Implementation of stepped care for patients with chronic fatigue syndrome in community-based mental health care: outcomes at post-treatment and long-term follow-up

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Abstract

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

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

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

Results: Fatigue decreased and physical functioning increased significantly following implemented stepped care (both p < .001). The follow-up was completed by 94 patients (78%) within 1–6 years after treatment. Treatment effects were sustained to follow-up. Patients in the MHC showed less improvement directly following stepped care compared with patients in a CFS specialist centre (p < .01).

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

Keywords: chronic fatigue syndrome; cognitive behavioural therapy; implementation; minimal intervention; stepped care

Introduction

Chronic fatigue syndrome (CFS) is characterized by medically unexplained, chronic and severe fatigue that is associated with significant impairment. According to the case definition of the US Centres for Disease Control and Prevention (CDC), patients must also report at least four additional symptoms out of the following eight: muscle pain, sore throat, multi-joint pain, tender lymph nodes, unrefreshing sleep, post-exertional malaise, headaches, and memory and/or
concentration problems (Fukuda et al., 1994; Reeves et al., 2003). Individual cognitive behavioural therapy (CBT), aimed at changing fatigue-perpetuating cognitions and behaviour, leads to a significant reduction of fatigue and disability (Knoop et al., 2007a; White et al., 2013). CBT for CFS was developed in tertiary research centres. This is true for most psychological treatments; these treatments are usually tested in specialist treatment centres (Harvey and Gumport, 2015). To determine if interventions are similarly effective when implemented in routine clinical settings, studies are needed that compare the effects of implemented care with care delivered in specialist centres (Harvey and Gumport, 2015; Shafran et al., 2009). Several implementation studies have been published on CBT for CFS. Generally, face-to-face CBT has been successfully implemented (Scheeres et al., 2008; Wiborg et al., 2014) with effect sizes comparable to the effect sizes of randomized controlled trials (RCTs) that tested CBT for CFS in research centres (Scheeres et al., 2008).

Face-to-face CBT is time intensive, requiring 12–14 sessions. The Dutch healthcare system is under continuous pressure to reduce costs, resulting in budget cuts and limited treatment capacity. The need to use this limited treatment capacity more optimally has stimulated efforts to develop minimal interventions for CFS, based on the protocol of face-to-face CBT. A minimal intervention consisting of a workbook with self-instruction and fortnightly email contact with a trained CBT-for-CFS therapist was first tested in a CFS specialist centre (Knoop et al., 2008). Subsequently, this minimal intervention was used as a first step in a stepped care model. Patients could step up to a higher intensity of treatment (Richards, 2012) in the form of face-to-face CBT if the minimal intervention did not suffice (Tummers et al., 2010). Within a CFS specialist centre, the stepped care model was more time efficient and non-inferior compared with face-to-face CBT alone (Tummers et al., 2010).

Subsequently, the minimal intervention was implemented in a community-based mental health centre (MHC). An RCT showed that the minimal intervention was effective, compared with a waiting list (Tummers et al., 2012), with effect sizes comparable to when the intervention was delivered in a CFS specialist centre (Knoop et al., 2008). Patients who participated in this implementation study were offered stepped care, i.e. the wait list group could start with the minimal intervention; after the minimal intervention patients could step up to face-to-face CBT if needed.

The primary aim of the present study was to evaluate the effectiveness of implemented stepped care in a MHC, both directly following treatment and at long-term follow-up. The secondary aim was to compare post-treatment outcomes of implemented stepped care with treatment outcome of CBT delivered in a CFS specialist centre (Janse et al., 2017).

**Method**

**Participants**

In the original minimal intervention study in the MHC, 181 patients were referred for treatment of CFS. Of this group of 181 patients, 123 patients were randomized. Thirty-nine referred patients did not meet the inclusion criteria: 34 did not meet CDC criteria, and five were younger than 18 or older than 65. Of the 142 patients eligible to enter the trial, 14 patients refused participation; four preferred face-to-face contact; four did not believe that treatment would help; three preferred another treatment; and for three patients, the reason for refusal was unknown (Tummers et al., 2012). All patients were diagnosed with CFS according to the CDC criteria (Fukuda et al., 1994; Reeves et al., 2003). Patients were severely fatigued, operationalized as scoring ≥35 on the subscale ‘fatigue severity’ of the Checklist Individual Strength (CIS) (Worm-Smeitink et al., 2017). Their fatigue was medically unexplained, present for at least half a year and patients were disabled, operationalized as scoring ≤70 on the subscale ‘physical functioning’ and/or the ‘social functioning’ subscale of the Medical Outcomes Survey Short Form-36 (SF-36) (Stewart et al., 1988). All patients reported at least four additional symptoms (Fukuda et al., 1994; Reeves et al., 2003).
In the original study, patients were first randomly assigned to the first step of stepped care, consisting of a minimal intervention or a delayed start with the minimal intervention after a waiting period of 6 months (Tummers et al., 2012). Treatment outcome of the minimal intervention at 6 months post-randomization was previously reported (Tummers et al., 2012). There was a significant reduction in fatigue following the intervention compared with the waiting list.

The current study used a reference group with CFS patients who met the CDC criteria for CFS and had received CBT in one CFS specialist centre (n = 583). Detailed characteristics of the reference group are described in a previous study (Janse et al., 2017).

**Design and procedures**

This is a secondary analysis of patients who participated in the original study (Tummers et al., 2012) testing the efficacy of an implemented minimal intervention compared with a waiting list. The study was approved by the ethics committee of the Radboud University Medical Centre. Patients who were still severely fatigued after the minimal intervention, i.e. patients who scored 35 or higher on the CIS fatigue severity subscale (Worm-Smeitink et al., 2017), were offered face-to-face CBT by trained therapists. The wait-list group was offered stepped care after the waiting period, i.e. a minimal intervention followed by face-to-face CBT if needed (see Fig. 1). All patients of the prior RCT (Tummers et al., 2012) were used in the current study and treated as one stepped care cohort. Patients who only completed a baseline assessment were excluded from analysis.

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

All 123 patients who participated in the original study (Tummers et al., 2012) were contacted by telephone for a follow-up assessment. If they agreed to participate, they received an invitation

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**Figure 1.** Study overview of implemented stepped care at post-stepped care and follow-up. The post-stepped care assessment was used for analysis. *Half of the stepped care group was randomized to a direct start with the minimal intervention or a delayed start after 6 months waiting list; **18/20 patients were first randomized to the waiting list.*
letter and questionnaires by post, or e-mail with a link to complete questionnaires online. Detailed design and procedure information is provided in the Supplementary Material.

CFS patients treated in one CFS specialist centre were the reference group consisting of patients from two cohort studies and two RCTs, all treated following the same protocol (Janse et al., 2016; Knoop and Bleijenberg, 2010). Different treatment formats were applied in the studies of the reference group: individual CBT \((n = 179)\) (Heins et al., 2013; Knoop et al., 2007a), stepped care consisting of a minimal intervention and individual CBT (RCT, \(n = 169\)) (Tummers et al., 2010) and group CBT (RCT, \(n = 135\)) (Wiborg et al., 2015). The reference group was treated as one cohort (Janse et al., 2017).

**Intervention**

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

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

If patients were still severely fatigued, they were referred to a CBT therapist within the MHC for additional face-to-face CBT for CFS. This additional face-to-face CBT was the second step of stepped care. Following the protocol (Knoop and Bleijenberg, 2010), a full therapy would consist of 12 to 14 sessions over a period of 6 months. However, dependent on the progress made during the minimal intervention, the therapist decided which elements of the protocol should be discussed during the face-to-face CBT (Tummers et al., 2010). Detailed information on the minimal intervention, and the training and supervision of the nurses and the CBT therapists, can be read in the Supplementary Material.

**Measures**

*Fatigue severity* was measured with the fatigue severity subscale of the CIS. The CIS consists of 20 items. The fatigue severity subscale of the CIS has eight items and each item is scored on a Likert-scale from 1 to 7. The total score ranges from 8 (no fatigue) to 56 (severe fatigue) (Worm-Smeitink et al., 2017). The CIS has good psychometric characteristics (Worm-Smeitink et al., 2017). We determined the number of patients with a fatigue score in the normal range following treatment, defined as a score of less than 35 on the ‘fatigue severity’ subscale of the CIS. This is below the cut-off for severe fatigue (Worm-Smeitink et al., 2017).

*Physical functioning* was assessed with the physical functioning subscale of the Medical Outcomes Survey Short Form-36 (SF-36). This subscale measures the extent to which health problems interfere with a variety of physical activities. Weighted scores on this subscale range from 0 (no limitations) to 100 (maximum limitations), i.e. higher scores indicate better physical functioning (Ware and Sherbourne, 1992). The SF-36 is considered a reliable and valid instrument (Scheeres et al., 2008; Ware and Sherbourne, 1992). Following treatment, we determined the number of patients with a level of physical functioning comparable to healthy people defined as scoring 80 or higher (Knoop et al., 2007a). Healthy adults without a chronic condition (Aaronson et al., 1998) were used as a norm group. The score of 80 is approximately one SD (11.7) below the mean of the norm group (mean = 93.1).

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

**Depression** at baseline was assessed with the Beck Depression Inventory-Primary Care questionnaire (BDI-pc, Cronbach’s alpha .86, seven items, 4-point scale) (Beck et al., 1997).

The **CDC symptoms** at baseline (eight in total) (Fukuda et al., 1994; Reeves et al., 2003) were reported on a 4-point scale ranging from ‘not at all’, ‘a few times per month’, ‘a few times per week’ to ‘every day’. Symptoms had to be present for at least 6 months.

**Additional measures at follow-up**

A general questionnaire was used at follow-up that contained items on presence of somatic co-morbidity that occurred since end of treatment and still present, and significant life events in the past year. Mental health and pain at the time of follow-up were assessed with the subscales ‘mental health’ and ‘bodily pain’ of the SF-36 (Ware and Sherbourne, 1992).

**Data analyses**

*The effect of implemented stepped care*

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

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

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

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

**Results**

*The effect of implemented stepped care*

Patient characteristics at baseline are described in Table 1. Following stepped care in the MHC, fatigue severity significantly decreased \((-12.6, p < .001; \text{pre–post } Cohen’s \ d = 1.19,\)

(Bloot et al., 2015; Knoop et al., 2007b; Menting et al., 2017).
95% CI 0.91 to 1.46) and physical functioning significantly increased (17.1, \( p < .001 \); pre–post Cohen’s \( d = 0.75 \), 95% CI 0.48 to 1.01).

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

From post-stepped care up to follow-up, fatigue severity and physical functioning did not significantly change (mean change fatigue 1.4, \( p = .32 \); mean change physical functioning –1.0, \( p = .69 \); Table 2). The number of patients with fatigue scores in the normal range and physical functioning comparable to healthy people did not significantly change from post-stepped care (fatigue: 36%, 40/111; functioning: 40%, 44/111) to follow-up (fatigue: 28%, 26/94; \( \chi^2 = 1.6, p = .2 \); functioning: 35%, 30/86, \( \chi^2 = .5, p = .49 \)).
We added the covariates significant life events, somatic co-morbidity, pain and mental health to the model to assess if this would change the non-significant result of outcome during the follow-up phase (Table 2, model with covariates). These covariates have found to be related to fatigue and/or physical functioning (Bloot et al., 2015; Hempel et al., 2008; Jansse et al., 2017; Knoop et al., 2007b) and may influence long-term effects of CBT when they occur in the follow-up phase. Of the patients who participated in the follow-up study, 12/94 (13%) reported somatic co-morbidity which had occurred after treatment, and 37/94 (39%) reported life events during the last year with an impact on health (see Table 1). The addition of the covariates did not change the non-significant development of our outcomes during the follow-up phase (fatigue: \( p = .91 \) and functioning: \( p = .64 \)).

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

There was a significant treatment setting \( \times \) time interaction \( (p < .001) \) on fatigue severity (supplementary fig. 1; Table 3). Fatigue severity decreased more when treated in a CFS specialist centre \( (B = -19.6, p < .001) \) than with implemented stepped care \( (B = -12.6, p < .001) \). There was also a significant setting \( \times \) time interaction \( (p = .009) \) in physical functioning (supplementary fig. 2; Table 3). Physical functioning improved more in the CFS specialist centre \( (B = 23.2, p < .001) \) than after implemented stepped care \( (B = 17.1, p < .001) \). We added covariates to the model to test if this would change the effects for the different treatment settings. Both interactions remained significant when baseline patient characteristics were added as covariates (see model B of Table 3). Significantly fewer patients after implemented stepped care \( (\chi^2 = 25.6, p < .001) \) had fatigue scores in the normal range (36%, 40/111) than when treated in the CFS specialist centre (62%, 337/543). The same pattern of results was found for the number of patients with physical functioning scores comparable to healthy people (implemented stepped care: 40%, 44/111; for a CFS specialist centre: 63%, 340/543; \( \chi^2 = 20.1, p < .001 \)).

**Discussion**

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

The current finding that implemented stepped care is effective is in line with previous studies of stepped care in CFS specialist centres that have also shown significant treatment effects.
Ali et al. (2017; Tummers et al., 2010). It is encouraging for implemented CBT that after stepped care patients were able to maintain the gains made on fatigue and physical functioning.

The minimal intervention implemented in the MHC had similar controlled effect sizes on both fatigue and physical functioning when compared with a CFS specialist centre (Knoop et al., 2008; Tummers et al., 2012). However, when patients proceed with face-to-face therapy within a stepped care model, therapy in the MHC was less effective than care in a CFS specialist centre, targeting the second objective of this study. This difference between the effects of the implemented minimal intervention and the effects of implemented stepped care suggests that the second step in the stepped care model, i.e. face-to-face CBT, has to be improved in the MHC.

Some characteristics of implemented stepped care may have negatively affected outcome. First, shortly after face-to-face CBT had been implemented in the MHC, stepped care was introduced (Wiborg et al., 2014). The newly trained therapists had only limited experience in delivering face-to-face CBT for CFS outside the context of stepped care. It is likely that it is more difficult to deliver CBT to patients who were already unsuccessfully treated with the minimal intervention. Future implementation of CBT for CFS should give therapists enough time to first learn to effectively treat patients with regular CBT for CFS.

Another relevant implementation factor was the involvement of two different professionals in the delivery of stepped care. Trained nurses performed intakes and carried out the first step of care in the form of the minimal intervention. The second step of care, i.e. face-to-face therapy, was delivered by a CBT for CFS therapist, unknown to the patient. This change of caregiver may have been associated to the fact that only a small group (one-third) of patients with an indication to step up, i.e. still severely fatigued, actually stepped up. If patients do not step up to a higher treatment intensity while they are indicated to do so, this may diminish outcome of stepped care (Bower and Gilbody, 2005). In contrast, patients in a CFS specialist centre were supported by the same therapist during all steps of care. Here, two-thirds of the still severely fatigued patients proceeded to the second step of care, i.e. face-to-face CBT (Tummers et al., 2010). The treatment outcome of implemented stepped care may be enhanced if the therapist delivering the second step of treatment is involved early in the diagnostic process and with the evaluation after the minimal intervention.

Lastly, and irrespective of the setting, we highlight two common issues with stepped care: (1) patients who do not start with a minimal intervention, or (2) do not step up to a higher treatment intensity (Bower and Gilbody, 2005). In the MHC, approximately 15% of patients did not start with the minimal intervention at all (for a similar percentage of non-starters in CFS specialist care, see Knoop et al., 2008). In the future, if patients will not start with the minimal intervention in the first 2 weeks, a therapist could contact the patient and discuss the reason for not starting. The outcome of this shared decision making may be that they decide to still start or stop treatment. Stepping up at an early stage is another option, although it is unknown if these patients would benefit from stepping up to a higher treatment intensity at this stage. The second limitation of stepped care was patients who do not step up to a higher treatment intensity. Patients who have started with the minimal intervention and gain minimal benefits may have lost motivation to step up, since they had to wait 6 months until the second step of treatment was provided. A previous process study into face-to-face CBT showed that patients have different trajectories of change (Heins et al., 2013). These trajectories of change are as yet unknown for patients following stepped care. A prospective process study could assess outcome and changes in fatigue perpetuating factors every month to reveal different change trajectories. This knowledge could help to decide when to step up to a higher treatment intensity. More pragmatically, a stepped wedge design (Brown and Lilford, 2006) can be applied to test the benefit of stepping up to face-to-face CBT earlier than the current 6 months.

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

Limitations
The current study has several limitations. Patients were not randomly assigned to the MHC or to the CFS specialist centre and may therefore differ. The route of referral that patients had followed differed between centres. In the CFS specialist centre, patients were usually referred via the department of internal medicine, whereas in the MHC patients were usually referred by the general practitioner or internal consultant. This may have led to differences in patient characteristics between both settings. However, outcome differences between treatment settings could not be explained by patient’s age, gender, number of CDC symptoms, fatigue severity, physical functioning, pain, and level of depression at baseline. This is a relevant finding as there are concerns that RCTs performed in specialist centres use strict inclusion criteria and that patients therefore differ from patients in implementation settings. Moreover, these hypothesized patient differences are assumed to explain the differences in effect sizes between specialist centres and implementation settings (Shafran et al., 2009). One note to our comparison of treatment outcome between treatment settings was that it had an unbalanced sample size, making the comparison to test for patient differences between settings probably under-powered.

A recent validation study of the Checklist Individual Strength proposed new norms for severe fatigue. The study found a higher cut-off score of 40 to discern severe fatigue of lower scores representing fatigue scores in the normal range (Worm-Smeitink et al., 2017). The present study still used 35 as a cut-off to make comparisons with previous studies easier.

One could argue that the comparison between stepped care and different formats of CBT delivered in a CFS specialist centre is a limitation of the present study as it is unclear if these treatment formats are equally effective. However, a previous analysis showed similar changes in outcome over time for all the different formats of CBT without differences in outcome between stepped care and other formats (Janse et al., 2017).

Most patients who did not start treatment were first randomized to a 6-month waiting list before they could start with the minimal intervention. This may have reduced the effectiveness of the stepped care (Tummers et al., 2012) and is a limitation of our study design. The absence of a control group and the variety in treatment experiences in the MHC are limitations of our study. Unfortunately, information about the care patients received between post-treatment assessment and follow-up was lacking. This is a further limitation of our study.

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

Ethics statement. The authors assert that all procedures included in this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975 and its most recent revision. No ethical approval was needed as these patients were investigated in a follow-up of already approved studies. Furthermore, the authors have abided by the Ethical Principles of Psychologists and Code of Conduct as set out by the American Psychological Association (2003).

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