Journal Pre-proof

Feasibility trial of cognitive behavioural therapy for fatigue in haemodialysis (BReF intervention)

Recruitment

- **320 approached** from 2 National Health Service (NHS) sites in England
- **53 consented**
- **24 eligible** after screening & **randomised**
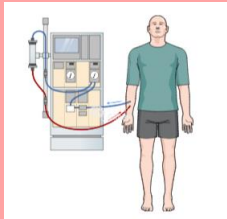
BReF intervention N=12

Waiting-list N=12

Results

- The consent rate was 16.6% (95% CI 12.66% to 21.10%)
- It was necessary to approach 13 patients for every 1 patient randomised
- The rate of retention at follow-up was 75% (95% CI 53.29% to 90.23%)
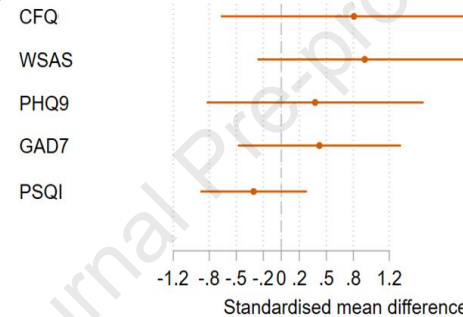
Moderate to large treatment effects were observed in favour of BReF on fatigue severity (CFQ), fatigue-related functional impairment (WSAS), depression (PHQ9), and anxiety (GAD7), but not sleep quality (PSQI). The large confidence intervals indicate considerable uncertainty.

The time demanding nature of BReF intervention is an important barrier to uptake for patients

Conclusion

Promising evidence in support of BReF intervention, but it needs to be more appealing and practical for patients to improve uptake.

Picariello et al., 2020

Feasibility trial of cognitive behavioural therapy for fatigue in haemodialysis (BReF intervention)

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Abstract

Objective: Fatigue affects at least half of patients who are on haemodialysis with considerable repercussions on their functioning, quality of life, and clinical outcomes. This study assessed the feasibility, acceptability, and potential benefits of a cognitive-behavioural therapy (CBT) intervention for fatigue (BReF intervention).

Methods: This was a feasibility randomised-controlled trial of the BReF intervention versus waiting-list control. Outcomes included recruitment, retention, and adherence rates. Exploratory estimates of treatment effect were computed. The statistician was blinded to allocation.

Results: Twenty-four prevalent haemodialysis patients experiencing clinical levels of fatigue were individually randomised (1:1) to BReF (N=12) or waiting-list control arms (N=12). 53 (16.6% 95% CI 12.7% to 21.1%) out of 320 patients approached consented and completed the screening questionnaire. It was necessary to approach 13 patients for screening for every 1 patient randomised. The rate of retention at follow-up was 75% (95% CI 53.29% to 90.23%). Moderate to large treatment effects were observed in favour of BReF on fatigue severity, fatigue-related functional impairment, depression, and anxiety $SMD_g=0.81$, $SMD_g=0.93$, $SMD_g=0.38$, $SMD_g=0.42$, respectively), but not sleep quality ($SMD_g=-0.31$). No trial adverse events occurred.

Conclusion: There was promising evidence in support of the need and benefits of a CBT-based intervention for fatigue in haemodialysis. However, uptake was low, possibly as a result of an already high treatment burden in this setting. Considerations on the context of delivery are necessary before pursuing a definitive trial.

Key message

This article describes a feasibility randomised-controlled trial of a CBT-based intervention for fatigue in haemodialysis. The results indicate that a psychological intervention may be a viable alternative to pharmacological management and exercise for the management of fatigue, but careful consideration is necessary of the already high treatment burden in haemodialysis.

Keywords: fatigue; dialysis; cognitive behavioral therapy; kidney failure; quality of life

Introduction

Fatigue is common among people with kidney failure who receive maintenance dialysis and has a profound impact on patient-reported and clinical outcomes [1, 2]. Effective management of symptoms in this patient population, particularly fatigue, remains a top of research priority globally and the Standardized Outcomes in Nephrology (SONG) initiative has identified fatigue to be a core outcome for haemodialysis (HD)[3]. Fatigue is a complex, subjective, and multi-factorial symptom characterized by extreme and persistent tiredness, unrelated to activity or exertion and not relieved by rest and recuperation [4]. The aetiology of fatigue in kidney failure is yet to be fully defined, consequently, no consistent treatment model exists and a clear fatigue management treatment pathway is lacking in routine care [2, 5].

There is growing evidence that fatigue in the context of physical long-term conditions (LTCs) is best understood from a biopsychosocial perspective which integrates the biological, cognitive, behavioural and emotional factors and explains how these factors can interact in a vicious cycle to perpetuate or worsen fatigue [6]. Primary disease factors, such as anaemia, inflammation, and HD-related effects are likely to be implicated in the onset of fatigue in this population, while thoughts, emotions, and behaviours in response to fatigue can maintain, exacerbate, and perpetuate fatigue over time. For instance, in multiple sclerosis (MS), a tendency to attribute a wide range of symptoms to MS, embarrassment about fatigue, and unhelpful behaviours in response to fatigue, like excessive resting or overdoing things followed by long resting periods to recover; were found to be strongly associated with fatigue, above and beyond the role of demographic and clinical factors, such as neurological impairment and remission status [7]. A recent scoping review of fatigue interventions across LTCs, including 52 reviews, found little support for pharmacological treatments, while promising evidence was available for exercise and cognitive-behavioural therapy (CBT) interventions [8]. CBT is a structured, tailored and time-limited talking therapy that focuses on changing unhelpful beliefs and behaviours, as well as relaxation techniques and stress management to foster resilience [9]. Despite being originally developed for the treatment of mood disorders [9], CBT can also be targeted at adjustment and symptom management in the context of LTCs [10].

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Similarly, pharmacological treatments appear ineffective, while exercise intervention although beneficial may not be suitable for all patients [11, 12] and no theory-driven and evidence-based psychological intervention aimed at fatigue in kidney failure currently exists, although there is some promising evidence in favour of psychological interventions not aimed at fatigue specifically [13].

In order to address this clinically-important gap, we conducted prospective and qualitative studies; to understand the role of thoughts, emotions, and behaviours in fatigue of kidney failure patients [1, 14, 15]. Based on the findings and extensive Patient and Public Involvement (PPI) input, we adapted an existing CBT manual for fatigue in MS [16, 17] to fatigue in kidney failure. Through this treatment approach, the perpetuators of fatigue can be targeted which is likely to lead to improvements in fatigue severity and its impact on functioning.

Objectives

The overarching aim of this study was to evaluate the feasibility and acceptability of the CBT-based intervention for fatigue in kidney failure and trial methodology for a future definitive trial. For the detailed study objectives please see the published protocol [18].

Methods

A detailed description of the methodology employed in this feasibility trial is available elsewhere [18](ISRCTN91238019).

This was a two-arm parallel group randomised-controlled feasibility trial (RCT), with an assessment at baseline via post before randomisation (T0), and at follow-up 3 months post-randomisation (T1). Participants in the intervention arm also took part in a qualitative evaluation interview after T1.

Outpatient HD patients were recruited from two National Health Service (NHS) sites in England. Adults (aged 18 or older) with a confirmed End-Stage Kidney Failure (ESKF) diagnosis, receiving in-centre HD for at least 90 days and experiencing clinical levels of fatigue, defined as scoring >18 on the Chalder Fatigue Questionnaire, when using continuous

scoring [19, 20], able to read and write in English, and willing and able to take part in the study were eligible.

Patients were excluded if they had any known cognitive impairments, severe mental health disorder, were failing on dialysis and approaching end of life, were receiving psychotherapy or participating in any other interventional trial, or experienced spontaneous improvement in fatigue after screening, by scoring below the CFQ cut-off score at T0. Patients were approached during a stable dialysis session at least 20 min after treatment initiation. Following consent, patients were screened either in person on dialysis or over the phone according to their preferences.

Randomisation, allocation concealment, and blinding

Eligible participants were randomised into the trial following a 1:1 ratio at the individual level to receive either the BReF intervention or to the waiting-list control. Randomisation was stratified by centre and randomly varying block sizes were used to maintain balance of numbers in each arm across the period of recruitment while maintaining allocation concealment. King's College London's Independent Randomisation Service was used. Because the randomisation sequence was automated in real time, the allocation sequence was concealed from researchers.

The nature of the trial meant participants were unblinded to their allocations. Follow-up measures were completed independently by participants via post. An independent researcher, who was not involved in the intervention development or delivery, assisted seven participants with the completion of the follow-up measures. The statistician (SN) remained blind to treatment allocation until after the analyses were conducted.

BReF Intervention

The intervention is a tailored CBT-based self-management intervention aimed at fatigue specifically (not depression, anxiety, or sleep quality) with therapist support. Briefly, BReF targets individuals' fatigue thoughts, emotions, and behaviours by creating consistent activity and rest routines, graded increase of daily activity, and identifying and managing unhelpful thoughts in relation to fatigue. Further detail on the intervention is available elsewhere [18]. A self-management manual was provided, which was accompanied by three

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to five sessions depending on engagement and personal model of fatigue discussed in clinical supervision (first and last sessions face-to-face for 1-hour, remaining over the phone for 30 minutes) with either the primary researcher who has an academic background in Health Psychology, basic CBT training and experience in working with fatigued patient groups (FP), or a Registered Health Psychologist working in the renal setting (HC). The protocol, including the amount of therapist contact; was based on an existing CBT approach initially developed by one of the authors (RMM) and colleagues for fatigue in MS [16, 17]. This intervention protocol was adapted using evidence and patient and public involvement (PPI) to the renal setting. Renal-specific considerations included the triggers of fatigue in this setting, particularly haemodialysis and anaemia; activity and rest scheduling according to haemodialysis or non-haemodialysis days as this is a key idiosyncratic challenge to establishing consistency in activity and rest in this population; and beliefs, behaviours, and emotions associated with changes in renal replacement therapy.

Waiting-list control (control arm)

Participants allocated to the control arm of the study received their usual renal care, consisting of attending dialysis plus any other medical management, such as receipt of erythropoiesis-stimulating agents (ESA). After completion of T1, participants in the control group received the manual without the therapist support sessions.

Data collection

The primary focus of the trial was to evaluate feasibility-related outcomes.

Feasibility outcomes

Feasibility was assessed by collecting descriptive data on recruitment and retention rates, and willingness to be randomised, according to Consolidated Standards of Reporting Trials (CONSORT) feasibility and pilot trial guidelines [21]. Descriptive data were collected on the degree of adherence to the intervention.

Sociodemographic and clinical data

Self-reported sociodemographic and clinical data were collected at T0. Routinely collected biochemical data were extracted from medical records at T0 and T1 [18]. Extra renal comorbidity was evaluated using the Charlson comorbidity score [22].

Psychological measures

Participants completed psychological measures at T0 and T1. All psychological constructs were assessed using well-validated scales previously used in studies with patients with physical LTCs, including dialysis patients, specifically: fatigue severity (Chalder Fatigue Questionnaire; CFQ[19]), fatigue-related functional impairment (Work and Social Adjustment Scale; WSAS[23]), depression (Patient Health Questionnaire-9; PHQ-9[24]), anxiety (Generalised Anxiety Disorder-7; GAD-7[25]), and subjective sleep quality (Pittsburgh Sleep Quality Index; PSQI[26]).

The following putative process variables were also measured: fatigue perceptions (Brief Illness Perception Questionnaire; BIPQ[27]), cognitive and behavioural responses to fatigue (Cognitive and Behavioural Responses to Symptoms Questionnaire; CBRSQ[28]), sleep hygiene (Sleep Hygiene Index; SHI[29]), and physical activity (International Physical Activity Questionnaire–short form; IPAQ-SF[30]). These measures have been previously described in detail elsewhere [18].

At T1, participants were also asked to self-report any serious adverse events or receiving any pharmacological, psychological, or exercise-based treatment for depression and/or anxiety and/or fatigue during the study.

Qualitative interviews

Nine participants[1] from the intervention arm took part in a qualitative evaluation interview after T1 to further assess acceptability of the intervention and identify any issues needing revision, in line with current MRC process evaluation guidelines [31]. The interviews were semi-structured and conducted one-to-one, with more interviews over the phone (N=7) than face-to-face (N=2). The mean length of the interviews was 42.44 minutes

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[1] 5 males (56%); 5 identified as White British (56%), 2 as Asian (22%), 1 as Black African (11%), and 1 as Mixed White and Black Caribbean (11%); mean age=56.3 years old (SD=18.9; range=30-80); median time on dialysis=24 months (range 9-84 months); 8 reported improvement in fatigue severity on the CFQ (89%) and 1 a deterioration in fatigue severity.

(SD=14.00, range=19-68 minutes). The interviews were conducted by independent researchers, who have not been involved in the intervention development or delivery. Qualitative data were analysed using inductive thematic analysis in *NVivo* [32].

Sample size

The sample size estimation is available elsewhere [18]. Based on the size of the target population at each site (N=1,060 expecting to approach 60%) and assumptions around consent to the study, eligibility, and consent to be randomised rates (40%, 30%, 50%, respectively) 40 participants would have allowed us to estimate the true population consent rate with a 11% margin of error (95% binomial exact confidence level) for those meeting eligibility criteria; and assuming retention rates of 80%, the true population consent rate would have been estimated with a margin of error of 13% (95% binomial exact confidence interval). However, changes at recruitment sites[2] and a slow recruitment rate prevented us from approaching 636 patients in total from both sites (N=320), as anticipated in the sample size estimation.

Analysis

Questionnaire total scores were computed with missing items accounted for using proration. A threshold of at least 50% of items on a questionnaire being completed (i.e. 6 out of 11 items on CFQ) was set, where if this was not met the total score was set to missing. Proportion of missing data at baseline was negligible and internal reliability of the questionnaires was acceptable (Supplementary Material A).

Descriptive statistics (with 95% CIs) were used to summarise the number of patients approached, screened, eligible, consented, and randomised. Reasons for non-consent, exclusion, and drop-out, at each stage of the study are reported. Similarly, descriptive statistics were computed to report a detailed breakdown of adherence to the intervention.

Estimates of treatment effect at T1 were based on adjusted mean differences using linear regression models following the intention-to-treat principle (ITT)[33]. Covariates in

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[2] During the recruitment window, a satellite unit at KCH was closed and a satellite unit established in a new location, as a consequence, patients across all satellite units associated with KCH were re-assigned to different units based on proximity to where they live. The transition took approximately two months during which time recruitment was disrupted.

the model were an indicator variable for group assignment, the baseline level of the outcome variable, and an indicator variable for recruiting centre as this was a stratification factor in the randomisation. Residual diagnostics indicated heteroscedasticity. Robust standard errors were estimated using the Huber-White sandwich estimator to counter the biasing effect of any deviations from the assumption of residual non-normality and homoscedasticity on estimated standard errors. Since this is a feasibility RCT that is not powered to detect differences in outcomes, p-values are not reported [34]. Inferences based on confidence intervals consider the range of effect sizes included rather than the inclusion or exclusion of the null. Standardised mean differences were estimated as Hedge's g (SMD_g) with a small sample adjustment [35]. All analyses were conducted using Stata 15.1 with the analysis reproducible by saved statistical code.

Results

Feasibility of screening and recruitment rates

After a pre-screen conducted by the medical team, based on the following criteria: age (18 or older), time on dialysis of at least 90 days, no significant learning or cognitive impairment, English proficiency, not taking part in any interventional trial, and ability to take part (no hearing or visual impairments); 247 HD patients could be approached at KCH and 73 at Lister Hospital. Ten patients declined to be approached. Out of the approached patients, 230 declined to take part immediately, and the most common reason for declining was not suffering from fatigue (N=93)(see Figure 1 for further details). It is important to note that this was self-reported by patients during approach and may reflect that they found the study unappealing or too demanding.

Fifty-three patients consented and completed the screening questionnaire, out of 90 who originally expressed interest (58.9%; 95% CI 48.02%-69.16%). Out of the consenting patients, 28 were eligible. Reasons for ineligibility included: scoring below 18 on CFQ (N=23), and either taking part in an interventional study or receiving regular psychotherapy or physiotherapy (N=2). 24 participants were randomised to the intervention (N=12) or waiting-list control arm (N=12). Four participants could not be randomised due to spontaneous recovery. It was necessary to approach 13 patients for screening for every one patient randomised (320/24=13.3; 95% CI 8.44-24.25). The consent rate was 16.6% among

those approached (53/320; 95% CI 12.66%-21.10%) and 53% of those consenting were eligible (95% CI 38.64%-66.70%). A flow diagram of the recruitment is shown in Figure 1.

[INSERT FIGURE 1]

Baseline characteristics of the sample

Twenty-four participants were recruited and randomised into the trial. The sample consisted of 12 women (50%), with a mean age of 56.4 years. There was a fairly equal distribution of white and non-white participants. The mean numbers of years of education was 12.71 (SD=3.16), suggesting that on average participants completed primary and secondary education. Most of the participants were retired or unemployed. The median length on dialysis was 30 months (interquartile range=52.00; range=9-240 months). At baseline, half of the sample (54.2%) had high levels of C-Reactive Protein (>5 mg/L), a marker of inflammation. Mean levels of haemoglobin and dialysis adequacy based on the Urea Reduction Ratio were in line with recommended levels (Hb mean=110.63, SD=10.53; URR mean=69.82%, SD=8.26)[3]. The majority of the sample (83%) was receiving Erythropoiesis-Stimulating Agents (ESAs) for anaemia. The mean fatigue severity, fatigue-related functional impairment, depression, anxiety, and sleep quality scores at baseline across the arms were: 22.88 (SD=3.81), 25.47 (SD=9.21), 12.38 (SD=5.77), 7.76 (SD=6.06), and 10.64 (SD=4.21), respectively.

Further detail on the sociodemographic, clinical, and psychological characteristics of the sample at baseline is available in Tables 1-3. There were no significant differences in baseline sociodemographic and clinical characteristics between participants included in the ITT analysis (N=18) and those who dropped out (N=6; see Supplementary Material B).

[INSERT TABLES 1-3]

Adherence to the BReF intervention

All participants completed the first two sessions. Uptake of cognitive therapy sessions was 73%. The last session was completed by 67% of participants. Chapter 3 on improving

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[3]KDOQI Clinical Practice Guidelines for Dialysis: URR of >65% for thrice weekly haemodialysis and haemoglobin of >100 g/L

sleep quality and Chapter 4 on learning how to relax were the most commonly selected chapters in week 3. Two-thirds of participants completed at least three sessions. The delivery mode of the majority of the sessions followed the intervention protocol. In some instances, delivery of the sessions during dialysis was required. The majority of telephone sessions greatly exceeded the prescribed 30-minute duration, particularly session 2 (mean duration of 46 minutes). A detailed breakdown of adherence per session is available in Supplementary Material C.

Comparison of self-report outcomes between the arms at T1

Eighteen participants completed the follow-up measures at T1. The overall rate of retention was 75% (95% CI 53.29%-90.23%). In the BReF intervention arm, 11 (92%) participants were retained at follow-up (95% CI 61.52%-99.79%) and 7 (58%) in the waiting-list arm (95% CI 27.67%-84.83%). No trial adverse events occurred (Supplementary Material D).

Table 4 provides a summary of the pre- and post- scores for the key variables: fatigue severity, fatigue-related functional impairment, depression, anxiety, and subjective sleep quality; and the estimates of treatment effect at T1 adjusted for baseline levels. There were moderate to large effects in favour of the intervention for the outcomes of fatigue severity (SMD_g=0.81), fatigue-related functional impairment (SMD_g=0.93), depression (SMD_g=0.38), and anxiety (SMD_g=0.42). The treatment effect for sleep quality favoured the waiting-list control arm (SMD_g=-0.31). The estimates of treatment effect for these variables are visually displayed in Figure 2. It is important to note that the large confidence intervals for the effect size estimates indicate considerable uncertainty; therefore, the findings should be interpreted with caution.

[INSERT TABLE 4 & FIGURE 2]

Lower rates of questionnaire completion were observed for the putative process variables due to burden (N=13, 54% of the baseline sample), as such these data are summarised visually (Figure 3). Improvements from T0 to T1 could be observed across the putative process variables in both arms.

[INSERT FIGURE 3]

Qualitative feedback from intervention participants

The interviews revealed that most participants perceived an improvement in their fatigue, felt they understood their fatigue better, were more in control of it and were trying to implement lifestyle changes suggested in the intervention (N=8):

"From the intervention, I've got ways of coping with it [fatigue]…I know I'm going to feel fatigued all the time but, I've learnt how to combat it and cope with it" (female, 80 years old)

and

"Before [the thoughts were] more like negative…I was sometimes thinking 'I don't want to do that', but now it's better…My mind doesn't stop me" (male, 32 years old)*.*

Concentration and time required to fully engage with the intervention were frequently raised as important barriers (N=6). Additionally, many participants (N=6) felt that the intervention would be most suitable earlier on from dialysis initiation. Participants also offered suggestions, such as including video materials, shorter and more frequent sessions, or an opportunity for group sessions. The full qualitative findings will be reported in a separate publication.

Discussion

The aim of this study was to establish the feasibility, acceptability, and potential benefits of a theory- and evidence-based CBT intervention for fatigue in haemodialysis patients and to determine whether a full trial using this design can be pursued. The findings of this study are promising, but also highlighted important issues in relation to the appeal and subsequent uptake of the intervention by haemodialysis patients.

According to the qualitative data and exploratory treatment effects, the intervention appeared both acceptable and beneficial to haemodialysis patients, particularly for fatigue severity, fatigue-related functional impairment, depression, and anxiety, with medium to large effect sizes in favour of the BReF intervention. The minimum clinically important difference on the CFQ is 2.3 points [36], this would represent a standardised mean difference of d=0.60 using the baseline CFQ standard deviation here (3.81). Following therapy, the mean change in WSAS has been reported to be 5.07 [37], this would represent a standardised

mean difference of d=0.55 using the baseline WSAS standard deviation here (9.21). Therefore, the treatment effects for fatigue severity and fatigue-related functional impairment reported here are clinically meaningful. While these treatment effects cannot be taken as evidence for efficacy, they do not show any indication not to continue to a trial to determine efficacy. Adherence to the intervention was generally acceptable, particularly based on a systematic review of CBT interventions for fatigue in MS where adherence ranged from 4.3% to 100% [38]. Once consented, retention of participants was satisfactory [39]. Therefore, these data allude to the acceptability and potential benefits of the BReF intervention.

However, uptake of the intervention was low. It was necessary to approach 13 patients for each patient randomised. As such, this study did not recruit to its intended target of 40 patients. A common reason of declining participation revolved around the time and effort necessary for BReF, in addition to dialysis. This is a key and distinctive barrier to uptake of and engagement with psychological interventions in this patient population; therefore, further considerations are necessary to minimise patient burden if this treatment is to be a viable fatigue management option in routine care. A digitally-delivered intervention could be more interactive and scalable; however, low computer literacy has previously emerged as a key barrier to digital intervention among dialysis patients in South East London [40]. Instead, a more flexible approach to delivery providing patients with choice and targeting multiple symptoms rather than one may be a more appealing and practical approach here.

Kidney failure is accompanied by a significant symptom burden [41]. Similarly to fatigue, pruritus and pain are common among dialysis patients [41]. An intervention that can simultaneously address multiple symptoms is likely to be more appealing and practical to patients, but also efficient and cost-effective for the health care system [42].

Availability of psychological support is sporadic, with only 5% of NHS renal units employing the recommended number of psychologists [43]. In light of this, an intervention like BReF that relies on psychologist support is unlikely to be integrated into routine care. It is increasingly clear that building an understanding of the context of delivery is necessary in parallel to the development of the intervention to ensure that the intervention is developed with the NHS in mind [44, 45]. Further focus is necessary on identifying what health care

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professional input is feasible, by whom it can be delivered, and what training is needed and is feasible.

Previous research

There is growing evidence in support of CBT for fatigue across LTCs [8], as also observed here. The estimates of treatment effect here were larger for fatigue severity and fatigue-related functional impairment, compared to depression and anxiety. This may be reflective of the fatigue-specific focus of the intervention and activation of relevant treatment mechanisms, rather than non-specific benefits of improved mood on fatigue [46]. Larger treatment effects for fatigue have been observed in interventions targeted at fatigue versus those addressing other targets like self-management and mood [47].

Although process analysis does not fall within the remit of feasibility studies, descriptive data here showed improvements across all putative variables from baseline to follow-up in line with the proposed biopsychosocial cognitive-behavioural model of fatigue. According to mediation analyses of CBT, changes in negative perceptions of fatigue and fear avoidance beliefs are key mediators of the reduction in fatigue severity, rather than changes in anxiety and depression [46, 48, 49]. However, improvements in the putative process variables were observed in both arms here. It is important to note that attrition was particularly problematic in the waiting-list control arm, as such this may indicate attrition bias with the most fatigued participants dropping out and this being reflected in the changes observed. In the future, it would be valuable to interview patients who decline to take part and those who drop out to understand how to enhance the appeal and reach of psychological interventions in this population.

Strengths and limitations

This is the first feasibility RCT of a CBT-based intervention, developed using theory and evidence, for the management of fatigue among haemodialysis patients in the UK.

Several limitations should be noted. Efficacy was not the focus of this feasibility trial, as such treatment effect estimates are likely to lack precision, due to the small sample size, and differ considerably from the true effect. An appropriate attention control comparison arm will need to be identified for a full-scale trial, as well as formal assessment of fidelity. Non-

response bias is likely given the 17% response rate. Additionally, the mean age of the sample was 59 years old, which is somewhat lower than the national median age of prevalent haemodialysis patients (67 years old)[50]; however, a variety of age groups has been captured (sample age range 23-83 years old).

Finally, another important weakness of this feasibility trial is utilizing medical records for screening of cognitive impairment, instead of including a validated cognitive screening instrument, such as The Mini-Mental State Exam (MMSE)[51]. Cognitive impairment is common in HD, with an estimated prevalence between 16% and 38% [52, 53]. There is evidence that cognitive impairment may preclude engagement with CBT or exercise and may require adaptations [8]. On average participants had primary and secondary education, adaptations to the treatment protocol may also be necessary for those with lower educational attainment.

Conclusion

The preliminary findings of the trial support the acceptability and benefits of BReF, a CBT-based intervention aimed at fatigue in haemodialysis. Despite these promising findings, uptake of the intervention was low, which would likely limit the wider effectiveness for such an intervention. Further considerations are necessary around how to make this intervention more appealing and practical for patients, but also implementable within routine care.

List of supplementary materials:

- Supplementary Material A: Quality of the self-report questionnaires used
- Supplementary Material B: Comparison of participants retained at follow-up versus those who dropped out
- Supplementary Material C: Therapy adherence
- Supplementary Material D: Adverse events

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Conflict of interest

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Contributors

All authors (FP, RMM, ICM, SN, MDS-G, KF, HP, JC) contributed to the design of the study and manuscript preparation. FP, RMM, JC, ICM were involved in the development of the BReF intervention. FP, JC, and SN were involved in the statistical analysis.

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. The study protocol has been published: doi: 10.1136/bmjopen-2017-020842. The statistical analysis plan and statistical code are also available on request.

Ethical approval

The study received ethical approval from the London Bridge NHS Research Ethics Committee (17/LO/1406) and received local Research and Development (R&D) approval. The study was co-sponsored by King's College London and King's College Hospital NHS Foundation Trust. All participants provided written informed consent. The study adhered to the Declaration of Helsinki (1964) ethical standards.

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Table 1. *Sociodemographic Characteristics of the Sample at Baseline (N=24)*

	TOTAL	BReF intervention	Waiting-list control
Variable	**Statistic**	**Statistic**	**Statistic**
Female (N, %)	12 (50%)	4 (33.3%)	8 (66.7%)
Age (M, SD, range)	56.41 (SD=17.86; range=22.05-82.85)	59.81 (SD=17.82; range=30.33-82.85)	53.00 (SD=18.01; range=22.05-78.29)
Ethnicity (N, %)			
Caucasian	14 (58.3%)	7 (58.3%)	7 (58.3%)
Black	6 (25.0%)	3 (25.0%)	3 (25.0%)
Asian	4 (16.7%)	2 (16.7%)	2 (16.7%)
Marital status (N, %)			
Married	6 (25.0%)	2 (16.7%)	4 (33.3%)
Divorced/separated /single/widowed/single parent	18 (75.0%)	10 (83.3%)	8 (66.7%)
Living arrangements (N, %)			
Living with partner, friends, relatives	15 (62.5%)	8 (66.7%)	7 (58.3%)
Living alone	9 (37.5%)	4 (33.3%)	5 (41.7%)
Years of education (M, SD)	12.71 (3.16)	13.25 (SD=2.49)	12.22 (SD=3.73)
Employment status (N, %)			

Working full-time/working part-time/housekeeping/ self-employed	4 (16.7%)	0	4 (33.3%)
Retired	9 (37.5%)	5 (41.7%)	4 (33.3%)
Unemployed	9 (37.5%)	6 (50.0%)	3 (25.0%)
None of the above	2 (8.3%)	1 (8.3%)	1 (8.3%)
Smoking status (N, %)			
Smoker	1 (4.2%)	0	1 (8.3%)
Ex-smoker	9 (37.5%)	3 (25.0%)	6 (50.0%)
Non-smoker	14 (58.3%)	9 (75.0%)	5 (41.7%)
Alcohol consumption (N, %)			
Never	10 (41.7%)	6 (50.0%)	4 (33.3%)
Only on special occasions	14 (58.3%)	6 (50.5%)	8 (66.7%)
Exercise status (N, %)			
More than 3 times per week	2 (8.3%)	2 (16.7%)	0
Less than 3 times per week	4 (16.7%)	3 (25.0%)	1 (8.3%)
Not at all	18 (75.0%)	7 (58.3%)	11 (91.7%)
Primary renal diagnosis (N, %)			
Type 2 diabetes	5 (20.8%)	3 (25.0%)	2 (16.7%)

Hypertensive renal failure	3 (12.5%)	3 (25.0%)	0
Hypertension and diabetes	6 (25.0%)	2 (16.7%)	4 (33.3%)
Glomerulonephritis	5 (20.8%)	2 (16.7%)	3 (25.0%)
Systemic lupus erythematosus	1 (4.2%)	1 (8.3%)	0
Unknown	1 (4.2%)	0	1 (8.3%)
Time on Dialysis in months (M, SD, range)	48.92 (SD=53.37; range=9-240 months)	38.75 (SD=26.83; range=9-84)	59.08 (SD=70.78; range=9-240 months)
Charlson comorbidity score (M, SD, range)	4.75 (SD=2.23; range=2-8)	4.83 (SD=2.12; range=2-8)	4.67 (SD=2.42; range=2-8)
ITT sample (N, %)			
Yes	18 (75%)	11 (91.7%)	7 (58.3%)
No	6 (25%)	1 (8.3%)	5 (41.7%)

Notes. N=total number; M=mean; SD=standard deviation; ITT=intention-to-treat.

Table 2. *Biochemical Characteristics of the Sample at Baseline (N=24)*

	TOTAL	BReF intervention	Waiting-list control
	Mean, SD, range	**Mean, SD, range**	**Mean, SD, range**
Haemoglobin (g/L)	110.63 (10.53; range=89-129)	112.75 (SD=9.58; range=98-129)	108.50 (SD=11.41; range=89-122)
Ferritin (ng/mL)	557.88 (SD=363.77; range=19-1414)	461.58 (SD=322.97; range=57-1004)	654.17 (SD=390.06; range=19-1414)
Serum Albumin (g/L)	39.67 (SD=4.04; range=30-51)	38.75 (SD=5.14; range=30-51)	40.58 (SD=2.43; range=36-44)
Creatinine (μmol/L)	624.17 (SD=225.78; range=111-1150)	595.42 (SD=251.52; range=111-1150)	652.92 (SD=203.76; range=234-979)
Urea (mg/dL)	18.66 (SD=7.05; range=3.60-33)	18.13 (SD=7.85; range=3.60-33)	19.18 (SD=6.47; range=3.70-32.10)
C-reactive protein (CRP; mg/L)	9.20 (SD=7.59; range=2.00-32.30)	7.59 (SD=6.57; range=2.00-23)	10.81 (SD=8.47; range=2.20-32.30)
CRP (low versus high)*	High CRP N=13 (54.2%) Low CRP N=11 (45.8%)	High CRP N=5 (41.7%) Low CRP N=7 (58.3%)	High CRP N=8 (66.7%) Low CRP N=4 (33.3%)
Calcium (mmol/L)	2.31 (SD=0.17; range=2.06-2.77)	2.32 (SD=0.20; range=2.06-2.77)	2.29 (SD=0.14; range=2.13-2.55)
Potassium (mmol/L)	5.00 (SD=0.87; range=3.50-6.60)	4.87 (SD=0.96; range=3.50-6.60)	5.13 (SD=0.78; range=3.80-6.30)
Phosphate (mmol/L)	1.55 (SD=0.49; range=0.42-2.75)	1.42 (SD=0.50; range=0.42-2.03)	1.69 (SD=0.47; range=1.11-2.75)

URR (%)	69.82 (SD=8.26; range=45.80-80.00)	68.63 (SD=10.60; range=45.80-80.00)	71.00 (SD=5.24; range=61.50-79.0)
IDWL (Kg)**	-1.71 (SD=0.88; range=-3.40 - -0.50)	-1.71 (SD=0.89; range=-3.30- -0.60)	-1.72 (SD=0.91; range=-3.40 - -0.50)
IDWG (Kg)**	1.33 (SD=1.09; range=-1.10-3.50)	1.15 (SD=1.03; range=-1.10-2.40)	1.54 (SD=1.17; range=0.10-3.50)
Receipt of ESA (n, %)			
Yes	Yes=20 (83.3%)	Yes=10 (83.3%)	Yes=10 (83.3%)
No	No=4 (16.7%)	No=2 (16.7%)	No=2 (16.7%)

Notes. *CRP dichotomized into low (<5 mg/L) and high (>5 mg/L) based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical guidelines; **based on 23 participants; URR=urea reduction ratio (how effectively a dialysis treatment removed waste products from the body); IDWL= intradialytic weight loss; IDWG= interdialytic weight gain; ESA=erythropoiesis-stimulating agents.

Table 3. *Psychological Characteristics of the Sample at Baseline (N=24)*

Questionnaire		BReF intervention		Waiting-list control	
		Mean (SD)	Response range	Mean (SD)	Response range
CFQ	Fatigue severity	22.43 (SD=3.71)	18-27	23.33 (SD=4.03)	18-30
WSAS	Fatigue-related functional impairment	27.69 (SD=10.61)	5-40	23.25 (SD=7.35)	11-32
PHQ-9	Depression	13.41 (SD=6.84)	2-25	11.33 (SD=4.52)	5-18
GAD-7	Anxiety	10.93 (SD=6.25)	2-21	4.58 (SD=3.96)	0-11
PSQI	Subjective sleep quality	10.92 (SD=4.81)	4.00-21.00	10.36 (SD=3.71)	4-16
BIPQ (item A excluded)	Total illness perception	36.00 (SD=5.94)	26-45	38.67 (SD=9.83)	21-51
CBSQ	Fear avoidance	12.50 (SD=4.58)	5-19	12.17 (SD=3.66)	7-20
	Catastrophizing	9.67 (SD=2.71)	4-13	8.50 (SD=2.84)	4-13
	Symptom focusing	14.08 (SD=3.80)	6-18	13.75 (SD=4.92)	6-23
	Damage beliefs	12.50 (SD=2.20)	9-15	11.85 (SD=3.06)	6-18
	Embarrassment avoidance	14.58 (SD=5.05)	6-23	9.58 (SD=4.56)	3-18
	All-or-Nothing Behaviours	10.08 (SD=4.06)	2-15	8.58 (SD=5.25)	1-17
	Avoidance/resting	15.58 (SD=7.46)	2-27	13.83 (SD=3.21)	10-19

	behaviours				
SHI	Sleep hygiene	15.45 (SD=9.15)	0-33	17.00 (SD=8.72)	4-37
	Physical activity	Low activity=6 (50.0%)	N/A	Low activity=11 (91.7%)	N/A
IPAQ-short form (N, %)		Moderate activity=4 (33.3%)		Moderate activity=1 (0.08%)	
		High activity=2 (16.7%)			

Notes. CFQ=Chalder Fatigue Questionnaire; WSAS=Work and Social Adjustment Scale; PHQ-9=Patient Health Questionnaire-9; GAD-7=Generalised Anxiety Disorder-7; PSQI=Pittsburgh Sleep Quality Index; BIPQ=Brief Illness Perception Questionnaire; CBSQ=Cognitive and Behavioural Responses to Symptoms Questionnaire; SHI=Sleep Hygiene Index; IPAQ=International Physical Activity Questionnaire.

Table 4. *Means of Key Variables at Each Assessment and Post-Randomisation Treatment Effects*

Variable	Visit	BReF Intervention			Wating-list control			Adjusted mean difference						
		N	Mean	SD	N	Mean	SD	Mean diff	SE	95%ll	95%ul	SMD_g	95%ll	95%ul
Fatigue severity (CFQ)	Baseline	12	22.42	3.71	12	23.33	4.03							
	3-months follow-up	11	14.09	6.37	7	17.76	6.10	3.67	3.43	-3.05	10.39	0.81	-0.67	2.29
Fatigue-related functional impairment (WSAS)	Baseline	12	27.69	10.61	12	23.25	7.35							
	3-months follow-up	10	20.20	10.02	7	28.43	12.75	8.53	5.59	-2.43	19.49	0.93	-0.26	2.12
Depression (PHQ-9)	Baseline	12	13.42	6.84	12	11.33	4.52							
	3-months follow-up	10	10.82	4.84	7	12.68	7.68	2.23	3.65	-4.93	9.40	0.38	-0.83	1.58
Anxiety (GAD-7)	Baseline	12	10.93	6.25	12	4.58	3.96							
	3-months follow-up	9	7.56	2.07	7	7.57	6.24	2.57	2.81	-2.93	8.08	0.42	-0.48	1.33
Subjective sleep quality (PSQI)	Baseline	12	10.92	4.81	12	10.36	3.71							
	3-months follow-up	10	9.93	2.83	6	8.54	2.94	-1.34	1.32	-3.93	1.24	-0.31	-0.90	0.28

Notes. Mean diff=Mean difference; SE=Standard error; ll=lower limit; ul=upper limit.

List of figures:

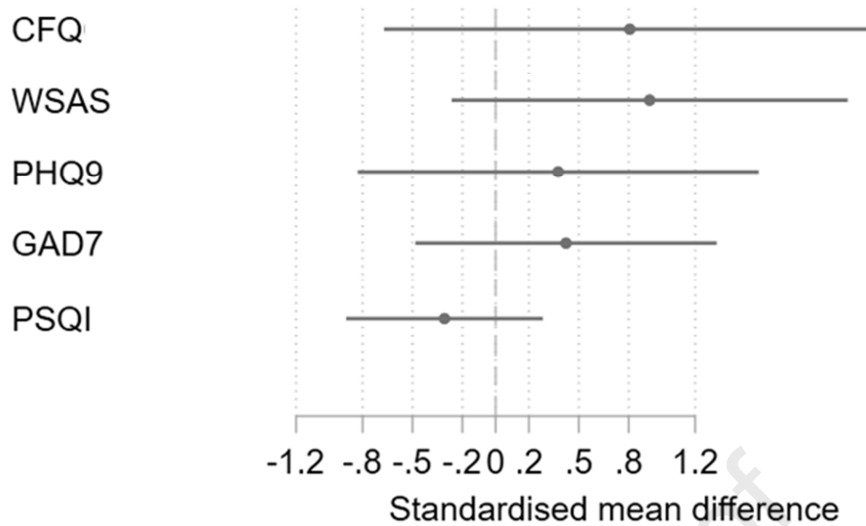*Figure 1.* Patient flow through each stage of the study.

Figure 2. Treatment effects sizes and confidence intervals for key variables. CFQ=Chalder Fatigue Questionnaire (fatigue severity); WSAS=Work and Social Adjustment Scale (fatigue-related functional impairment); PHQ9=Patient Health Questionnaire-9 (depression); GAD7=Generalised Anxiety Disorder-7 (anxiety); PSQI=Pittsburgh Sleep Quality Index (subjective sleep quality).
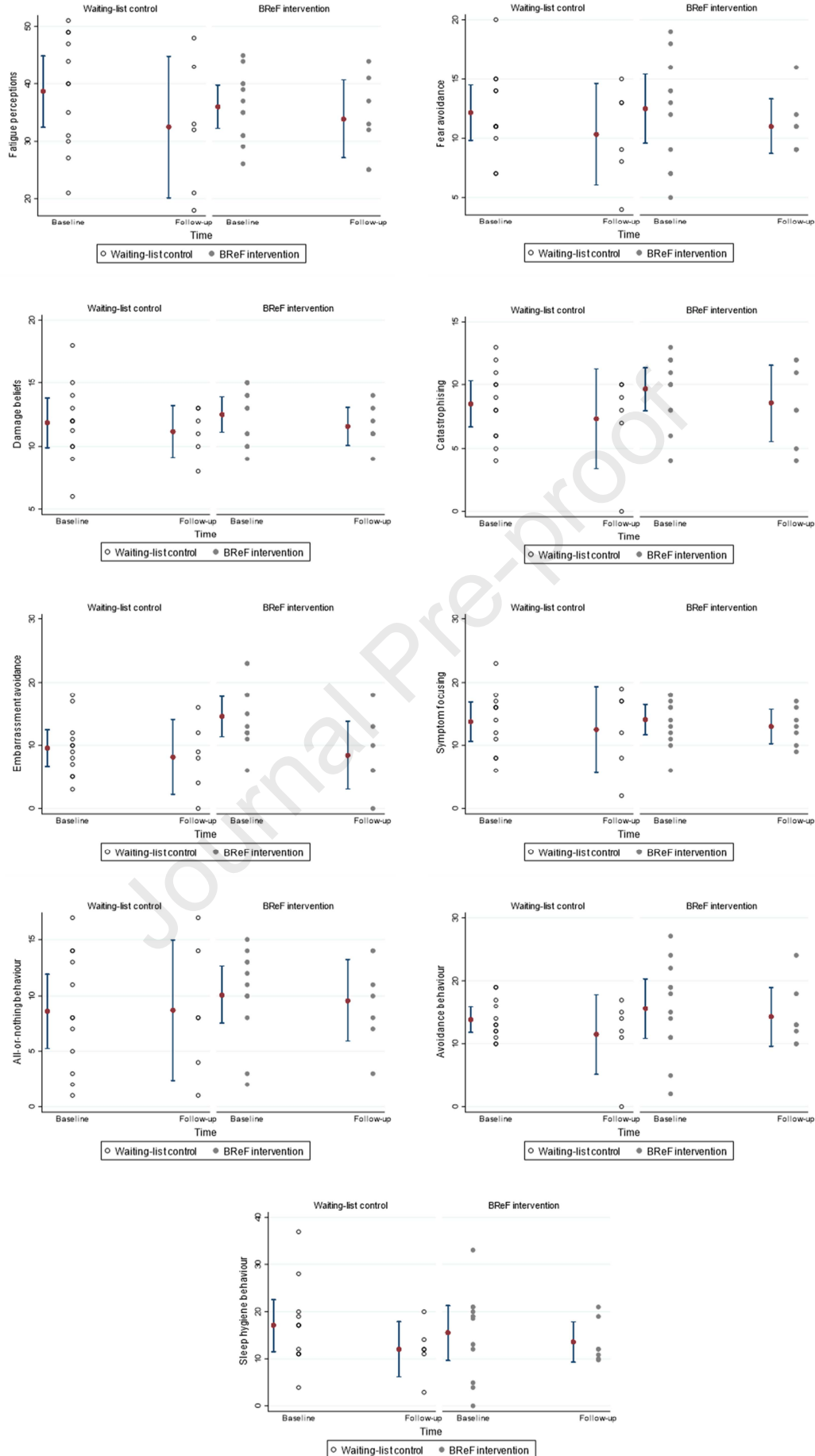
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Figure 3. Dot plot of putative process variable scores from baseline to 3-months follow-up by arm (BReF intervention versus waiting-list control) with 95% confidence intervals.