Comparison of cognitive behaviour therapy versus activity management, both delivered remotely, to treat paediatric chronic fatigue syndrome/myalgic encephalomyelitis: the UK FITNET-NHS RCT

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Scientific summary

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Scientific summary

Objectives

Primary objective

To investigate whether cognitive–behavioural therapy (CBT) specifically designed for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and delivered over the internet [Fatigue In Teenagers on the interNET in the National Health Service (FITNET-NHS)] is effective and cost-effective compared to Activity Management for children with ME/CFS who do not have access to a local specialist ME/CFS service.

Secondary objectives

(1) Estimate the effectiveness of FITNET-NHS compared to Activity Management for those with mild/moderate comorbid mood disorders (anxiety/depression). (2) Estimate the cost-effectiveness of FITNET-NHS compared to Activity Management. (3) Estimate the cost-effectiveness of FITNET-NHS compared to Activity Management for those with mild/moderate comorbid mood disorders (anxiety/depression).

Methods

Trial design

Randomised controlled trial (RCT) comparing FITNET-NHS with Activity Management. Participants were allocated in a 1 : 1 ratio, minimised by age and gender. We conducted an internal pilot (first 12 months) and integrated qualitative methods to optimise recruitment and retention.

Participants

Adolescents aged 11–17 years with a diagnosis of ME/CFS [defined using National Institute for Health and Care Excellence (NICE) 2007 Criteria], who did not have a local specialist ME/CFS service. To have a confirmed diagnosis, potential participants were required to have been assessed by a paediatrician (or equivalent specialist doctor), and to have had screening bloods taken. We excluded adolescents if: they were not disabled by fatigue; their fatigue was due to another cause (including primary anxiety/depression); they had access to a local specialist service; they were unable to complete video calls or FITNET-NHS treatment modules; they were pregnant.

Setting

We identified potentially eligible adolescents at referral to the specialist paediatric ME/CFS service at the Royal United Hospital, Bath. Patients were referred to the service by their general practitioner (GP) or paediatrician (or equivalent specialist).

Between September 2018 and March 2020, we offered GP surgeries the opportunity to become patient identification centres. In these sites, database searches were conducted to identify potentially eligible adolescents, who were then offered referral to the Bath Royal United Hospital for eligibility assessment.

Recruitment

Potentially eligible adolescents were contacted by the clinical team by telephone to discuss the opportunity to take part in the FITNET-NHS trial. Interested adolescents were sent study information, including a link to the Revised Children's Anxiety and Depression Scale (RCADS) questionnaire.

Eligibility assessment

Adolescents who were interested were invited to an eligibility assessment conducted by a specialist nurse. The nurse checked if: (1) they had debilitating persistent or relapsing fatigue for at least 3 months, but not life-long; (2) fatigue was not the result of ongoing exertion and not substantially alleviated by rest; (3) they had post-exertional malaise (and increase in fatigue and other symptoms after exertion); and (4) their fatigue was severe enough to cause substantial reduction in previous levels of occupational, educational, social or personal activities. The recruiting nurse checked that the screening blood tests had been done within the previous 12 months and were normal.

The nurse then assessed whether the adolescent had comorbid mental health problems or a primary mental health problem. Patients were asked to complete the RCADS. Those scoring within the borderline or above the age-/gender-validated threshold answered further questions to determine if they were at risk of harm and whether their anxiety/depression was sufficiently severe to explain the fatigue.

This enabled us to ensure that those recruited had a diagnosis of ME/CFS from a specialist but also had 3 months of disabling fatigue plus one further symptom and did not have an exclusionary diagnosis and therefore had ME/CFS according to the contemporary United Kingdom (UK) guideline.

Consent

If adolescents were eligible and interested in taking part in the FITNET-NHS trial, consent and assent (patients aged 11–15 years) were obtained using an online form.

Randomisation

We used an automated web randomisation service operated by Bristol Trials Centre. Participants were allocated in a 1 : 1 ratio. Allocation used minimisation to balance by age and gender with a random component to preserve allocation concealment.

Blinding

It was not possible to blind the participant, family or the clinical service. The investigators (including the senior statistician who wrote the statistical analysis plan) were blinded to treatment allocation. The study statistician was unblinded as they reported to the Data Safety and Monitoring Committee.

Interventions

Fatigue In Teenagers on the interNET in the National Health Service (FITNET-NHS)

This is a web-based modular specialist CBT programme designed to be used by adolescents with ME/CFS and their parents. We adapted the Dutch FITNET platform for UK adolescents. FITNET-NHS is delivered using asynchronous individualised e-consultations within the web-based platform. Contact is weekly initially and then becomes less frequent. The therapist works with patients and parents separately. FITNET-NHS has psycho-educational and CBT chapters for patients and a parallel programme for parents. There are 19 chapters. *Chapters 1–3* introduce ME/CFS, CBT and the role of therapists; *Chapter 4* discusses treatment goals; *Chapters 5–19* are about cognitive and behavioural strategies. There are diaries for patients that are visible to the therapist. FITNET-NHS is individualised for patients. *Chapters 5–19* are unlocked (made available) by the therapist according to clinical presentation, needs and formulation. Fidelity was assessed in clinical supervisions.

Activity Management

Participants and their families received information on ME/CFS, Activity Management, sleep and symptoms management. Participants could use an online app to record their activity. Activity Management was delivered via videocall. In the initial assessment, participants had a detailed assessment of physical and cognitive activity. The participant and therapist agreed a ‘baseline’ of activity,

which is the average level of activity. Participants were asked to record activity, and then, when activity was stable, to increase activity gradually in a flexible and individual way. The initial assessment was 90 minutes (but this could be split into two shorter sessions). Follow-up video calls (60 minutes each) were organised 2–6 weeks apart. In November 2017, the number of follow-up sessions was increased from 3 to 6 in response to participant feedback. Fidelity was assessed using a checklist of mandatory, flexible and prohibited elements.

Data sources

Adolescent- and parent-completed measures, collected online using research electronic data capture. Therapist reports. Routinely collected data from local systems and from NHS Digital. Qualitative interviews with adolescents, parents and therapists.

Measures

Primary outcome

Disability measured using the 36-item Short Form Health Survey Physical Function subscale (SF-36-PFS) measured 6 months after randomisation. We included outcome data returned in a 5-to-9-month window post randomisation.

Secondary outcomes

(Measured at 3, 6 and 12 months unless specified): Physical function (3 and 12 months); fatigue [Chalder fatigue scale and checklist individual strength (CIS) fatigue scale]; school attendance (self-reported days per week attending school, or whether receiving home tuition); mental health {RCADS; pain [visual analogue scale (VAS)]; Clinical Global Impression Scale; quality of life [EuroQol-5 Dimensions Youth (EQ-5D-Y)]; parent-completed resource use questionnaire; parent-completed work productivity and activity impairment questionnaire general health (WPAI:GH)}.

Demographic data

were collected at recruitment and included: age, sex, postcode, ethnicity, symptoms, months since illness onset, presence of comorbid illnesses.

Harms/adverse events

We prospectively collected the following data: (1) clinician-reported serious deterioration in health, (2) a decrease of ≥ 20 in SF-36-PFS between baseline and 3, 6 or 12 months or scores of 'much' or 'very much' worse on the Clinical Global Impression scale or (3) withdrawal from treatment because of feeling worse. Safety outcomes were reported to the Data Safety Monitoring Committee.

Resource use data

In addition to study documentation and patient/parent questionnaires, we used patient-level data recorded on the Royal United Hospitals Bath NHS Trusts electronic patient record system (Millennium). We obtained secondary care data on outpatient visits, inpatient visits and emergency department attendances from NHS Digital. Costs were valued using 2019/20 prices.

Analysis

Sample size

Our sample size of 314 participants (assuming 15% attrition) gives 90% power at 5% significance to detect a 10-point (0.4 standard deviation) difference for the SF-36-PFS for our primary outcome. The original sample size was powered to detect a difference in the subgroup with mental health problems, but this was revised during the study.

Statistical methods

We used an intention-to-treat analysis in study participants who completed the primary outcome. We used multivariable linear regression analysis adjusting for baseline values of the outcome, age and gender. The treatment effect was estimated as an adjusted difference between sample means. We conducted the following pre-planned sensitivity analyses: we adjusted for variation across participants in the time between randomisation and the 6-month outcome; the primary analysis was repeated with an additional binary covariate distinguishing participants recruited before or after 1 September 2019 (distinguishing those with a 6-month assessment before or during the COVID-19 pandemic); we repeated the analysis in those who completed one or more modules/sessions of their allocated intervention. We conducted a sensitivity analysis for participants with ME/CFS according to the NICE (2021) criteria.

We adapted the regression model used for the primary analysis to the secondary outcome variables. We estimated the effectiveness of FITNET-NHS compared with Activity Management in participant subgroups defined by the presence or absence of anxiety or depression (defined by the RCADS).

Health economic analysis

We used an intention-to-treat approach and multiple imputation by chained equation to minimise bias due to missing data. We combined cost and quality-adjusted life-year (QALY) data to calculate an incremental cost-effectiveness ratioand an incremental net monetary benefit (iNMB) statistic. We performed a subgroup analysis to explore the interaction between comorbid anxiety/depression and cost-effectiveness. Prespecified sensitivity analyses include conducting a complete-case analysis and repeating the primary analysis using the tariff paid by Clinical Commissioning Groups instead of reference costs.

Qualitative methods

We integrated qualitative methods into the pilot and main phase of the trial to explore trial conduct, recruitment and intervention acceptability. We analysed recruitment to trial consultations and conducted in-depth interviews with recruiters, trial therapists and participants. Results were used to improve recruitment and make small changes to the interventions.

Qualitative analysis was ongoing and iterative, commencing soon after data collection. Audio recordings were transcribed, checked and imported into NVivo (QSR International, Warrington, UK). The data were systematically assigned codes and analysed thematically using techniques of constant comparison.

Results

Of 892 referrals between 1 November 2016 and 31 October 2020, 550 were eligible, of which 155 were allocated to FITNET-NHS and 159 to Activity Management. 265 adolescents were included in the primary analysis (127 for FITNET-NHS and 138 for Activity Management). The baseline characteristics were similar between the treatment arms. 147 participants had either comorbid depression or anxiety (145 depression, 34 anxiety and 32 both). The number completing 80% or more of expected modules/sessions was lower for FITNET-NHS participants (58, 38%) compared to Activity Management participants (124, 78%).

Participants in the FITNET-NHS group had a greater improvement in physical function compared to the Activity Management group at 6 months [mean difference 8.2, 95% confidence interval (CI) 2.7 to 13.6]. The sensitivity analyses confirmed the primary analysis. This was true for participants with ME/CFS defined using the NICE (2021) criteria.

At 6 months, those allocated to FITNET-NHS were, on average, attending half a day more of school per week compared to Activity Management, and this difference was maintained at 12 months. They experienced less fatigue (with the CIS fatigue measure) at both 6 and 12 months. There was no strong evidence that either treatment was more effective in those with comorbid depression/anxiety, and similar levels of improvement were noted for pain, the Clinical Global Improvement Score, and fatigue measured using the Chalder Fatigue Scale. Participants continued to improve between 6 and 12 months in both treatment arms, and there was little difference in physical function between the two treatment arms at 12 months.

Fatigue In Teenagers on the interNET in the National Health Service participants had a small gain in QALYs (0.002, 95% CI −0.041 to 0.045) compared to Activity Management but substantially higher mean costs (£1047.51, 95% CI £624.61 to £1470.41). In the primary analysis, from an NHS perspective, at a threshold of £20,000 per QALY, the iNMB was −£1001.74 (95% CI −£2041.31 to £37.83), indicating that FITNET-NHS is unlikely to be cost-effective. The wide Cis show there is considerable uncertainty in this result. The subgroup analysis suggests that FITNET-NHS is more likely to be cost-effective among those with comorbid anxiety and depression at baseline.

In the qualitative interviews, families felt online treatment could fit around everyday life and reduce the increase in symptoms that can accompany travelling to face-to-face appointments. However, some participants still preferred in-person treatment and found it difficult to build a rapport with therapists online. Personalised contact with a therapist was valued in both treatments and remains essential even in online treatment. The reading and writing required on the FITNET-NHS platform was difficult for younger children and those with cognitive symptoms such as brain fog; therefore, adaptations may be needed for these groups. Therapists felt they had to develop a different set of skills to engage patients online.

Conclusions

Despite the fact that adolescents are more likely to have better physical function at 6 months and attend more school (at 6 and 12 months) after receiving FITNET-NHS compared to Activity Management, FITNET-NHS is unlikely to be cost-effective.

This study is consistent with previous RCTs that demonstrated the effectiveness of CBT for children and young people with ME/CFS. It is the first study to attempt to look at cost-effectiveness. The high additional cost of FITNET-NHS and limited substantial sustained impact mean that it may not be a cost-effective use of NHS funds. Alternatively, it is possible that the EQ-5D-Y is not sensitive enough to appropriately reflect the improvements in physical function and school attendance.

Most participants in the FITNET-NHS group did not complete 80% or more of the recommended treatment modules. While our qualitative data suggest that FITNET-NHS was acceptable to most patients, it was considered burdensome by some.

Implications for health care

This study strengthens the evidence that CBT is effective for adolescents with ME/CFS and should be the first line of treatment offered. FITNET-NHS is an intensive treatment approach and is unlikely to be cost-effective. However, the online approach was popular with patients and families.

Recommendations for research

1. Would a shorter intervention with less intensive therapist input increase retention and reduce costs without jeopardising effectiveness?
2. We need a validated health economic measure for children and young people that is sensitive to change.
3. Further research needs to be conducted on the best method to deliver remote treatment. A large implementation study in the Netherlands suggested that many patients (and therapists) prefer a mixture of face-to-face and online treatment.

Trial registration

This trial is registered as ISRCTN18020851.

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This article

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