFS. The implications of the findings for the treatment of CFS patients and possible directions for future research were formulated. The importance of further development of a model of stepped care for CFS was emphasized. It was concluded that it is likely that the central disorder in CFS is one of perception of bodily symptoms and one's own performance and activity levels in relation to the symptoms. Future research should be aimed at investigating this disorder in perception and the possible mechanisms of change in CBT for CFS. This research is necessary to better understand CFS and to further improve CBT for CFS.

Samenvatting

In dit proefschrift werden de resultaten van zes studies beschreven waarin verschillende aspecten van de behandeling van patiënten met het chronische vermoeidheidssyndroom (CVS) zijn onderzocht. CVS wordt gekenmerkt door ernstige vermoeidheid, die langer dan 6 maanden aanhoudt en samengaat met aanzienlijke beperkingen in het dagelijkse functioneren. Er is geen lichamelijke verklaring voor de vermoeidheid. Cognitieve gedragstherapie (CGT) is een evidence based behandeling voor CVS die leidt tot een afname van de vermoeidheid en beperkingen. Hoewel het meeste onderzoek dat verricht is laat zien dat CGT een effectieve behandeling is, bestaat er wel discussie over de aard en omvang van de behandeleffecten. In vijf verschillende studies, die zijn beschreven in de hoofdstukken 2 tot en met 6, werden de effecten van CGT nader onderzocht. In de zesde studie, beschreven in hoofdstuk 7, werd een nieuwe behandelvorm, gebaseerd op het CGT protocol voor CVS, op zijn werkzaamheid getoetst.

In *hoofdstuk 1* werd een inleiding gegeven over CVS en werden de achtergronden van de studies die in het kader van dit proefschrift zijn verricht besproken.

CVS patiënten zijn niet alleen ernstig moe, vaak rapporteren zij ook chronische pijnklachten. Binnen het CGT protocol voor CVS zijn er geen specifieke interventies die gericht zijn op deze pijnklachten. In *hoofdstuk 2* werd de studie beschreven waarin de hypothese werd getoetst dat succesvolle behandeling van CVS met CGT samengaat met een afname van pijnklachten. Een behandeling werd als succesvol beschouwd als de patiënt niet langer ernstig vermoeid was. Het tweede doel van het onderzoek was na te gaan welke mechanismen een rol spelen bij de (eventuele) afname van pijnklachten. Het derde doel was te bepalen of de ernst van de pijnklachten bij aanvang van de behandeling een voorspellende waarde had voor het behandeleffect. Om deze vragen te beantwoorden werden gegevens van twee eerdere studies gebruikt die de effectiviteit van CGT hadden onderzocht. Een van deze studies was bij volwassen CVS patiënten gedaan, de andere bij adolescenten met CVS. In beide patiëntgroepen was er een significante afname van pijnklachten na een succesvol verlopen CGT. Bij volwassen patiënten nam ook het aantal pijnlijke plekken op het lichaam af na behandeling. De afname in vermoeidheid tijdens de behandeling voorspelde de afname van de pijnklachten. Bij CVS patiënten met zeer ernstige pijnklachten bij aanvang van de therapie was het resultaat van de behandeling van vermoeidheid met CGT geringer. Dit gold overigens alleen voor de volwassen CVS patiënten. Geconcludeerd werd dat CGT voor CVS ook een effectieve behandeling is voor de pijnklachten van CVS patiënten.

Patiënten met CVS klagen vaak over concentratiezwakte en vergeetachtigheid. Een deel van de patiënten heeft afwijkende prestaties op neuropsychologische tests. In *hoofdstuk 3* werd de hypothese getoetst dat CGT leidt tot een afname van klachten over het mentaal functioneren en tot een verbetering van prestaties op neuropsychologische tests. Om deze hypothese te toetsen werden de gegevens gebruikt van twee gerandomiseerde en

gecontroleerde studies waarin de effectiviteit van CGT werd onderzocht. Een van deze studies was bij volwassen CVS patiënten gedaan, de andere bij adolescenten met CVS. In beide groepen namen de klachten met betrekking tot het mentaal functioneren significant af. De prestaties op neuropsychologische tests verbeterden niet na behandeling. De resultaten van deze studie zijn in overeenstemming met de hypothese dat niet zozeer de mentale prestaties verstoord zijn in CVS, maar dat veeleer de perceptie van het functioneren van mentale processen veranderd is.

In *hoofdstuk 4* werden de veranderingen in de ervaring van vermoeidheid na CGT beschreven. Voor dit doel werd de Fatigue Quality List (FQL) ontwikkeld. Dit is een checklist met bijvoeglijke naamwoorden waarmee wordt beoogd de verschillende percepties van vermoeidheid te meten. De psychometrische eigenschappen van de FQL werden bepaald en er werd een componenten- en conformatorische factoranalyse uitgevoerd. Er bleken verschillen te zijn in de perceptie van vermoeidheid tussen de verschillende ziektebeelden die werden onderzocht. CVS patiënten werden gekenmerkt door een zeer negatieve perceptie van de vermoeidheid. Als CVS patiënten herstelden na CGT en niet langer ernstig moe waren, veranderde ook hun perceptie van de vermoeidheid. Deze perceptie was na CGT hetzelfde als die van gezonde proefpersonen.

Er bestaan verschillende opvattingen over de aard van de veranderingen die worden bewerkstelligd met CGT voor CVS. Sommigen zijn van mening dat patiënten beter leren omgaan met hun chronische aandoening. Dit leidt tot een verbetering van hun toestand zonder dat sprake is van herstel. Anderen daarentegen stellen dat een volledig herstel van CVS na CGT mogelijk is. In *hoofdstuk 5* werd nagegaan of herstel van CVS na CGT mogelijk is. Van een cohort van 96 CVS patiënten die met CGT behandeld was, werd het behandelresultaat onderzocht. Er werden verschillende definities van herstel gehanteerd die onder andere waren gebaseerd op de internationaal algemeen geaccepteerde criteria voor CVS van het Center for Disease Control (CDC). Er werd niet alleen gekeken naar het effect van de behandeling op vermoeidheid en de activiteiten van patiënten, maar ook naar de perceptie van vermoeidheid en de gezondheidsbeleving. Er werden zeer strikte criteria voor herstel bepaald waarbij gebruik gemaakt werd van normgegevens van de gezonde populatie. Na behandeling voldeed 69% van de patiënten niet langer aan de CDC criteria voor CVS. Afhankelijk van de definitie van herstel die werd gehanteerd varieerde het percentage herstelde patiënten. Patiënten met een lichamelijke aandoening naast CVS, hadden een minder grote kans op herstel. Geconcludeerd werd dat het zeer waarschijnlijk is dat volgend op CGT een aanzienlijke verbetering in klachten en functioneren optreedt en dat een volledig herstel van CVS mogelijk is. Het delen van deze informatie met patiënten kan maken dat patiënten meer gaan verwachten van therapie. Dit kan een positief effect hebben op het daadwerkelijke behandelresultaat.

In *hoofdstuk 6* kwamen de lange termijn effecten van CGT bij adolescenten met CVS aan de orde. Ook werd onderzocht welke factoren het behandelresultaat op langere termijn voorspellen. Gekeken werd naar de voorspellende waarde van de ernst van de vermoeidheid en fysieke beperkingen van de adolescent gemeten bij aanvang van de therapie. Ook werd de voorspellende waarde van de ernst van de vermoeidheid van de moeder van de adolescent voor het behandelresultaat bij follow-up bepaald. De patiënten die werden benaderd voor het follow-up onderzoek hadden meegedaan aan een gerandomiseerde en gecontroleerde studie waarin het effect van CGT direct na behandeling was onderzocht. Deze studie had aangetoond dat CGT ook bij adolescenten met CVS leidde tot een afname van vermoeidheid en beperkingen. In het huidige onderzoek was er gemiddeld meer dan twee jaar verstreken tussen afsluiting van de behandeling en de follow-up meting. In de groep patiënten die behandeld was met CGT was er geen verandering opgetreden in de ernst van de vermoeidheid; de bereikte verbetering was behouden gebleven. Het fysieke functioneren was verder verbeterd en het schoolverzuim was verder afgenomen. De groep niet-behandelde patiënten was meer vermoeid, had meer fysieke beperkingen en had een hoger schoolverzuim bij de follow-up meting dan de groep patiënten die met CGT waren behandeld. Naarmate de moeder van de adolescent ernstiger vermoeid was bij aanvang van de therapie van haar kind, was het behandelresultaat op langere termijn minder gunstig.
Op grond van dit onderzoek kan geconcludeerd worden dat de positieve effecten van CGT bij adolescenten met CVS ook op langere termijn aanhouden en dat zelfs sprake is een verdere verbetering.

De behandelcapaciteit voor CGT voor patiënten met CVS is ontoereikend. Het is onwaarschijnlijk dat op korte termijn voldoende therapeuten getraind kunnen worden om deze behandeling op grotere schaal te geven. Er is behoefte aan minder intensieve interventies waarmee grotere groepen patiënten behandeld kunnen worden. Wij ontwikkelden een minimale interventie voor CVS die bestaat uit zelfbehandelingsinstructies (ZBI) gecombineerd met tweewekelijks email contact met een therapeut. De minimale interventie is gebaseerd op het CGT protocol voor CVS. In een gerandomiseerde en gecontroleerde studie die beschreven werd in *hoofdstuk 7*, hebben we de effectiviteit van ZBI onderzocht. Hierbij werd tevens nagegaan voor welke groep patiënten de minimale interventie toereikend is. De effecten van ZBI werden vergeleken met een wachtlijstconditie. De primaire uitkomstmaten, ernst van de vermoeidheid en ernst van de beperkingen, werden gemeten voor en na de interventie of de wachtperiode. In totaal werden 85 patiënten toegewezen aan de ZBI conditie en 86 aan de wachtlijstconditie. De resultaten lieten zien dat de vermoeidheid en de beperkingen meer afnamen na ZBI. Hoe ernstiger vermoeid en hoe meer beperkt een patiënt was, hoe kleiner de kans was dat hij of zij profiteerde van behandeling. Dit bracht ons tot de conclusie dat ZBI een effectieve behandeling is voor relatief minder ernstig vermoeide en beperkte patiënten. Op deze wijze ingezet, zou ZBI de eerste stap kunnen vormen in een model van getrapte zorg voor CVS.

In *hoofdstuk 8* werden de resultaten van de onderzoeken geplaatst in het kader van wat uit eerder onderzoek reeds bekend was over de effecten van CGT voor CVS. De implicaties van de resultaten van de studies uit dit proefschrift voor de behandeling van CVS patiënten werden besproken en er werden suggesties gedaan voor vervolgonderzoek.

List of publications

Papers, published or in press

Knoop H, Stulemeijer M, de Jong LWAM, Fiselier THW, Bleijenberg, G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: long term follow-up of a randomised, controlled trial. Pediatrics, in press.

Knoop H, Stulemeijer M, Prins JB, Van der Meer JWM, Bleijenberg G. Is cognitive therapy for chronic fatigue syndrome also effective for pain symptoms? Behaviour Research and Therapy 2007; 45: 2034-2043.

Knoop H, Prins JB, Stulemeijer M, Van der Meer JWM, Bleijenberg G. The effect of cognitive behaviour therapy for chronic fatigue syndrome on self-reported cognitive impairments and neuropsychological test performance. Journal of Neurology, Neurosurgery and Psychiatry 2007; 78: 434-436.

Knoop H, Bleijenberg G, Gielissen MFM, Van der Meer JWM, White PD. Is a full recovery possible after cognitive behavioural therapy for chronic fatigue syndrome? Psychotherapy and Psychosomatics 2007; 76: 171-176.

Knoop H, Kan CC, Mickers FC, Barnhoorn D. Het voorspellen van het succes van benzodiazepine-afbouw: mythes of klinische wijsheden? Tijdschrift voor Psychiatrie 2006; 48: 685-703.

Knoop H, Bleijenberg G. Preoccupaties in het chronisch vermoeidheidssyndroom. Tijdschrift voor Directieve Therapie 2005; 25: 205-217.

Knoop JA. Neuropsychology and cognitive rehabilitation; congresbespreking. De Psycholoog 2000; 35: 395-396.

Scheeres K, Wensing M, Knoop H, Bleijenberg G. Implementing Cognitive Behavioral Therapy for CFS in a MHC: a Benchmarking Evaluation. Journal of Consulting and Clinical Psychology, in press.

Gielissen MFM, Knoop H, Servaes P, Kalkman JS, Huibers MJH, Verhagen C, Bleijenberg G. Differences in the experience of fatigue in patients and healthy controls: patients descriptions. Health and Quality of Life Outcomes 2007; 5:36.

Bleijenberg G, Gielissen M, Knoop H. Het chronisch vermoeidheidsyndroom. Psychopraxis 2006; 8:104-110.

Van der Linde H, Snoek GJ, Geurts ACH, Knoop JA, Van Limbeek J, Mulder T. Kinematic assessment of manual skill following functional hand surgery in tetraplegia. American Journal of Hand Surgery 2000; 25: 1140-1146.

Geurts ACH, Knoop JA, Van Limbeek J. Is postural control associated with mental functioning in the persistent post-concussion syndrome? Archives of Physical Medicine and Rehabilitation 1999; 80:144-149.

Groet E, Balen van HGG, Knoop JA. Diagnostiek en behandeling na niet-aangeboren hersenletsel: enige verruiming in het zorgaanbod. Medisch Contact 1997; 52:191-192.

Geurts ACH, Ribbers GM, Knoop JA, Van Limbeek J. Identification of static and dynamic postural instability following traumatic brain injury. Archives of Physical Medicine and Rehabilitation 1996; 77: 639-644.

Van Balen HGG, Knoop JA. Revalidatie na Mild Hersenletsel: Kering van het tij? Nederlands Tijdschrift voor Kinderrevalidatie 1993; 73: 7-14.

Papers, submitted

Knoop H, Van der Meer JWM, Bleijenberg G. The effectiveness of self-instructions for chronic fatigue syndrome: a randomised controlled trial, submitted.

Knoop H, Oerlemans M, Rombouts, M., Oostendorp R., Folgering H, Bleijenberg G. Pervasively passive chronic fatigue syndrome patients perform poorly on a squat test, submitted.

Gielissen MFM, Knoop H, Kalkman JS, Verhagen C, Bleijenberg G. Pictorial representation of self and illness measure (PRISM) in patients suffering from severe fatigue: a useful tool in research and clinical practice, submitted.

Goedendorp MM, Knoop H, Schippers GM, Bleijenberg G. Is the lifestyle of patients with chronic fatigue syndrome related to fatigue and functional impairments? submitted.

Scheeres K, Knoop H, Bleijenberg G. Clinical assessment of the physical activity pattern of chronic fatigue syndrome patients: a validation of three methods, submitted.

Contributions to books

Hoogduin CAL, Spinhoven Ph, Hagenaars M, Bleijenberg G, Knoop H. Somatoforme stoornissen. In: Vandereycken W, Hoogduin CAL, Emmelkamp PMG. (eds). Handboek Psychopathologie deel 1: Basisbegrippen. 2e herziene druk. Houten/Diegem: Bohn Stafleu Van Loghum, in press.

Bleijenberg G, Prins J, Bazelmans E, Knoop H. Het chronisch vermoeidheidssyndroom. In: Feltz-Cornelis van der C, Horst van der H (eds). Handboek Somatisatie-lichamelijk onverklaarde klachten in de eerste en tweede lijn. 2e herziene druk. Utrecht: De Tijdstroom, in press.

Bleijenberg G, Gielissen M, Knoop H. Chronische vermoeidheid. In: Kaptein AA, Beundermans R, Dekker J, Vingerhoets AJJM (eds). Psychologie en Geneeskunde. Derde, geheel herziene druk. Houten: Bohn, Stafleu, van Loghum, 2006: 275-302.

Knoop JA, Van der Heijden HP, Hulstijn W, Van Hoof J. Difference in effect of age and psychiatric illness on cognitive and motor components of writing in a symbol-digit substitution test. In: Proceedings of the sixth international conference on handwriting and drawing. Paris: Telecom, 1993: 52-54.

Dankwoord

Ik schreef dit proefschrift naast mijn klinisch werk en dat was alleen mogelijk door de hulp en steun van velen. Graag wil ik hen op deze plaats bedanken.

Allereerst wil ik de patiënten bedanken die meededen aan de verschillende studies. Uw medewerking maakte het mogelijk de effecten van cognitieve gedragstherapie te onderzoeken. U kwam eigenlijk alleen naar ons centrum voor behandeling, maar stemde ook in met deelname aan wetenschappelijk onderzoek. Ook degenen waarbij de behandeling niet het verwachte resultaat gaf, waren desondanks vaak bereid alsnog een indrukwekkende batterij aan vragenlijsten in te vullen, een dagboek bij te houden en een actometer te dragen. Ik wil u allen bedanken voor uw bijdrage.

Gijs Bleijenberg en Jos van der Meer hebben mij de afgelopen jaren begeleid. Beste Gijs, ik wil je bedanken voor wat jij mij de afgelopen jaren geleerd hebt als onderzoeker en therapeut. Het was leuk samen te zoeken naar oplossingen, altijd had jij wel een verrassend nieuw gezichtspunt als het even niet verder leek te kunnen. Ik leerde niet alleen dat in behandeling en onderzoek vaak meer mogelijk is dan ik dacht, jij leerde mij ook dat ik meer kon dan ik voor mogelijk hield. Daar pluk ik nog elke dag de vruchten van, bedankt hiervoor. Beste Jos, voor een dokter weet je ongelofelijk veel van gedragstherapie. Je was meer op afstand betrokken, maar ik weet dat je een belangrijke rol speelt in het faciliteren van ons werk. Ik wil je bedanken voor de bruikbare commentaren op mijn teksten en vooral de bemoedigende adviezen.

Voor onderzoek zijn data nodig. Bij het verzamelen hiervan hebben de psychologisch medewerkers, Carel, Tiny, Harmen, Lianne en Judith vaak en veel geholpen. Op elke (bijna) onmogelijke vraag van mij hadden jullie een gevat antwoord, doken vervolgens in de bestanden en vonden de gegevens, bedankt hiervoor.

Bij het merendeel van de studies werden de gegevens van eerdere projecten gebruikt. Ik wil Maja Stulemeijer en Judith Prins bedanken voor hun bereidwilligheid om zich opnieuw te verdiepen in hun (vaak al lang geleden afgesloten) projecten. Terwijl jullie zelf vaak al druk bezig waren met andere zaken, lukte het toch mijn vele vragen tussen de bedrijven door te beantwoorden. Ook de bijdragen van Lieke de Jong en Theo Fiselier aan het follow-up onderzoek van adolescenten heb ik zeer op prijs gesteld. Speciale dank gaat uit naar Ria te Winkel, die ook toen zij niet langer bij onze afdeling werkte altijd bereid was oude gegevens op te diepen en de data voor mij op een rijtje te zetten.

Theo de Boo wil ik bedanken voor zijn hulp bij de statistische analyse.

Hoewel ik de afgelopen jaren veel onderzoek heb gedaan, was ik het grootste deel van mijn tijd werkzaam als behandelaar. De samenwerking met de andere therapeuten (Agaat, Hein, Annemarie, Thea, Gerrie, Henriette, Hanneke, Sanny, Ines, Inge en Pauline) was niet alleen

goed en leuk (vooral de groep, Agaat!), jullie leverden ook een belangrijke bijdrage aan mijn onderzoek. Jullie behandelden niet alleen een deel van de patiënten die meededen aan de studies, voor het onderzoek naar de effecten van de zelfbehandelingsinstructies hebben jullie heel wat voor mij geregistreerd, uitgezocht en bijgehouden terwijl daar eigenlijk geen tijd voor was. Bedankt hiervoor!

Liesbeth, zonder jou zou elke verjaardag op de afdeling vergeten worden en zou ik niet weten welke goede films ik allemaal mis! Laat je niet (al te) gek maken!

De collega-onderzoekers (Marieke 'de Koningin'; Martine; Dewey; Korine; Marcia; Gerard; Joke; Marjolein; Ingrid; Sanne) wil ik bedanken voor de wandelingen in het park, het gezellige kletsen, de confrontaties met mijn leeftijd en het ontbreken van enige gelijkenis met Brad Pitt, het verbod nog langer de Kermit de Kikker trui te dragen en last but not least het maandagochtendoverleg.

Beste Klaartje, het sprak voor zich dat jij paranimf zou zijn, bedankt voor alle vriendschap van de afgelopen jaren. Peter, na al die aandachtsvolle uitstapjes mogen we ons nu in het pak hijsen. Jacques, een betere vriend kan ik mij niet voorstellen, bedankt voor de broodnodige afleiding. Het kon niet anders dan dat jij je ermee ging bemoeien toen het op het eten en drinken aankwam. Lieve Mirjam, dank je wel voor alle hulp bij de finishing touch bij het proefschrift, jij ziet een lay-out fout van een kilometer afstand.

Gerda, wie zou ooit gedacht hebben dat jij 9 uur vliegen verder de teksten van mijn proefschrift zou corrigeren? Dank voor al je (snelle) inzet en de goede tijden die wij hadden bij de bezoeken aan jouw nieuwe plek.

Mijn ouders hebben een belangrijke bijdrage geleverd aan veel dingen die ik heb gedaan, ook aan dit proefschrift. Ma, zolang ik maar doe wat ik graag wil vind jij het goed, wat het dan ook moge zijn, bedankt hiervoor. Pa, jij was altijd apetrots op al onze prestaties en zou ook aan dit moment veel lol hebben beleefd. Je hebt mij veel gegeven, het is zo jammer dat je niet meer bij ons bent.

David, jij kan dit nog niet lezen, maar jij was zonder twijfel de afgelopen jaren de beste en leukste reden om niet te werken.

Lieve Monique, samen hebben wij al veel gedeeld, heel veel leuke en sommige minder leuke dingen. En toen kwam ook deze klus nog voorbij. Soms was dit wat veel, maar altijd was je steunend, dacht en hielp je mee. Dank je wel, en ook voor al die, al die andere dingen.

Curriculum Vitae

Hans Knoop werd op 14 december 1966 geboren in ‘s-Hertogenbosch. Na het behalen van het VWO diploma begon hij in 1986 met de studie psychologie aan de Katholieke Universiteit Nijmegen. In 1992 studeerde hij cum laude af in de neuro- en revalidatiepsychologie.

Hij was als neuropsycholoog van 1992 tot 2001 werkzaam in het revalidatiecentrum van de St. Maartenskliniek in Nijmegen. Hij hield zich bezig met patiëntenzorg en de ontwikkeling en evaluatie van revalidatieprogramma’s voor patiënten met hersenletsel. In 1998 werd hij geregistreerd als Gezondheidszorgpsycholoog.

Van 2001 tot 2003 was hij verbonden aan de polikliniek van de afdeling Psychiatrie van het UMC St. Radboud. Daar combineerde hij patiëntenzorg met onderwijs- en onderzoekstaken en was praktijkopleider en supervisor van de opleiding tot Gezondheidszorgpsycholoog. In 2003 volgde de registratie tot gedragstherapeut.

Van 2003 tot en met 2004 was hij als psycholoog verbonden aan het Diabetesteam van de afdeling Algemeen Interne Geneeskunde. Vanaf eind 2003 is hij werkzaam op het Nijmeegs Kenniscentrum voor Chronische Vermoeidheid (NKCV) van het UMC St. Radboud. Naast de patiëntenzorg had hij onderwijstaken en deed onderzoek naar de behandeling van patiënten met het chronische vermoeidheidssyndroom (CVS). Het proefschrift is gebaseerd op dit onderzoek. Als trainer en supervisor is hij betrokken (geweest) bij diverse implementatieprojecten voor cognitieve gedragstherapie voor CVS. In 2007 behaalde hij zijn BIG registratie Klinisch Psycholoog.

Momenteel heeft hij naast zijn klinische werkzaamheden een aanstelling als post-doc onderzoeker op het NKCV.

Hans Knoop leeft samen met Monique de Lugt. Zij hebben één zoon, David.