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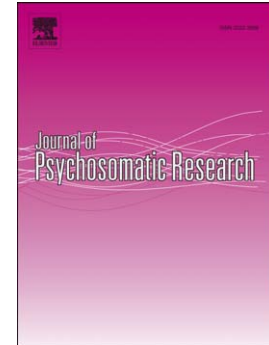
Cognitive behaviour therapy for chronic fatigue syndrome: Differences in treatment outcome between a tertiary treatment centre in the United Kingdom and the Netherlands

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Title: Cognitive behaviour therapy for chronic fatigue syndrome: differences in treatment outcome between a tertiary treatment centre in the United Kingdom and the Netherlands.

Running head: Comparing treatment outcome after CBT for CFS internationally.

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Abstract**Objective**

Cognitive behaviour therapy (CBT) reduces fatigue and disability in chronic fatigue syndrome (CFS). However, outcomes vary between studies, possibly because of differences in patient characteristics, treatment protocols, diagnostic criteria and outcome measures. The objective was to compare outcomes after CBT in tertiary treatment centres in the Netherlands (NL) and the United Kingdom (UK), using different treatment protocols but identical outcome measures, while controlling for differences in patient characteristics and diagnostic criteria.

Methods

Consecutively referred CFS patients who received CBT were included (NL: n=293, UK: n=163). Uncontrolled effect sizes for improvement in fatigue (Chalder Fatigue Questionnaire), physical functioning (SF-36 physical functioning subscale) and social functioning (Work and social adjustment scale) were compared. Multiple regression analysis was used to examine whether patient differences explained outcome differences between centres.

Results

Effect sizes differed between centres for fatigue (Cohen's D NL=1.74, 95% CI=1.52-1.95; UK=0.99, CI=0.73-1.25), physical functioning (NL=0.99, CI=0.81-1.18; UK=0.33, CI=0.08-0.58) and social functioning (NL=1.47, CI=1.26-1.69; UK=0.61, CI=0.35-0.86). Patients in the UK had worse physical functioning at baseline and there were minor demographic differences. These could not explain differences in centre outcome.

Conclusion

Effectiveness of CBT differed between treatment centres. Differences in treatment protocols may explain this and should be investigated to help further improve outcomes.

Keywords

Cognitive behaviour therapy; Chronic fatigue syndrome; Treatment outcome; Treatment protocols; Outcome prediction.

Introduction

Chronic fatigue Syndrome (CFS) is characterized by severe and chronic fatigue that cannot be explained by a medical disease or psychiatric disorder. Other symptoms such as pain, post-exertional malaise, and unrefreshing sleep are present (1; 2). CFS patients report substantial disabilities in daily functioning. The prognosis is poor if untreated; the median spontaneous recovery rate is 5% (3). To operationalize CFS, the US Centres for Disease Control (CDC) criteria (1; 2) and the Oxford criteria (4) are most widely used. Both state that fatigue should be severe and ongoing, but there are differences in the symptoms required to diagnose CFS.

Research has shown that fatigue related behaviour and beliefs play a crucial role in the persistence of CFS (5; 6; 7). Cognitive behaviour therapy (CBT) for CFS aims at changing behaviour and beliefs that maintain fatigue and disability and has proven effective (8; 9; 10). It leads to a significant reduction of fatigue and functional impairment, which seems to be mediated by changes in behaviours and cognitions (11; 12; 13; 14). A subgroup of patients fully recovers (15; 16; 17; 18).

Treatment effect on fatigue severity varies between studies. In one meta-analysis, effect sizes ranged from -0.06 to 1.67 (overall effect size: 0.48; 19), with significant heterogeneity. Another meta-analysis also found heterogeneity, before outliers were winsorized (10). Fewer therapy sessions were associated with lower effect sizes in this meta-analysis. It is not known which other factors may be responsible for this heterogeneity. Possible explanations are the use of different diagnostic criteria for CFS, variations in the interventions applied, patient characteristics and the use of different outcome measures. Using different diagnostic criteria for CFS may lead to the selection of different patient groups that do not benefit equally from CBT. Additionally, as CBT is a complex intervention, different versions of CBT for CFS may lead to different outcomes. Furthermore, different fatigue questionnaires could measure different aspects of fatigue, which are affected differently by the interventions (20).

This study investigated variation in outcome in two leading centres internationally, that use different approaches of CBT for CFS. Both centres developed treatment protocols for CFS which were tested in several RCT's (8; 18; 21; 22; 23; 24; 25;26). In all these studies CBT led to a significant reduction of fatigue and impairment. The use of different outcome measures makes a direct comparison difficult. In this study, we used the same outcome measures in both centres and corrected for possible patient differences. Gaining more insight into contributors to treatment outcome variability could help improve treatment effect.

The treatment protocols for both versions of CBT have been published (23; 27). They are based on cognitive behavioural models of CFS, which differ in emphasis. The model on which the Dutch protocol was based (6) assumes that a low self-efficacy with respect to fatigue, a reduced level

of physical activity and a tendency to focus on symptoms play a central role in the perpetuation of fatigue and disability. The model on which the UK protocol was based (6; 28) assumes that fear of engaging in activity, symptom focusing and avoidance of activity perpetuate CFS. Both protocols include an initial adoption of a consistent approach to activity, a gradual increase in activity, sleep management, and cognitive restructuring. Both require 12-15 treatment sessions over a period of six months and are delivered by trained cognitive behavioural therapists. Although the treatment elements overlap, the protocols emphasise different treatment elements. Table 1 shows an overview of the protocol differences.

First, in the Dutch protocol treatment recovery is set as a therapy goal more explicitly. Although recovery rates are similar (16; 17; 29), stating recovery as the treatment goal may boost treatment effect, as outcome expectation of patients, especially the idea that recovery is possible, is known to contribute to treatment outcome (13).

Both interventions underline the importance of graded activity. The Dutch protocol distinguishes between patients with a low physical activity level and patients with a fluctuating activity pattern. The former increase their activity level early in therapy, the latter first balance their activities more evenly (29). The UK approach to activity is not protocol driven but individualized. When appropriate, patients learn to adopt a consistent approach to activity.

The Dutch protocol includes a specific physical activity program, in which the patient learns to increase physical activity regardless of symptoms and to modify cognitions that reflect low self-efficacy with respect to being active. These same principles are applied during the gradual increase of social and mental activity. This graded activity program is prescriptive. Patients increase walking or cycling by a minute per day, from an achievable level. The increase is time contingent, irrespective of the symptom level. The UK approach is formulation based and individualised. Increases in activities of daily life, like household chores, socialising and taking on responsibilities are negotiated with the patient. The patients learn that they can manage increases in activity, and although symptoms may get worse before they get better, over time the level of fatigue usually reduces. The activity increase is to some extent dependent on the percentage of activities accomplished earlier. If a patient is unable to attain the negotiated goals then harder goals will not be negotiated. This approach is therefore not fully time contingent.

In both protocols, unhelpful cognitions are identified and modified. Different cognitions are aimed at. In the Dutch protocol the physical activity program is aimed at increasing self-efficacy regarding fatigue and activity. Furthermore, specific interventions are applied to teach patients to redirect attention from symptoms towards other stimuli. First, the effect of attention on the perception of bodily symptoms is illustrated during therapy and its role in the perpetuation of fatigue is discussed. Then patients are invited to no longer talk about fatigue and to ask significant

others not to inquire about fatigue. Finally, patients practice with redirecting the focus of their attention away from the fatigue to an activity or their environment, e.g. during social interactions or the graded activity program. In the UK protocol, patients learn that they can manage an increase in activities, knowing that symptoms may get worse before they get better. The UK protocol advocates a shift in the focus of attention from fatigue, but no specific intervention targets this.

In the comparison of treatment outcome in the two centres, we corrected for the fact that both centres used different operational criteria for CFS. The Dutch centre used CDC criteria for CFS, while the UK centre used Oxford criteria. The groups were compared with respect to demographics, symptom levels and duration. Where differences were found in treatment effects between the Dutch and the UK treatment centres, it was explored to what extent differences in patient characteristics and diagnostic criteria for CFS could explain this.

Methods

Participants

Consecutively referred patients with CFS who commenced CBT, defined by attendance at both assessment sessions and at least one treatment session, were included. In the Dutch centre, the Expert Centre for Chronic Fatigue of the Radboud University Medical Center in Nijmegen, the inclusion period was September 2010 - January 2012. In the UK centre, the Chronic Fatigue Research and Treatment Unit at the South London and Maudsley NHS Trust and King's College London, the inclusion period was September 2009 - December 2011. Patients that received CBT for CFS previously or started other treatment for fatigue during the CBT were excluded. In the Netherlands all patients met the CDC criteria for CFS (1; 2). In the UK patients met Oxford criteria for CFS (4). Both case definitions define CFS as a syndrome characterized by fatigue as principal symptom. The fatigue must be severe, disabling, with a definite onset (not lifelong present) and present for 6 months or more. According to the Oxford criteria the fatigue has to affect both physical and mental functioning. This is not explicitly stated in the CDC definition. Both case definitions state that a medical explanation for the fatigue should be ruled out. According to the CDC definition at least 4 out of the following 8 additional symptoms should be present: headache; post-exertional malaise; joint pain; muscle pain; sore throat, sensitive lymph nodes; unrefreshing sleep; memory problems or difficulty concentrating. The Oxford guideline does not have this criterion.

Measures

Fatigue severity

Fatigue severity was measured with the Chalder Fatigue Questionnaire (CFQ), a widely used questionnaire, consisting of 11 items. Likert scoring was used (range 0-3; total score 0-33; 31) in preference to binary scoring, as it was suggested that more variance results in greater sensitivity in detecting change (26). The CFQ is reliable and valid (32, 33). For the Dutch centre, we developed and validated a Dutch version of the CFQ (Appendix 1).

Physical functioning

Physical functioning was measured using the subscale physical functioning of the MOS Short form-36 (SF-36; 34), a reliable and valid instrument to measure self-reported physical functioning ranging from 0-100 (higher scores indicate less impairment; 35).

Social impairment

Impairment in social adjustment was measured using the Work and Social Adjustment scale (WSAS; 36). It assesses functioning at work, in home management, social and leisure activities, and in relationships. The WSAS was validated for use in CFS populations (37). The questionnaire consists of 5 items (range 0-8; total score 0-40; higher scores reflect more impairment). A Dutch version was created and used in the Dutch group (Appendix 1).

Other symptom information

The number of additional symptoms, as stated in the CDC criteria for CFS, was assessed in each patient (range 0-9). Concentration and memory problems were counted separately. Symptom duration at referral was registered. Depressive symptoms were assessed in the Netherlands with the Beck Depression Inventory (BDI), primary care version (38) and in the UK with the Hospital Anxiety and Depression Scale (HADS) depression subscale (41). A score above the cut-off for clinically significant level of depressive symptoms was registered (>4 for BDI, >10 for HADS; 9; 41).

Demographics

Patients reported age, sex, education level, living situation (together or alone) and employment status (being employed and number of working hours in the past week). Since the Dutch and UK education system differ substantially, education levels were categorised as low or high. For the Dutch patients, no education, lower and middle vocational education were considered low and higher education was considered high. For the UK patients, no education or only secondary education were considered low and polytechnic and university education high.

Treatment characteristics

Treatment duration in months and number of sessions were recorded. Dropout was registered when a patient completed less than five treatment sessions after the two assessment sessions.

Statistical analysis

Analyses were performed using SPSS statistics for Windows, version 20.0 (IBM, USA). When at most two items on a questionnaire (subscale) were missing, the missing value was replaced by the mean item score on that subscale.

Uncontrolled effect sizes were calculated for the CFQ, SF-36 physical functioning and the WSAS, using the within group Cohen's *d* (42). The difference between the mean at pre- and post-treatment assessment was divided by a pooled standard deviation. Confidence intervals were

calculated (43). When post-treatment measurements were missing, but follow-up measurements were available, these were used. Follow-up was on average 3 months after post-assessment. To control for the use of different diagnostic criteria for CFS, effect sizes for the UK were also calculated for the subgroup of patients who met CDC criteria for CFS.

To determine if outcomes of both cohorts were comparable to the outcomes of previous RCT's conducted in these centres we compared effect sizes. In this way we wanted to test if differences in outcomes between both treatments centres could be explained by differences in effectiveness between care delivered in the context of an RCT and routine clinical care. Effect sizes from both cohorts were compared to within-group effect sizes of recent RCT's, in which the treatment centres participated, by comparing the confidence intervals. Cohen's D and confidence intervals were calculated as in the cohorts, using the raw data of the patients who received CBT in the RCT's and completed both pre and post-assessment. In the RCT in which the treatment centre from the UK participated (25), four treatments were compared: (1) specialist medical care (SMC), (2) SMC + CBT, (3) SMC + graded exercise therapy (GET) and (4) SMC + adaptive pacing therapy (APT). Scores at pre-assessment and at 24 weeks for the SMC+CBT group were used. In the first RCT in which the Dutch centre participated (25), two treatments were compared: (1) minimal CBT intervention + CBT and (2) waiting list + CBT. The latter group was used for calculation of the effect sizes for fatigue (CIS) and physical functioning (SF-36). In the second RCT in which the Dutch centre participated (18), group therapy was compared to waiting list. The intervention group was used. Since the Dutch RCT's used the CIS to measure fatigue, which correlates only moderately with the CFQ (Appendix 1), the effect size for fatigue of the UK cohort was not compared with the Dutch RCT's. The Dutch cohort also completed the CIS, allowing for comparison to the Dutch RCT's. Furthermore, the Dutch RCT's did not use the WSAS, so effects sizes for this measure could not be compared.

Treatment duration, number of sessions and drop-out rates for the Dutch and UK centre were compared, as well as baseline characteristics. This was done for all patients who started treatment and also for the groups that completed post-assessment, since they were the patients included in the effect size calculation. For all comparisons, t-tests and their non-parametric counterparts were used for continuous variables, while Chi-square tests of independence were used for dichotomous variables.

For each of the outcome measures (CFQ, SF-36 physical functioning and WSAS) a multiple linear regression analysis was performed. The dependent variable was the change score between baseline and post-treatment of that outcome measure. In the first step of each analysis, a dummy

variable for treatment centre was entered in the analysis as predictor (0=UK, 1=NL). In the second step, the variables age, sex, education level, living together with a partner, depressive symptoms (z-scores), number of CDC symptoms and fatigue and impairment at baseline and symptom duration were entered as predictors. All predictors that were continuous variables were centred, with zero as mean. The difference in the parameter estimate of the variable treatment centre between both models was determined. If the treatment centre parameter estimate decreased when all the predictors assessing patient characteristics were entered in the model, such that centre was no longer a significant predictor of within-group change in treatment, this suggested that the differences in patient factors rather than treatment centre explained the differences in the within-group treatment effect. Significance was at $p < 0.05$ for all analyses.

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Results

Participants

In the Netherlands, 445 patients were diagnosed with CFS during the inclusion period and 293 patients started CBT and were included (66%). Of the 152 patients not included, 81 patients participated in a study testing the efficacy of group therapy (18), 60 declined CBT, nine received CBT elsewhere and two received a treatment protocol for adolescents instead (30).

In the UK centre 246 patients were diagnosed with CFS and 163 were included in the study (66%). Of the other 83 patients, 35 did not receive treatment, 32 chose graded exercise therapy, nine did not complete their pre-treatment assessment, three received another treatment during CBT, two received a specific treatment for housebound patients, one received the treatment before and one did not receive the full course of therapy due to NHS funding issues.

Examining treatment characteristics

There was no significant difference in treatment duration in months (NL: 7.7, Standard deviation (SD): 3.5; UK: 7.8, SD:3.0; $t(351)$: -.46, $p=0.65$). In the Netherlands 23 patients dropped out (8%) and in the UK 11 patients dropped out (7%; $\chi(1)$:0.17, $p=0.68$). The number of treatment sessions was significantly higher in the Netherlands (13.5, sd: 4.1) compared to the UK (12.5, sd:2.8; $t(400)$: 2.63, $p<0.05$).

Comparing treatment outcome

There were 34 patients in the UK who did not complete post-treatment CFQ (21%), and 68 in the Netherlands (23%; $\chi(1)$:0.33, $p=0.56$). Effect sizes are shown for the patients who completed both pre- and post-treatment assessments (table 2). For fatigue severity, physical functioning and social functioning, the Dutch effect sizes were larger than those in the UK. The 95% confidence intervals for each estimate excluded the estimate from the other country. The within-group effect sizes were large for fatigue severity (NL: 1.74 (1.52-1.95); UK: 0.99 (0.73-1.25)), moderate (UK: 0.33 (0.08-0.58)) to large (NL: 0.99 (0.81-1.18)) for physical functioning and moderate (UK: 0.61 (0.35-0.86)) to large (NL: 1.47 (1.26-1.69)) for impairment in social adjustment (41). When including only the UK patients that met CDC criteria, the results were the same (data not shown).

Comparing treatment outcome to outcome from RCT's

The effect sizes in these cohorts were compared with within-group effect sizes in recent RCT's in which the centres participated (Table 3). Compared to the within-CBT group effect size in the UK RCT (26), the effect size for fatigue severity in the Dutch cohort of the present study was larger. The 95%

confidence intervals did not overlap. The effect size of the UK cohort did not differ from the UK RCT. The confidence intervals of the Dutch cohort overlapped with both RCT's (Table 3).

For physical functioning the Dutch cohort effect size did not differ from the RCT's. The UK effect size was lower than in all RCT's, although the higher boundary of the confidence interval fell within the lower boundary of the UK RCT and one of the Dutch RCTs (25).

For social impairment, the effect size in the Dutch cohort was higher than the effect size in the RCT from the UK. The effect size of the UK cohort did not differ from the UK RCT.

For both the Dutch and the UK sample, the percentages of patients that did not complete post-assessment were significantly higher than the percentages in two out of three RCT's (26; 25).

Comparing baseline characteristics

See table 4 for the comparison of baseline characteristics between the Dutch and UK cohorts. Significantly more Dutch patients were on sick leave and the number of hours that patients worked per week was significantly lower in the Netherlands than in the UK. More Dutch patients lived together with a partner. Patients from the UK had significantly worse physical functioning and reported significantly less additional CDC symptoms. Symptom duration was longer in the Netherlands. There were no significant differences in all other variables.

The baseline characteristics of the patients that completed post-assessment were compared between cohorts as well. This showed no significant differences other than those found in the total group.

Contribution of patient characteristics to differences in treatment effect

Results of the multiple regressions used to assess the independent effect of treatment centre are shown in table 5. For fatigue, when unadjusted, the change in the CFQ was on average about 3.95 points smaller in the UK group. Treatment centre remained a significant predictor after including the patient characteristics as predictors (difference in the CFQ change between UK and NL = -6.00). The pattern of results was similar for the changes in physical and social functioning. The analyses do not allow for the identification of predictors of treatment effect, as treatment variables were not controlled for and the magnitude and direction of the predictors of treatment effect may differ in both countries.

Discussion

This study is the first to our knowledge to compare treatment outcomes of CBT for CFS in two tertiary CFS treatment centres in different countries. Both centres developed treatment (27; 23) protocols that are effective in reduction of fatigue and impairment in CFS patients (8; 18; 21; 22; 23;24; 25; 26). In the present study, treatment outcomes differed significantly between treatment centres. The Dutch centre had significantly larger within-group effect sizes for fatigue, physical functioning and impairments in social adjustment. This could not be explained by patient characteristics, the use of different diagnostic criteria for CFS or different outcome measures. It seems likely that differences in CBT as delivered in the two centres could be responsible for these variations. It would be useful to know which differences in treatment protocols are associated with differences in treatment effect.

There is considerable overlap in the approaches. Both emphasize the role of unhelpful behaviour and beliefs in the perpetuation of symptoms and include goal setting. They also include the adoption of a consistent approach to activity, sleep management, a gradual increase of activity and cognitive restructuring.

One prominent difference between the protocols is that the Dutch protocol includes a specific physical activity program, in which the patient walks or cycles on a daily basis with a systematic increase of a minute per day, regardless of symptoms. During this program dysfunctional beliefs with respect to fatigue and the ability to become active are modified.

If this physical activity program is responsible for the difference in treatment effect, it is important to know why. One hypothesis is that the increase in physical activity in itself improves outcome. Mediation analysis of the treatment effect in the PACE trial showed that the increase in activity measured in walked metres was a mediator of treatment effect in graded exercise therapy (14). In the CBT group this did not mediate treatment effect, but walking was not a primary focus in the CBT delivered in this UK RCT. If this increase in activity boosts treatment outcome, one would expect that in the Dutch CBT, where this was specifically aimed at, this increase would mediate the reduction of fatigue. Mediation analysis of three RCT's testing the effectiveness of the Dutch CBT showed that actual changes in level of physical activity assessed with actigraphy did not mediate effects of CBT on fatigue. The reduction of fatigue was however mediated by an increase in self-efficacy, a reduction in symptom focusing and a change in perceived activity (11; 12; 13). These findings suggest that in the Dutch version of CBT for CFS increasing physical activity is not a mediator but a catalyst of change. The activity program seems to help the patient to change beliefs that perpetuate symptoms and disability.

Other possible explanations of the differences in treatment effect could be that in the Dutch protocol recovery is set as a treatment goal, which may increase outcome expectations and hence

positively influence outcome (13), or the fact that different fatigue related beliefs are addressed during the therapy. The Dutch protocol focuses on the role of low self-efficacy regarding fatigue and focusing on symptoms as possible perpetrators of fatigue. In the UK CBT, more emphasis is laid on avoidance of activity and fear avoidance beliefs. Perhaps the outcomes of the Dutch treatment protocol are more favourable because it focuses more on empowering people, working on a positive change rather than ameliorating the negative consequences of the fatigue, such as fear-avoidance beliefs or avoidance.

Another possible explanation is the use of a specific intervention, namely attentional training in the Dutch protocol. Some of the elements of this intervention, focussing on attentional factors, originate in meta-cognitive therapy (43). Perhaps this 'add-on' in the Dutch protocol increased its effectiveness.

It is possible that factors other than protocol differences caused the variations in within-group treatment effect. For example, in the Dutch centre patients received on average one treatment session more. Number of sessions has been found to be a moderator of treatment outcome (10). However, we find it unlikely that this small difference can explain the substantial effect sizes differences.

Differences between the Dutch and UK patient groups could not explain differences in treatment outcome. However, there were some interesting differences between both groups. Dutch patients had longer symptom duration and were more often living together with a partner. They worked fewer hours per week on average and were more often on sick leave. The latter is perhaps due to different laws and rules with respect to sick leave. Interestingly, the Dutch patients were less impaired in physical functioning on average at baseline. This was unexpected, as mean scores on the scales for population controls do not differ between the countries (42;44). There were no differences in all other studied variables.

It is possible that other, unmeasured patient, therapist, or centre characteristics influenced the within-group differences in treatment outcome between centres. Using this study design we cannot identify predictors of treatment outcome with certainty. Only a direct comparison of the two treatment protocols in a randomised controlled trial, with a mediation analysis, can demonstrate the relative contribution of factors on treatment outcome.

The comparison between within-cohort changes to within-treatment group changes in the RCTs showed that there is little variation in treatment outcome between the cohorts and the RCT's from the same countries. This may suggest that both interventions or treatment centres are consistent in their effect.

There were several limitations to this study. Because routine clinical care was provided during the study with locally used measures, not all measures used in the different centres were

comparable. For example, depressive symptoms were measured with two different questionnaires. Also the education systems differ and the categorisation of low and high education level may have been imprecise. As mentioned, since patients were not randomly assigned to treatment in one centre or the other, it is not possible to compare the effect of both treatments directly, which would more effectively investigate predictors of treatment outcome. Furthermore, since only the patients who completed post-treatment assessment were included in the effect size calculations, a selection bias may have occurred.

In conclusion, our findings support the idea that different protocols may have different effects on fatigue severity and disability in CFS patients. This could partially explain variations in the effect sizes of CBT for CFS between studies, found in meta-analyses (10; 19). Understanding which aspects of CBT treatment protocols may be associated with larger treatment effects would be useful for treatment refinement. This could help us to a better understanding of cognitions and behaviours crucial in maintaining CFS. These findings suggest further study of the relative efficacy of different elements of CBT for CFS and different treatments protocols for CFS could be fruitful.

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Tables

Therapy aspect	Protocol of Knoop & Bleijenberg (2010)	Protocol of Burgess & Chalder (2004)
Goal of the therapy	Recovery of CFS is explicitly aimed at.	Improved functioning and reduction of fatigue. Learn how to manage setbacks to be able to maintain and build on progress.
Activity program	<ul style="list-style-type: none"> - Highly structured and partly prescribed. - The patient starts with walking or cycling, before working towards his own goals. - Activity is increase by one minute per day, irrespective of symptom level. Therefore fully time contingent. 	<ul style="list-style-type: none"> - Negotiated with the patient. - Targets are the goals of the patient. - Activity increase is negotiated with the patient and takes into account how much was accomplished earlier. Goals are not fully time contingent.
Cognitions	<p>"I can increase my activity level, following specific principles and irrespective of symptoms."</p> <p>"I think I can influence my fatigue."</p> <p>Increasing self-efficacy with respect to fatigue.</p> <p>Aimed at reducing the focus on fatigue.</p>	"I can increase my activity level and will be able to cope with an increase in symptoms." This focuses on reducing fear avoidance of symptoms.
Symptom focusing	<ul style="list-style-type: none"> - Effect of symptom focusing is discussed and beliefs with respect to the need to pay attention to the fatigue are restructured. - Patients no longer talk about fatigue. - Elements of attentional training are applied to train patients to focus less on fatigue. 	Advocates a shift in the focus of attention from fatigue, but no specific intervention targets this.

			Pre	Post	Change	
	Location	N*	M (SD)	M (SD)	Δ M	Cohens D
CFQ	The Netherlands	225	24.91 (4.5)	13.82 (7.8)	-11.1	1.74 (1.52-1.95)
	United Kingdom	129	24.47 (6.4)	17.08 (8.7)	-7.4	0.99 (0.73-1.25)
SF-36	The Netherlands	243	60.12 (20.0)	80.35 (20.6)	20.2	0.99 (0.81-1.18)
	United Kingdom	125	54.20 (24.1)	62.72 (27.5)	8.5	0.33 (0.08-0.58)
WSAS	The Netherlands	217	24.03 (7.1)	11.06 (10.2)	-13.0	1.47 (1.26-1.69)
	United Kingdom	129	23.34 (9.5)	17.02 (11.2)	-6.3	0.61 (0.35-0.86)

* patients who completed pre- and post-assessment.

Table 3: Comparison of within-cohort with uncontrolled within-group effect sizes in RCT's

	Chalder Fatigue Questionnaire Cohens D (95% confidence interval)	SF-36 physical functioning Cohens D (95% confidence interval)	WSAS Cohens D (95% confidence interval)	CIS fatigue Cohens D (95% confidence interval)	% of patients lost to follow up
White et al., 2011	1.02 (0.77-1.26)	0.79(0.55-1.03)	0.73 (0.49-0.96)	-	11% ^{A, B}
Tummers et al., 2010	*	0.84 (0.51-1.17)	-	1.45 (1.10-1.80)	7% ^{A, B}
Wiborg et al., 2015 (Group CBT).	*	1.17 (0.88-1.45)	-	2.01 (1.68-2.33)	20%
Present study Dutch sample	1.74 (1.52-1.95)	0.99 (0.81-1.18)	1.47 (1.26-1.69)	1.83 (1.62-2.04)	21%
Present study UK sample	0.99 (0.73-1.25)	0.33 (0.08-0.58)	0.61 (0.35-0.86)	-	23%

^A: chi squares: difference with Dutch sample is significant (p<0.05).
^B: chi squares: difference with UK sample is significant (p<0.05).

Table 4: Comparison of baseline patient characteristics between the Netherlands and the UK.

	The Netherlands	United Kingdom	
Demographic characteristics	M (SD) / %	M (SD) / %	Comparison
Age	37.83 (11.90)	37.07 (11.53)	B
Sex: female	77.1%	74.8%	A
Education level: low	52.9%	25,8%	A, p<0.05
Living situation: living together with a partner	60.8%	42.9%	A, P<0.05
Work status: employed	67.6%	55.2%	A
Number of hours worked	9.88 (12.94)	13.80 (17.47)	B, P<0.05
On sick leave	51,5%	20%	A, P<0.05
Illness characteristics	M (SD) / %	M (SD) / %	Comparison
Chalder Fatigue Questionnaire score	24.69 (4.70)	24.84 (6.10)	B
SF-36 physical functioning subscale	58.28 (20.74)	50.44 (25.83)	B, P<0.05
Work and Social Adjustment Scale	24.23 (7.37)	24.37 (9.31)	B
Number of CDC symptoms	7.64 (1.22)	6.55 (1.76)	B, P<0.05
Symptom duration in years (medians*).	Median=5.0, IQR**=6.0	Median=3.0 IQR= 5.0	C, P<0.001
Depressed: above cut off	27.0%	28.8%	A

*: Medians were compared, because of outliers in the Dutch group. Symptom duration had a non-normal distribution. Therefore the Mann Whitney U Test was used to compare both groups.
**: IQR= interquartile range
Significance assumed at (p<0.05).
A: Chi square test of independence
B: Independent samples t-test
C: Mann-Whitney U test

Table 5: Controlling for patient variables: changes in the parameter estimate for treatment centre in multiple regression analyses

	Variable	CFQ change score		SF-36 change score		WSAS change score	
		(un) standardized beta	95% CI for beta	(un) standardized beta	95% CI for beta	(un) standardized beta	95% CI for beta
1	Treatment centre	(-3.95) -0.22	-5.96 – -1.96*	(-12.67) -0.28	-17.51 – -7.82	(-7.64) -0.36	-9.93 – - 5.34*
2	Treatment centre	(-6.00) -0.33	-8.41 – -3.60*	(-16.18) -0.35	-21.63 – -10.74*	(-7.77) -0.36	-10.57 – -4.97*
	CFQ at baseline	0.38	0.41 – 0.82*	-0.07	-0.73 – 0.19	-0.14	-0.51 – -0.03*
	SF-36 at baseline	-0.10	-0.09 – 0.01	-0.52	-0.59 – 0.37*	0.03	-0.04 – 0.07
	WSAS at baseline	-0.10	-0.25 – 0.04	-0.07	-0.50 – 0.15	0.42	0.35 – 0.68*
	Number of CDC symptoms	-0.11	-1.28 – 0.09	0.03	-1.18 – 1.89	-0.02	-0.91 – 0.67
	Depression z score	-0.09	-1.72 – 0.19	-0.03	-2.80 – 1.51	-0.06	-1.70 – 0.53
	Duration of symptoms	-0.05	-0.21 – 0.08	0.03	-0.23 – 0.38	-0.04	-0.23 – 0.10
	Employed and on sick leave	-0.15	-5.11 – -0.08*	-0.02	-6.44 – 4.81	-0.02	-3.33 – 2.51
	Not employed	-0.02	-3.25 – 2.66	-0.02	-7.54 – 5.69	0.03	-2.75 – 4.12
	Number of hours working per week	0.15	-0.01 – 0.17	0.09	-0.08 – 0.32	0.15	-0.01 – 0.20
	Sex	0.08	-0.61 – 3.61	-0.04	-6.78 – 2.89	-0.01	-2.69 – 2.20
	Age	-0.04	-0.11 – 0.05	-0.16	-0.46 – -0.10*	-0.18	-0.24 – -0.05*
	Living together	-0.04	-2.36 – 1.23	-0.01	-4.31 – 3.79	0.05	-1.05 – 3.13
Education level	-0.03	-2.24 – 1.32	0.05	-1.88 – 6.07	0.03	-1.54 – 2.59	

*: significant ($p < 0.05$).

Appendix 1: Translation and validation of the Dutch Chalder Fatigue Questionnaire and the Dutch Work and Social Adjustment Scale.

Chalder fatigue questionnaire

We translated the CFQ into Dutch and after back-translation into English the author of the questionnaire verified the translation (TC). The questionnaire was then validated in a group of 741 fatigued patients referred to the Dutch centre. Principal components analysis showed a two-factor solution with eigenvalues of 4.70 and 1.55, corresponding with the factor structure of the original CFQ (30). 10 out of 11 items loaded on the expected factors. The item '*Do you have difficulty concentrating*' loaded as expected on the mental factor (0.640), but also on the physical factor (0.405) in the Dutch version. To investigate construct validity, the CFQ was correlated with the fatigue severity subscale score of the Checklist Individual Strength (CIS; 43). This subscale is often used in CFS research and is a valid and reliable measure of fatigue severity (20), ranging from 8-56. Spearman rank correlations showed that the CFQ and the CIS subscale fatigue severity correlated only moderately (0.456, $p < .001$). The internal consistency of the Dutch version of the CFQ was high: Cronbach's alpha 0.86.

Work and Social Adjustment Scale

The same sample was used for the validation of the WSAS. A principal components analysis confirmed the one-factor structure that was found in the original version. Correlations were calculated between the WSAS, the SF-36 subscale 'Physical functioning' and the Sickness Impact Profile total score (SIP; 44). The SIP assesses disability in several aspects of daily functioning. The WSAS correlated moderately with the SF-36 physical functioning subscale (0.482, $p < 0.01$) and high with the SIP (0.600, $p < 0.01$). Cronbach's alpha was 0.89 in our sample.

Highlights

- We compared treatment outcome of cognitive behaviour therapy (CBT), an evidence based intervention for chronic fatigue syndrome (CFS), in two tertiary treatment centres in the Netherlands and the U.K..
- Effect sizes on fatigue severity and impairment differed between centres.
- Differences in patient characteristics could not explain variations in outcome.
- Differences in treatment protocols may be responsible for outcome differences.
- More attention should be paid to variation in treatment protocols in relation to outcome, to further develop and improve CBT for CFS.

ACCEPTED MANUSCRIPT