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Cognitive Behavioural Therapy for chronic fatigue and CFS: outcomes from a specialist clinic in the UK

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Full Title: Cognitive Behavioural Therapy for chronic fatigue and CFS: outcomes from a specialist clinic in the UK

Short Title: CBT for Chronic Fatigue and CFS

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Competing interests

Professor Chalder reports grants from UK NIHR, Guy's and St Thomas' Charity. She has delivered workshops on medically unexplained symptoms, during the conduct of the study (money paid into KCL for future research). Since this study was completed, a private company has signed a licence agreement with King's College London with a view to bringing the Regul8 website product to the NHS and other international markets. TC will be a beneficiary of this license through contracts with their respective universities. She is the author of self help books for which she has received royalties. Dr Santhouse was a member of the guideline development group for the NICE Guidelines CG53 (2007) Chronic fatigue syndrome/myalgic encephalomyelitis: diagnosis and management.

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Ethical approval

Audit approval was provided by the Psychological Medicine Clinical Academic Group (ID number PPF191115) at the South London and Maudsley Hospital. All patients provided informed written consent.

Guarantor

Professor Trudie Chalder

Contributorship

JA, SA & TC designed the research methodology and JA & SA analysed the data. All authors contributed to the writing, final editing and agreed on the final version.

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Abstract

Objectives

Cognitive Behavioural Therapy (CBT) is commonly used to treat Chronic Fatigue Syndrome (CFS) and has been shown to be effective for reducing fatigue and improving physical functioning. Most of the evidence on the effectiveness of CBT for CFS is from randomized control trials (RCTs) but there are only a few studies in naturalistic treatment settings. Our aim was to examine the effectiveness of CBT for CFS in a naturalistic setting and examine what factors, if any, predicted outcome.

Design

Using linear mixed effects analysis we analysed patients self-reported symptomology over the course of treatment and at three-month follow up. Furthermore we explored what baseline factors were associated with improvement at follow-up.

Setting

Data was available for 995 patients receiving CBT for CFS at an outpatient clinic in the UK.

Participants

Participants were referred consecutively to a specialist unit for Chronic Fatigue or CFS.

Main outcome measures

Patients were assessed throughout their treatment using self-report measures including the Chalder Fatigue Scale, Short Form Health Survey (SF-36), Hospital Anxiety and Depression Scale (HADS), Global Improvement and Satisfaction.

Results

Patients fatigue, physical functioning and social adjustment scores significantly improved over the duration of treatment with medium to large effect sizes ($|d|=0.45 – 0.91$). Furthermore 85% of patients self-reported that they felt an improvement in their fatigue at follow-up and 90% were satisfied with their treatment. None of the regression models convincingly predicted improvement in outcomes with the best model being ($R^2=0.137$).

Conclusions

Patients fatigue, physical functioning and social adjustment all significantly improved following CBT for CFS in a naturalistic outpatient setting. These findings support the growing evidence from previous RCTs and suggests that CBT could be an effective treatment in routine treatment settings.

Introduction

Fatigue is a ubiquitous symptom which is normally distributed in the population [1]. For some people fatigue becomes chronic and starts to affect quality of life. At the more severe end of the spectrum chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME), is characterised by long-term fatigue, post exertional malaise and other persistent symptoms such as sleep disturbance, cognitive problems, and muscle pain [2,3]. By definition CFS is associated with marked disability and is associated with reduced participation in social activities, sickness absence and unemployment [4,5].

There is no consensus on the most accepted diagnostic criteria. The most widely applied case definition is the CDC criteria [6]. According to Fukuda et al., to meet criteria for a diagnosis of CFS, an individual must have self-reported persistent or relapsing fatigue for at least 6 months, of new or definite onset, that is severe enough to impair occupational, educational, social or personal activities. They must also report four or more of the following symptoms: impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, headaches, unrefreshing sleep, and post-exertional malaise lasting for more than one day. These symptoms should last 6 or more consecutive months and not predate the fatigue [2].

The most widely used treatments for CFS are cognitive behavioural therapy (CBT) and graded exercise therapy (GET), both of which are recommended for CFS by the National Institute for Health and Care Excellence [7]. There is evidence from systematic reviews and meta-analyses that CBT and GET can lead to positive outcomes for patients with CFS [8 9 10]. A large-scale RCT evaluating CBT and GET combined with standard medical care (SMC) found both of them led to reductions in fatigue and improvements in physical functioning compared to SMC alone or a credible therapist matched control, adaptive pacing therapy (APT) [10].

Most of the research has taken place using RCT methodology. However, the complex and rigorous procedures, costs and governance around clinical trials may result in skewed samples, which limit the generalisability of the results. Those who take part in trials may have less comorbidity and better adherence than those who don't, and staff working on such trials may also differ from those delivering routine clinical treatments [11].

There is some evidence of positive outcomes from studies which have been conducted outside the confines of a RCT within the context of specialist services for CFS. A large cohort study of specialist services in the UK found positive outcomes such as reductions in fatigue, anxiety and depression [12]. Flo and Chalder (2014) conducted a study within routine practice and found that after CBT treatment, just under 40% of patients no longer met Oxford or CDC criteria for CFS, and just under 20% were recovered, similar to rates of recovery reported in the Netherlands [13].

The positive effects of CBT may be maintained long-term, regardless of the setting in which the treatment took place (RCT or clinic). Janse et al (2017) conducted a long-term follow up of four groups of patients with CFS who had received CBT. Two groups were recruited as part of an RCT and two were clinical cohorts. Fatigue severity and physical functioning improvements were stable up to 18 months following end of treatment. At 18-months to five years, a third of participants were not severely fatigued and almost three quarters had good levels of physical functioning [14].

Research suggests that older age has been consistently shown to be a predictor of poor outcomes [11,12,15]. Furthermore, worse social adjustment, catastrophizing and depression all predicted poor outcomes in patients with CFS in a specialist clinic [15]. Baseline physical functioning (SF-36) and increased levels of pain predicted poor outcomes in a large study across six specialist units [12]. However, duration of illness, counter intuitively, was not a predictor of outcome regardless of setting [12,16–18].

Most research investigating the effectiveness of treatment for CFS has been conducted in the context of a RCT. The aim of this study was to describe the outcomes of people with CFS treated at a specialist service with CBT. We assessed change over time and also investigated predictors of outcome at the end of treatment. We retrospectively analysed data collected during the previous 14 years of the clinic. We hypothesised that:

1. Fatigue would be reduced, and physical and social functioning improved, after treatment.
2. Older age, higher baseline fatigue, work and social adjustment, anxiety and depression scores and lower physical functioning will be correlated with worse outcome at time 2.

Methods

Participants

Participants were referred to a specialist unit for CFS by their GP or by a hospital consultant. This naturalistic study used data retrospectively from patients who were seen in the unit between August 2002 and August 2016. Data was collected from August 2002 to February 2018 inclusive, to include follow up appointments. All participants were assessed by a specialist during their first appointment with the service. Patients were excluded from the analysis if they had received home-based treatment, if they were still in active treatment at the time of analysis, if they had received a treatment other than CBT or if they had not completed a pre-treatment questionnaire measure.

Ethics

Audit approval was provided by the Psychological Medicine Clinical Academic Group (ID number PPF191115) at the South London and Maudsley Hospital. All patients provided informed written consent.

Treatment

All patients received individual CBT by therapists experienced in treating CFS. Therapists received individual supervision on a regular basis with training completed in-house, ensuring adherence to the protocol. Patients are usually offered up to 20 sessions, including follow-up appointments, and receive therapy on a fortnightly basis for eight to ten months, depending on interruptions, before transitioning to follow-up appointments.

Treatment was based on the protocol outlined in previous RCT's [19] and has remained fairly consistent across the years. CBT treatment is based on a model which assumes that certain triggers such as a virus and/or stress trigger symptoms of fatigue. Subsequently symptoms are perpetuated inadvertently by unhelpful cognitive and behavioural responses. After a detailed assessment was carried out, a formulation of the individuals problems was shared with them. Collaboratively patients were then supported with implementing strategies such as monitoring sleep and activity, setting goals, establishing routines, sleep hygiene, avoiding boom and bust cycles of behaviour, reducing excessive avoidance behaviour, tackling stress and addressing unhelpful beliefs which may be interfering with helpful changes. When relevant and appropriate, early childhood trauma will often be included in the formulation of patients' difficulties and may be referred to when patients are tackling unhelpful beliefs or schemas. Difficulties in emotion regulation linked to holding beliefs that expressing negative emotions

to oneself or to others is unacceptable are also addressed if such issues become apparent during therapy.

Measures

Participants were asked to complete questionnaire measures at the start of treatment, session 4 and 7, discharge and at 3 months follow up. The questionnaires consisted of the following:

Demographics
Patients were asked their age, gender, ethnicity, illness duration as well as duration, intensity and type of fatigue, in line with Oxford and CDC criteria for CFS [2,3].

Fatigue was measured using the Chalder fatigue scale. This has been shown to be reliable and valid [20,21]. It consists of 11 items, each of which have four possible response options, ranging from 'less than usual' to 'much more than usual'. Either a continuous scoring system (0,1,2,3) or a bimodal scoring (0,0,1,1) method can be used for each item which are summed to obtain a total score. A higher score is associated with greater fatigue severity. Using the bi-modal scoring system a cut-off score of 4 or more can be used as an indicator of fatigue caseness [20].

Social adjustment was measured using the Work and Social adjustment scale (WSAS), which has been validated in patients with CFS [22]. This is a five-item scale where each item receives a score between 0 and 8 and the items are summed to obtain a score out of 40. A higher score indicates greater impairment, i.e. worse social adjustment.

Physical functioning was measured using the 36-item Short Form Health Survey (SF-36), physical functioning subscale. This consists of ten items which are summed to give a total out of 100. A higher score indicates better physical functioning. This scale has been shown to be valid and reliable [23].

Anxiety and Depression was measured using the Hospital Anxiety and Depression Scale (HADS) [24]. HADS is a 14-item self-report questionnaire with seven questions assessing severity of each disorder related symptoms over the past week. Higher scores indicate more severe symptomology with a maximum possible score of 21 and a cut-off score of 8 [25]. HADS is assessed only at the start and end of treatment.

Global improvement was assessed on a six-point scale ranging from 1(very much better) to 6 (very much worse). In line with previous RCT's the responses were also coded into a dichotomous variable 1=improved (Very much better and much better), 0= not improved (little better to very much worse) [10].

Satisfaction with treatment was rated on a seven-point scale ranging from 1(very satisfied) to 7 (very dissatisfied).

Missing data

If a patient was missing 25% or less of the data from any questionnaire, a prorated score was calculated (this used the mean of the remaining items from the same individual to calculate a prorated score).

Analysis

Data management, descriptive statistics and analysis was conducted in SPSS version 24 [26]. Alpha was set at $p<0.05$. In addition, effect size of change in outcomes from start to end of treatment was estimated using Cohen's d (|d|)[27]. The effect size estimates were interpreted as small ($|d| \geqslant 0.2$), medium ($|d| \geqslant 0.5$) and large ($|d| \geqslant 0.8$). Demographic characteristics of the sample were described using measures of central tendency.

Drop-out

Patients who did not complete discharge or follow-up measures were considered to have dropped out from treatment. We compared those who dropped out to those who completed treatment using independent samples t-tests to compare demographic and baseline CFQ, SF-36 and WSAS.

Change in main outcomes over time

We measured the effect of time on CFQ and WSAS scores over all the observed time points using linear mixed models (compound symmetry model) with time as the main predictor. For SF-36, due to low numbers at session 4 and 7, we analysed the effect of time over start, discharge and three month follow-up. Post-hoc paired samples t-tests (Bonferroni corrected for multiple comparisons) [28] were used to assess changes between each time point for each outcome. Since anxiety and depression were not direct targets for the CBT intervention we were only interested if there was a clinically significant change in patients self-reported symptomology, i.e. patients moved from case to non-case, according to the HADS. We assessed how many people had shown global improvement and rates of satisfaction using descriptive statistics. Deterioration was assessed by number deteriorated, i.e. how many became a fatigue case (score >4) that were not a case at the start of treatment and how many people showed a worsening of fatigue (2 point increase out of 33).

Predictors of outcome

Predictors of outcome were assessed using the following variables: age, ethnicity (dichotomous), illness duration, and baseline fatigue, WSAS, SF-36 and HADS. Multiple Linear regression was used to analyse predictors of improvement with CFQ, SF-36 and WSAS improvement scores (difference in scores over time) used as dependent variables. For those patients without end of treatment scores, the nearest follow-up score was used to compute an end point and was defined as a computed follow-up score.

Results

Participants

Nine hundred and ninety five participants were included in the analysis. All participants were treated for CFS at the National Persistent Physical Symptoms Research and Treatment Unit. All met NICE criteria for CFS [7]. According to self-reported accounts of their symptoms, 754 (76%) participants met Oxford criteria for CFS and 518 (52%) met CDC criteria for CFS. Nine

hundred and fifteen (92%) of patients reported both physical and mental fatigue with 67 (7%) reporting either physical or mental fatigue.

Two hundred and sixty (26%) participants were male and 729 (73%) were female. Six (1%) did not state their gender. Participants were aged between 18 and 74 (Mean age 39.45, SD 11.5). 784 (78.7%) participants were white. Participants had been ill for a mean duration of 6.65 years (SD 6.48). 437 (44%) were married or living together and 423 (43%) were single. 228 (23%) were educated to school level (GCSE/O-Level) with 683 (69%) educated to university level (undergraduate).

Number of Sessions

All participants received CBT with a mean duration of 12 sessions (SD 4.9; range from 1-30). The majority had between 9 and 16 sessions (67.1%), 8.2% had 4 or less and 11.7% had 16 or more sessions.

Drop-Out

Drop-out was defined as those patients who did not complete any questionnaires at the end of treatment, or any follow-up and was 31% in this naturalistic setting. Reason for drop-out was only recorded since 2007 and therefore we have no data from 2002 to 2007. Data is presented for those with drop out information (n=140) with reasons for frequencies greater than 5%. Freqencies less than 5% are combined in 'other' and include; only funded for small amount of sessions, patient didn't engage with treatment and referred to another service, see table 1.

Table 1. Reason for drop-out.

Drop-out vs stay in

There were no statistically significant differences in demographic characteristics between those who dropped-out from treatment and those who completed. We did find a statistically significant difference in self-reported physical functioning at baseline between the groups ($t(763)=-3.74$, $p<.001$) with those that dropped out reporting lower physical functioning scores with a mean difference (MD) of -7.38. Furthermore, those who dropped out had more severe WSAS scores at baseline ($t(987)=2.48$, $p<.05$) with a MD of 1.55. However, no difference in level of fatigue was observed ($t(975)=1.61$, $p>.05$). Those who dropped out also had higher scores on self-reported depression symptoms at baseline ($t(981)=2.35$, $p<.05$) but no difference in anxiety scores ($t(978)=1.4$, $p>.05$).

Change in main outcomes over time

Estimated marginal means and standard errors for CFQ, SF-36 and WSAS seen in Table 2.

Table 2. Estimated marginal means and standard errors for main outcomes over time.

Using a linear mixed effects model we can see that there was a significant main effect of time on patients CFQ scores, $F(4,2069) = 150.88$, $p < .001$ with CFQ significantly improving over time; start of treatment M = 24.20 (SD=6.95); end of treatment M = 17.42 (SD=8.83). The effect size was large ($|d|=0.91$) with a mean difference (MD) of 6.52 [95% CI (5.65,7.39)]. The largest change appears to happen between the start of treatment and session 4 [MD=4.74, 95%

CI (3.73,5.75)] with subsequent time point differences not meeting significance, despite main effect being significant. Scores across all time points are displayed in figure 1.

Figure 1. Estimated marginal means for both CFQ and WSAS scores across all observed time points.

Due to low numbers of patients completing SF-36 at the 4th and 7th session, we analysed the main effect of time using three time points (start, discharge and three month follow-up). The main effect of time was significant ($F(2,873) = 111.16$, $p < .001$) with SF-36 significantly improving over treatment; start of treatment M = 47.81 (SD=25.74); end of treatment M = 59.56 (SD=27.3). The effect size was medium (|d|=0.45) with a mean difference of 9.91 [95% CI (7.94,11.88)]. Treatment improvements appear to be sustained at follow-up with there being no significant difference in scores between end of treatment and three-month follow-up (MD=1, p=.82).

There was a significant main effect of time on patients WSAS scores, $F(4,1961) = 155.75$, $p < .001$ with WSAS significantly improving over time; start of treatment M = 25.02 (SD=8.99); end of treatment M = 19.14 (SD=10.71). The effect size was medium (|d|=0.61) with a mean difference of 5.55 [95% CI (4.79,6.32)]. Improvement in patients' scores was statistically significant across each time point from start to end of treatment (P<.001) and then treatment improvements were sustained at follow-up with the difference in scores from discharge to follow-up being non-significant (MD=.37, p=1). Means with 95% CI are displayed in figure 1.

The presence of anxiety and depression

Table 3. HADS caseness for participants with complete data (using cut-off score of 8)

Global Improvement

Patients largely self-reported that they saw an improvement in their fatigue at discharge with 87% reporting that they felt at least a little better; only 2.5% felt like they were worse off. At three months follow-up 84% reported at least some improvement and only 5% reporting feeling worse. A full report of patient responses at both time points is displayed in table 4. Using previous RCT's methodology of dichotomosing global improvement scores, we see a 53% global improvement at discharge and 56% at three month follow-up.

Table 4: Self-reported global improvement and discharge and three months follow-up.

Deterioration in fatigue

According to patients self-reported CFQ scores, a large majority (72%) of patients reported a significant improvement in fatigue, with at least a 2 point decrease on the measure. Some patient's reported at least a 2 point increase in fatigue (16%) indicating a deterioration, according to the measure. The final 12% reported little or no change in fatigue.

Satisfaction with treatment

Patients were largely very satisfied with their CBT treatment with over 90% of patients rating their satisfaction as at least slightly satisfied and 45% saying they were very satisfied. Less than 10% of patients rated their satisfaction with treatment as dissatisfied.

Predicting outcome

A multiple linear regression was used to predict improvement in CFQ, WSAS and SF-36 scores with improvement defined as the difference between patients computed follow-up scores and their start of treatment scores. All participants, except three, had either a discharge or a 3-month follow-up score and this represents the computed follow-up score. For the three that had neither, we took the scores from the closest session to discharge we had. A significant regression equation was found for CFQ improvement scores ($F(8,436)=8.65$, $p<.001$), with an R^2 of .137. However, only baseline CFQ was positively correlated more than $r = 0.3$ with CFQ improvement and accounts for the majority of the model. We also found a significant regression equation for SF-36 improvement scores ($F(8,430)=6.18$, $p<.001$), with an R^2 of .103. Only baseline SF-36 had a notable positive correlation of $r = 0.2$. Finally, we found a significant regression equation for WSAS improvement scores ($F(8,438)=7.63$, $p<.001$), with an R^2 of .122. As above, the highest correlated variable with WSAS improvement scores was baseline WSAS scores being positively correlated, $r = 0.18$.

Discussion

This naturalistic outcome study investigated the impact of individual CBT on patients' self-reported fatigue and physical functioning, after outpatient treatment for CFS. The CBT intervention led to significant improvements in patients self-reported fatigue, physical functioning and social adjustment. Medium to large effect size improvements were observed across all measures between the start and end of treatment (0.45 to 0.91). Interestingly, initial gains in fatigue between the start of treatment and session four was where we saw the largest improvement in fatigue and WSAS scores. Furthermore, 72% of participants improved at least 2 points on the Chalder fatigue scale with 29% of participants scoring below cut-off and therefore becoming a non-case. This is in line with previous findings from Stahl, Rimes & Chalder (2014) who reported significant improvements in both CFQ and WSAS after CBT treatment [29]. However, the present findings differ in that the previous study included CFQ measures at only two time-points whereas the current study used multiple time-points throughout treatment, giving an indication as to when change happened. In this large chort, changes occurred within the first 4 sessions. In both studies, improvements were maintained post discharge and into follow-up on all three measures, indicating that the treatment effects were maintained.

Similarly to previous large RCT's these findings suggest CBT may be an effective intervention to target fatigue, physical functioning and social adjustment in patients with CFS [10]. By dichotomising self-reported global improvement, 50% of patients in the present study reported feeling much better or very much better. This is in line with previous results from Quarmby et al (2007) in which they found a global improvement score of 57% in routine care and Flo & Chalder et al. (2014) who reported a 60.8% global improvement, using the same methodology.

Reassuringly, we did not find any age or ethnic differences in treatment improvement outcomes across CFQ, SF-36 and WSAS. Neither, did we find any differences in age, ethnicity, martial status or illness duration for those who dropped out compared to those who completed

treatment. We were unable to find any predictors of outcome so cannot say with any certainty who will do well in treatment.

Limitations

This naturalistic study had high ecological validity. However, the lack of a control condition limits us from drawing any causal inferences as we can not be certain that the improvements seen are due to CBT alone and not any other extraneous variables. Furthermore, therapist effects were not considered, due to lack of power and results from our previous study in the same setting which suggested therapist effects were minimal [30]. Future studies should include a waiting list control sample within naturalistic settings to address these issues.

Drop-out rate was 31%, although large meta-analysis reviews found drop out rates for CBT studies range from 0-42% depending on stud y design and definition of drop out [9], suggesting that our drop out rate was not unusually high. Those who dropped out were more likely to have lower physical functioning, higher WSAS scores and higher depression scores. This suggests that there may have been some bias in the data, in that those who completed treatment may not represent all patients who access CBT treatment for CFS.

In conclusion these results demonstrate that CBT delivered in a naturalistic setting could lead to positive changes in fatigue, physical functioning and social adjustment. Furthermore, many patients no longer meet diagnostic criteria. Clinics should assess outcomes routinely and report on change in naturalistic settings. Future studies should consider a wait list control and explore other variables which may moderate the treatment effect.

Data accessibility

We will assess requests for data on a case by case basis.

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Table 1. Reason for drop-out.

Reason	*n*
Dropped out with no contact	29 (21%)
Discontinued treatment (did not want treatment)	21 (15%)
Cancelled numerous appointments and was discharged	14 (10%)
Moved away from area	14 (10%)
Felt better and discontinued treatment	7 (5%)
Treatment stopped due to other comorbid problem	7 (5%)
Had to stop treatment due to personal circumstances (e.g. life events)	7 (5%)
Other	41 (29%)
Total	140

Table 2. Estimated marginal means and standard errors for main outcomes over time.

Measure	Assessment	*n*	Mean	*SE*	95% Confidence interval	
					Lower Bound	Upper Bound
CFQ	Start	977	24.19	.25	23.69	24.68
	Session 4	392	19.45	.36	18.75	20.15
	Session 7	380	18.62	.36	17.91	19.32
	Discharge	581	17.67	.31	17.07	18.26
	Follow-up	503	18.60	.32	17.96	19.23
SF-36	Start	768	47.60	.95	45.73	49.46
	Discharge	441	57.50	1.07	55.40	59.61
	Follow-up	404	58.51	1.10	56.36	60.67
WSAS	Start	989	25.04	.31	24.43	25.65
	Session 4	395	22.91	.39	22.15	23.67
	Session 7	382	21.41	.39	20.65	22.18
	Discharge	582	19.49	.35	18.80	20,17
	Follow-up	507	19.12	.36	18.41	19.83

WSAS: Work and Social Adjustment Scale; SF-36: Short Form Health Survey, Physical Functioning Subscale; CFQ: Chalder Fatigue Questionnaire; HADS-A: Hospital Anxiety and Depression Scale, Anxiety Subscale; HADS-D: Hospital Anxiety and Depression Scale, Depression Subscale.

Table 3. HADS caseness for participants with complete data (using cut-off score of 8)

Measure	Caseness	Start	Discharge	Follow-Up
		n (%)	*n (%)*	*n (%)*
HADS-A	Case	257 (65%)	204 (52%)	204 (52%)
	Non-case	136 (35%)	189 (48%)	189 (48%)
	Total	393		
HADS-D	Case	215 (55%)	140 (36%)	161 (41%)
	Non-case	178 (45%)	253 (64%)	232 (59%)

HADS-A: Hospital Anxiety and Depression Scale, Anxiety Subscale; HADS-D: Hospital Anxiety and Depression Scale, Depression Subscale.

Table 4. Self-reported global improvement at discharge and follow-up, for participants with complete data.

Outcome	Discharge *n (%)*	Follow-Up *n (%)*
Very much better	67 (18%)	74 (20%)
Much better	129 (35%)	133 (36%)
A little better	124 (34%)	102 (28%)
About the same	35 (10%)	38 (10%)
A little worse	8 (2%)	13 (4%)
Very much worse	2 (.5%)	5 (1%)
Total	365	365

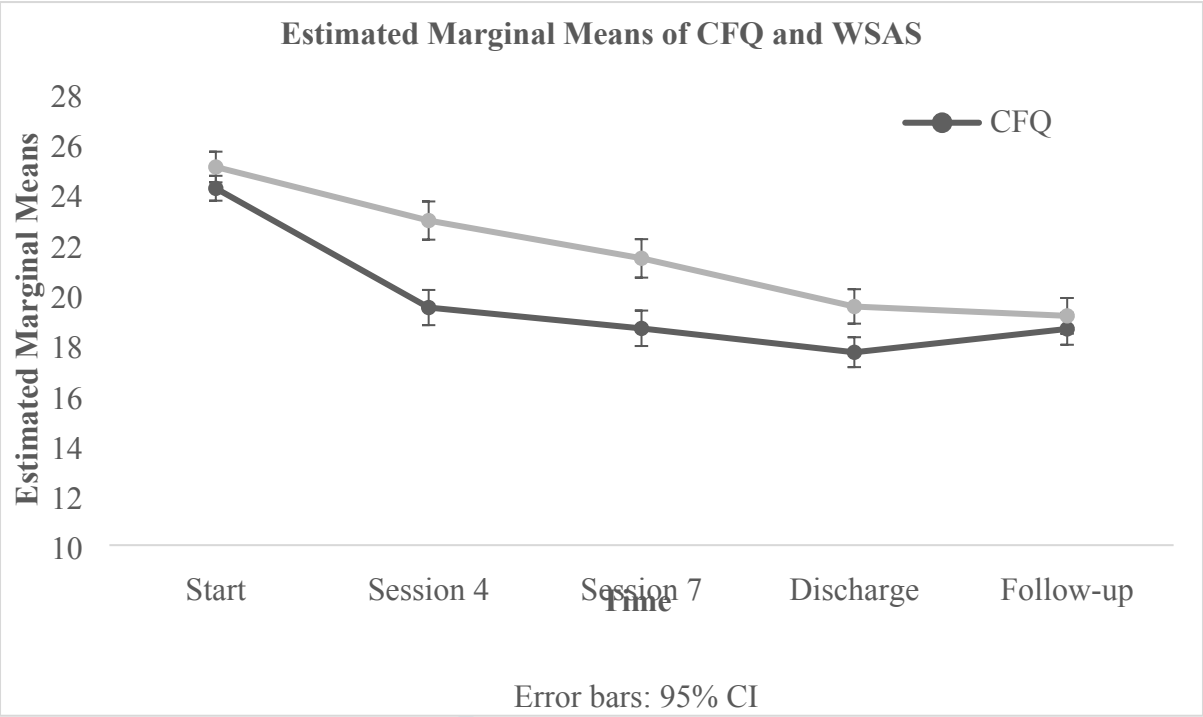

Figure 1. Estimated marginal means for both CFQ and WSAS scores across all observed time points.