ELSEVIER

Journal of Psychosomatic Research 56 (2004) 189–197

Journal of Psychosomatic Research

A randomised, controlled, triple-blind trial of the efficacy of homeopathic treatment for chronic fatigue syndrome

Elaine Weatherley-Jones[a,*], Jon P Nicholl[a], Kate J Thomas[a], Gareth J Parry[a], Michael W McKendrick[b], Stephen T Green[b], Philip J Stanley[c], Sean PJ Lynch[d]

[a] *Medical Care Research Unit, School of Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA, UK*
[b] *Communicable Diseases Directorate, Royal Hallamshire Hospital, Sheffield, UK*
[c] *Seacroft Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, UK*
[d] *St. James's University Hospital, University of Leeds, Beckett Street, Leeds, UK*

Received 11 June 2002

Abstract

Objective: There is no management regime for chronic fatigue syndrome (CFS) that has been found to be universally beneficial and no treatment can be considered a "cure" [1]. Patients with CFS may use complementary and alternative medicine (CAM) [1]. Our aim was to evaluate homeopathic treatment in reducing subjective symptoms of CFS. **Method:** Using a triple-blind design (patient and homeopath blind to group assignment and data analyst blind to group until after initial analyses to reduce the possibility of bias due to data analyst), we randomly assigned patients to homeopathic medicine or identical placebo. One hundred and three patients meeting the Oxford criteria for CFS were recruited from two specialist hospital out patient departments. Patients had monthly consultations with a professional homeopath for 6 months. Main outcome measures were scores on the subscales of the Multidimensional Fatigue Inventory (MFI) and proportions of each group attaining clinically significant improvements on each subscale. Secondary outcome measures were the Fatigue Impact Scale (FIS) and the Functional Limitations Profile (FLP). Ninety-two patients completed treatment in the trial (47 homeopathic treatment, 45 placebo). Eighty-six patients returned fully or partially completed posttreatment outcome measures (41 homeopathic treatment group who completed treatment, 2 homeopathic treatment group who did not complete treatment, 38 placebo group who completed treatment, and 5 placebo group who did not complete treatment). **Results:** Seventeen of 103 patients withdrew from treatment or were lost to follow-up. Patients in the homeopathic medicine group showed significantly more improvement on the MFI general fatigue subscale (one of the primary outcome measures) and the FLP physical subscale but not on other subscales. Although group differences were not statistically significant on four out of the five MFI subscales (the primary outcome measures), more people in the homeopathic medicine group showed clinically significant improvement. More people in the homeopathic medicine group showed clinical improvement on all primary outcomes (relative risk = 2.75, $P = .09$). **Conclusions:** There is weak but equivocal evidence that the effects of homeopathic medicine are superior to placebo. Results also suggest that there may be nonspecific benefits from the homeopathic consultation. Further studies are needed to determine whether these differences hold in larger samples.
© 2004 Elsevier Inc. All rights reserved.

Keywords: Chronic fatigue syndrome; Homeopathy; Randomised controlled trial

* Corresponding author. Tel.: +44-114-222-0744; fax: +44-114-222-0749.
E-mail address: e.weatherley-jones@sheffield.ac.uk (E. Weatherley-Jones).

0022-3999/04/$ – see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/S0022-3999(03)00377-5

Introduction

The point prevalence of chronic fatigue syndrome (CFS), according to the Oxford criteria, is estimated to be 0.5% for a population aged 18–45 without comorbid psychological disorders [2]. CFS is characterised by abnormal mental and physical fatigue associated with distress and functional impairment and no evident physical or psychological disorder that sufficiently explains the symptoms. Symptoms are largely subjective with no definitive physical markers or pathognomic signs. The syndrome is diagnosed by exclusion of other explanatory disease.

CFS has only relatively recently been defined by consensus criteria. Diagnostic criteria commonly used in research and clinical practice are the Oxford criteria [3] and the Center for Disease Control (CDC) criteria [4]. Table 1 shows the Oxford and CDC case definitions for CFS.

At present, there is no universally effective treatment for CFS and few evidence-based treatments for CFS [5,6]. There is evidence indicating that cognitive behavioural therapy (CBT), administered by skilled therapists in specialist centres, is more effective for adult outpatients with CFS than routine medical care or relaxation [7–10]. CBT has been shown to be more effective than guided support groups in reducing fatigue severity and self-improved ratings [11]. Graded exercise has modest effects for CFS patients compared to standardised medical care [12,13].

There are potentially high direct and indirect costs of CFS. In 1990, the economic impact of CFS was estimated at $59 million for the Australian population [14]. There are indications that patients seeking treatment for CFS may seek help from complementary and alternative medicines (CAM) [15]. There are no estimates of how many people use CAM specifically for CFS. It is estimated that there are 1.31 million annual visits to homeopaths in England [16].

A report of homeopathic treatment for CFS presented qualitative outcome data suggesting efficacy of treatment [17]. However, no quantitative analyses were presented. In a pilot study, without a control group, a multitherapeutic approach to the treatment of CFS was used, including homeopathic treatment of allergies and constitutional homeopathic treatment [18]. The therapeutic package had a positive impact on physical and psychological parameters. Given the multitherapeutic approach and the absence of an RCT design, it is not clear how much improvement can be attributed to the homeopathic treatment.

Table 1
Oxford and CDC criteria for CFS case definition

Oxford criteria	CDC criteria
Severe disabling fatigue affecting physical and mental functioning that is present for at least 50% of the time and has been present for at least 6 months. The condition is of definite onset and to reach a diagnosis, known physical causes of chronic fatigue should be excluded. The presence of psychosis, bipolar depression, eating disorders, or organic brain disease precludes the diagnosis of CFS.	Severe disabling fatigue with substantial functional impairment, which has been present for at least 6 months. Cognitive or neuropsychiatric symptoms may be present. Four other symptoms are required: impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, multijoint pain, new headaches, unrefreshing sleep, or post exertion malaise.

The current trial was designed to test the efficacy of homeopathic treatment for symptoms of CFS. A triple-blind, placebo-controlled RCT compared patients with CFS treated with homeopathic remedies in the context of a homeopathic consultation with patients treated with placebo in the context of a homeopathic consultation. Two research questions were posed:

Do patients treated with homeopathic remedies show more improvement in subjective symptoms of fatigue compared to patients treated with placebo?
Are changes in either group clinically significant?

The first question concerns the efficacy of homeopathic remedies; the second concerns the effectiveness of homeopathic treatment as a whole.

Methods

Patients

Patients over 18 years old were recruited from two hospital outpatient departments in the UK: The Fatigue Outpatient Clinic at the Seacroft Hospital (part of the Leeds Teaching Hospitals NHS Trust) in Leeds and the Infectious Diseases Outpatient Clinic at the Royal Hallamshire Hospital, Sheffield. Patients are usually referred to these clinics by their general practitioners with a provisional diagnosis of CFS. Consecutive new referrals to these two clinics were assessed for their eligibility for inclusion in the trial.

Patients were eligible for inclusion in the trial if they met the Oxford criteria [3] for CFS case definition. That is, severe disabling fatigue affecting physical and mental functioning, present for at least 6 months, for which physical causes of chronic fatigue have been excluded. The Oxford criteria were used rather than the more recent CDC criteria [4] because most CFS research in the UK up to 1996 (when this trial began) used the Oxford criteria. Using criteria in common with other studies facilitates comparisons, systematic reviews, and meta-analyses. Psychiatric exclusions were primary major depression, bipolar disorders, psychosis, eating disorders, substance abuse/dependence, and somatisation disorders. Symptoms of depression are a common comorbid phenomenon in CFS, so such symptoms in themselves did not preclude eligibility for the trial.

Patients were potentially eligible for the trial if there were no clinically significant abnormalities in full blood count,

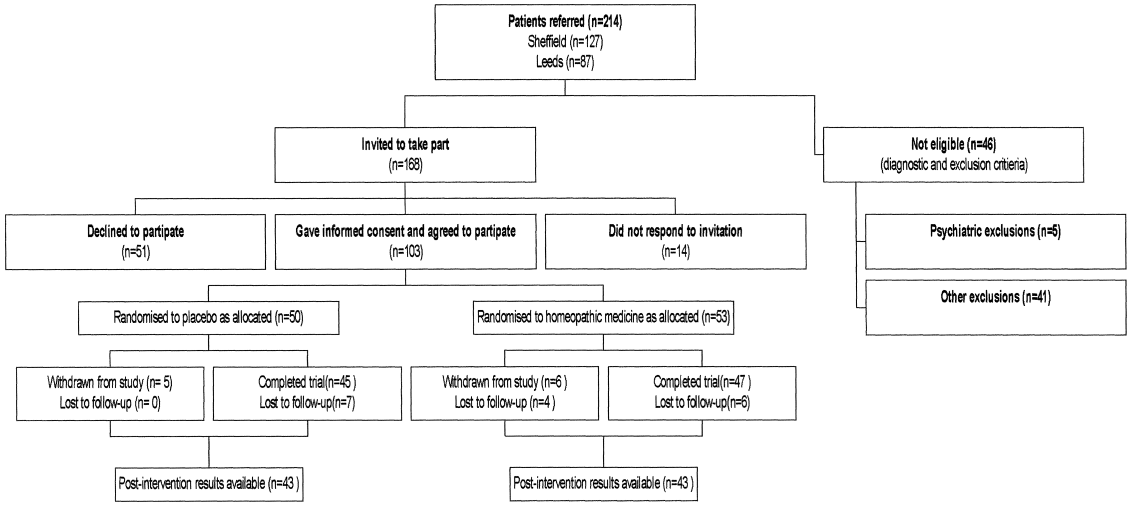


Fig. 1. Participant flow.

liver function tests, thyroid stimulating hormone, acute phase protein, urea and electrolytes, and there was absence of protein and sugar in urine [19]. Patients who reported severe disabling fatigue that substantially impaired functioning (according to published criteria [20]) were eligible for inclusion in the trial. Essentially these criteria require the patient to need simple aids for daily living or to be limited by their fatigue in any one of the following: moderate activity such as pushing a vacuum cleaner, walking 100 yards, and walking up hill.

After physical examination, blood testing, and assessment for functional impairment, patients were invited to an interview in which a subset of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders–IV [21] (SCID [22]) was used to record symptoms of psychopathologies that would preclude a diagnosis of CFS. These interviews were conducted by one of the authors (EWJ) after training in the Academic Department of Psychiatry at St. Thomas' Hospital, London, UK. These interviews were conducted immediately prior to inviting patients to take part in the trial. If patients were ineligible on the basis of the interview, the consultant in charge of the patient's care was informed with the patient's consent. Some patients at the Seacroft Hospital ($n = 5$) had already had an interview in the 6 months before entry to the trial with the consultant liaison psychiatrist (SL) as part of the routine provision as previously described [23,24]. For these people, the SCID interview was unnecessary for screening purposes and the psychiatrist's diagnosis was used to identify ineligible patients, that is, those with excluding psychopathologies.

Patients currently engaged in individual counselling or psychotherapy, in clinical trials for other CFS treatments and pregnant patients were excluded. Patients already receiving homeopathic treatment or cognitive behaviour therapy (CBT) or who had completed a course of homeopathy or CBT for CFS were excluded from the trial. Some patients had tried homeopathy for problems other than CFS.

A consecutive series of 103 patients meeting the eligibility criteria and who gave informed consent were recruited between April 1998 and August 2000.

The Central Sheffield University Hospital's local research ethics committee and the Leeds Health Authority/ St. James's University Hospital NHS Trust Clinical Research (Ethics) Committee approved the trial protocol and procedures before recruitment for the trial started.

Trial design

In designing the trial, criticisms of earlier trials of homeopathic interventions [25] were addressed. Nine homeopaths treated patients in the trial.

Patients were randomised equally between treatment and placebo within homeopaths using a computer-generated sequence concealed from the trialists. Leeds and Sheffield patients were randomised separately and about the same number of patients were randomised to each homeopath.

The intervention

Four homeopaths working at a homeopathic clinic in Leeds treated patients recruited from the Seacroft hospital. In Sheffield, five homeopaths working at a homeopathic clinic treated patients recruited from the Royal Hallamshire Hospital. All the homeopaths were either registered members of the Society of Homeopaths, the Faculty of Homeopathy, or the British Register for Complementary Therapists. Homeopaths were generalists with some experience of treating patients with CFS. Patients had consultations with a homeopath at approximately monthly intervals for 6 months. All consultations took place at two local complementary medicine clinics, one for patients recruited

from Leeds and one for patients recruited from Sheffield. Initial consultations lasted approximately 1 1/2 hours and follow-up consultations for approximately three quarters of an hour. Classical homeopathic prescribing methods are based on an assessment of the individual picture of illness and disease. Consequently, different homeopathic medicines are prescribed for different individuals with the same diagnosis. This essential part of classical homeopathic practice was incorporated into the design: Homeopaths conducted the consultation, case analysis, and decided the prescription according to routine practice. Homeopaths prescribed remedies according to their usual practice, generally a single remedy at each consultation. Homeopaths were instructed to prescribe only those remedies which have been proved [26] (that is, whose remedial effects have been experimentally demonstrated) and for which there is materia medica information [27]. After all patients had completed treatment, prescriptions made during case management were reviewed and common features are described in the Results section.

Blinding

The trial coordinator requested a homeopathic pharmacy to dispense the prescribed remedy directly to the patient. There was no direct contact between the homeopaths or patients and the homeopathic pharmacy in connection with the patients taking part in the trial. The homeopathic pharmacy is in Kent, approximately 300 miles from patients' homes and homeopaths' clinics so there was little chance of accidental meeting of patients or homeopaths with the pharmacist. The homeopathic pharmacist, his deputy, and the statistician who implemented the randomisation were the only people who were aware of the randomisation code. Codes were kept by the statistician who randomised the sequence and by the homeopathic pharmacy under confidential conditions. Only these two copies of the code were made.

Homeopathic medicines and placebo were identical in appearance and taste. Both placebos and homeopathic medicines were prepared in the same way by diluting and succussing (shaking vigorously) a solvent (90% alcohol:10% water) according to the instructions in homeopathic pharmacopoeia. The number of dilution and succussion processes was identical for the same potency (strength) of placebo and homeopathic medicine. The only difference between homeopathic medicines and placebos was that the former contained the indicated source material.

Homeopathic medicines and placebos were identically labelled as "the remedy." Patients were given instructions on how to take the medicine by the prescribing homeopath. Patients were asked after the end of their treatment period about whether they had complied, and to what extent, with the treatment. After collection of posttreatment outcome measures, both homeopath and patient were asked to indicate in which group they thought the patient had been and how confident they were of this. During the trial, some homeopaths were unavailable to continue patients' treatment, and it was necessary for four patients to change their homeopath. This was effected by using the same randomisation method.

Table 2
Comparisons between groups at baseline — all patients randomised to receive homeopathic medicine or placebo

Characteristics	Group: Homeopathic medicine ($n=53$) (mean, S.D.)	Group: Placebo ($n=50$) (mean, S.D.)	P value[a]
Age (years)	38.9 (10.6)	38.8 (11.2)	.95
Gender: female (%)	57	62	.69
Duration of symptoms (years)	4.8 (4.3)	3.7 (2.4)	.13
MFI general fatigue	18.4 (1.7)	18.1 (2.2)	.48
MFI physical fatigue	18.0 (2.2)	17.5 (3.1)	.37
MFI mental fatigue	16.7 (3.7)	16.5 (3.0)	.78
MFI reduced activity	16.1 (3.1)	16.4 (3.8)	.71
MFI reduced motivation	13.0 (3.9)	13.2 (3.7)	.81
FIS cognitive dimension	24.1 (9.0)	24.2 (8.0)	.95
FIS physical dimension	27.3 (6.8)	27.4 (7.1)	.93
FIS social dimension	44.8 (15.5)	44.7 (16.4)	.97
FLP physical dimension	20.4 (14.1)	22.1 (14.9)	.54
FLP psychosocial dimension	35.1 (14.8)	36.3 (15.0)	.69

[a] Based on t test or chi-square test.

Outcomes

Based on a review of recent studies of CFS using the Oxford criteria, the measures used were the Multidimensional Fatigue Inventory (MFI) [28], the Fatigue Impact Scale (FIS) [29], and the Functional Limitations Profile (FLP) [30]. In addition, the GHQ-28 [31] was used to monitor patients for symptoms of severe depression.

Primary outcome measures were changes in scores on the five subscales of the MFI because these reflect the objective symptoms of CFS. Secondary outcome measures were the three dimensions of the FIS and the two dimensions (physical and psychosocial) of the FLP. These reflect the impact of CFS.

MFI subscales are scored by summing four items, each has five possible responses giving a range of possible scores from 4 to 20. In consultation with the project steering committee, we have considered that a change of three points in these scores (i.e., by about 15%) might represent a clinically significant change. This represents a move of at

Table 3
Primary outcome measures: analyses of covariance

MFI dimensions	Mean change — unadjusted scores (post treatment, baseline) (S.D.)		Analysis of covariance	Levene's test for homogeneity of variance
	Homeopathic medicine	Placebo	$F(df_1,df_2)$ (P value)	$F(df_1,df_2)$ (P value)
MFI general fatigue	2.70 (3.93)	1.35 (2.66)	4.38(1,83) (.04)	1.97(1,84) (.17)
MFI physical fatigue	2.13 (4.00)	1.28 (2.74)	1.58(1,83) (.21)	3.44(1,84) (.07)
MFI mental fatigue	2.70 (4.01)	2.05 (2.86)	1.09(1,83) (.30)	1.02(1,84) (.32)
MFI reduced activity	2.72 (4.47)	1.81 (2.82)	2.01(1,83) (.16)	5.51(1,84) (.02)
MFI reduced motivation	1.35 (4.15)	1.65 (3.02)	0.05(1,83) (.82)	0.58(1,84) (.45)

least one category on most items in the subscale or of more than one category on some items. This percentage change is larger than that used in a study of CBT for CFS [8] where a 10% improvement in the Karnofsky Scale was considered to be of clinical significance.

At the point of recruitment to the trial, patients completed the MFI, FIS, FLP, and GHQ-28. Patients were asked to complete these questionnaires at 3 months after the start of treatment and 7 months after the end of randomisation. At recruitment, patients were given the questionnaires, asked to complete them at home, and return in a prepaid envelope (patients had already completed a screening interview at the point of recruitment and were likely to be too fatigued to complete the questionnaire at this point). At 3 months and posttreatment outcome points, questionnaires were posted to patients by the trial coordinator with a prepaid envelope for return. At recruitment, age, gender, and duration of CFS symptoms were recorded. Patients were asked whether they considered that homeopathic treatment would be an effective treatment, whether they belonged to a self-help group, and why they thought they were feeling tired.

Sample size

Using published data on the MFI mental fatigue subscale [28], we calculated that to have an 80% chance of detecting a significant difference (at the 0.05% level) of three or more points between the placebo and treatment groups in the mean change in the mental fatigue subscale of the MFI, 60 patients were needed in each group. Since the mental fatigue subscale has the largest variance, the power of detecting such a difference will be greater than 80% for all the other subscales.

Statistical analyses

The aim of the trial was to assess whether there are any differences between treatment and placebo groups in scores on any of the primary outcome measures and also whether changes were clinically significant (predefined as a change of at least three points on the MFI subscales). Mean posttreatment scores were compared between groups using analysis of covariance with the baseline pretreatment scores as the covariate. Prior to these analyses of covariance, homogeneity of variances was tested using Levene's test. The proportions of each group showing clinical improvement on all primary outcome measures and for each primary outcome measure separately were compared using chi-square (χ^2) statistics. These proportions were used to calculate the relative risk of improvement for each primary outcome measure and for all primary outcome measures together. Analyses of covariance, with homeopath as a fixed-effects factor, were used to explore whether there was any evidence of an interaction between homeopath and treatment effect indicating heterogeneity between homeopaths in this effectiveness.

Analysis was by intention to treat. Randomisation codes were broken only after preliminary analyses were completed.

Table 4
Proportion of each group showing clinically significant improvement (an improvement of at least three points) from baseline to posttreatment

MFI dimensions	Proportion (number/total) improving clinically		χ^2 (Yates' correction) (P value)	Relative risk of improvement with homeopathic medicine	Absolute risk of improvement reduction (CI)
	Homeopathic medicine	Placebo			
MFI general fatigue	0.47 (20/43)	0.28 (12/43)	2.44 (.12)	1.67	0.19 (− .01 to 0.39)
MFI physical fatigue	0.40 (17/43)	0.27 (12/43)	0.83 (.36)	1.42	0.12 (− 0.08 to 0.31)
MFI mental fatigue	0.47 (20/43)	0.37 (16/43)	0.43 (.51)	1.25	0.09 (− 0.11 to 0.30)
MFI reduced activity	0.44 (19/43)	0.35 (15/43)	0.44 (.51)	1.27	0.09 (− 0.11 to 0.30)
MFI reduced motivation	0.37 (16/43)	0.42 (18/43)	0.05 (.83)	0.89	− 0.05 (− 0.25 to 0.16)
Clinically significant (3 points) improvement on all primary outcomes	0.26 (11/43)	0.09 (4/43)	2.91 (.09)	2.75	0.16 (0.01 to 0.32)

Table 5
Analysis of covariance of secondary outcome measures

Measure	Mean change (post treatment, baseline) (S.D.)		
	Homeopathic medicine	Placebo	$F(df_1,df_2)$ (P value)
FIS Cognitive dimension	4.88 (9.3)	4.21 (7.18)	0.3(1,83) (.61)
FIS Physical dimension	4.98 (8.5)	5.30 (6.69)	0.001(1,83) (.98)
FIS Social dimension	7.92 (18.02)	8.20 (14.06)	0.07(1,83) (.79)
FLP Physical dimension	5.11 (8.82)	2.72 (8.40)	4.3(1,83) (.04)
FLP Psychosocial dimension	9.81 (14.19)	6.76 (10.67)	2.2(1,83) (.14)

Management of missing data

Patients who returned posttreatment questionnaires but who had omitted items were included in the analyses, and their missing item data were imputed using simple mean imputation from the mean for that patient of other items on the scale [32]. Patients who failed to return posttreatment questionnaires were excluded from the analyses. Patients were successfully blinded to their group allocation, and therefore we have assumed that whatever the reasons for nonresponse, they are the same for the treatment arm and the placebo arm and that the data are comparable. Therefore, intention to treat analyses was done on actual data plus imputed missing item data, but all unit missing data were excluded from analyses.

Analyses were done using SPSS for Windows [33].

Results

Two hundred and fourteen patients were referred to the trial by hospital clinicians and 103 patients were randomised into the trial. A CONSORT diagram showing how patients entered the trial is shown in Fig. 1. Six patients in the homeopathic treatment arm and five patients in the placebo arm did not complete 6 months of homeopathic treatment. These patients all started treatment and had at least one appointment and treatment duration ranged from 1 week to 5 months. For all patients in the trial, nonattendance at homeopathic appointments was reported to the trial coordinator. All noncompleting patients in the placebo arm and two noncompleting patients in the homeopathic treatment arm returned posttreatment questionnaires. These data were included in analyses. The mean age of placebo arm patients not completing treatment was 34.8 years, duration of symptoms was 4.3 years. For patients in the homeopathic treatment arm who did not complete treatment, mean age was 33.8 years, duration of symptoms was 3.6 years.

Forty-five patients in the placebo arm and 47 patients in the homeopathic arms completed treatment. Seven completing patients in the placebo arm and six completing patients in the homeopathic arm did not return posttreatment questionnaires. Thus, a total of 7 patients in the placebo arm and 10 patients in the homeopathic arm either did not complete treatment or did not return posttreatment questionnaires, or both. For these people in the placebo arm, mean age was 32.5 years, mean duration of symptoms was 2.3 years; in the homeopathic arm, mean age was 37.9 years, mean duration of symptoms was 6.4 years.

At baseline, patient groups were comparable (Table 2). There were no significant differences between groups in demographic variables or baseline outcome measures.

Analyses of covariance for each of the subscales showed statistically significant differences in outcome for only the general fatigue subscale of the MFI (mean improvement for placebo group = 1.35, mean improvement for homeopathic medicine group = 2.70, $P = .04$) (Table 3). For four of these scales, there was homogeneity of variance between groups; but for one, reduced activity, there was significant heterogeneity of variance between treatment and placebo groups, suggesting results should be interpreted with caution.

The difference in the proportion of patients clinically improving was not statistically significant for any primary outcome (Table 4). For all, except MFI-reduced motivation, the direction of difference favours treatment. Eleven patients (26%) in the homeopathic medicine group showed clinical improvements on all subscales of the MFI compared to 4 (9%) of the placebo group [$\chi^2 = 2.91$, P (Yates' correction) = .09].

Of the secondary outcome measures, only the difference between the two groups in score changes for the FLP physical dimension scale was significant (mean change treatment group = 5.1 percentage points; mean change placebo group = 2.7 percentage points; $P = .04$) (Table 5).

Analyses of primary outcomes by homeopath showed no significant heterogeneity of treatment effects.

Checking of double blinding showed that prediction of treatment group was made by neither homeopaths ($\kappa = .07$, $P \approx .60$) nor patients ($\kappa = 0.11$, $P \approx .48$).

Homeopathic prescriptions

Most frequently, single remedies were prescribed at each consultation. Occasionally, more than one remedy was prescribed in cases where remedies were to be taken sequentially. Remedies were changed throughout case management as indicated. LMs (liquid remedies of high potency given in minute doses) were the most common

potencies used, these being least likely to provoke an aggravation. For 18 patients (17%), case management commenced with the prescription of carcinosin as a specific antidote to glandular fever. Antidotes to specific viruses and vaccinations and bowel nosodes (remedies derived from intestinal bacteria) were prescribed where indicated by case history in eight cases (8%). Many prescriptions were of polycrest remedies (polycrest remedies are of application to a wide range of symptoms).

Discussion

1997, the quality of trials in homeopathic medicine was described as methodologically poor in two thirds of those reviewed [34]. The same article encouraged rigorous and systematic research on homeopathy. The trial reported here used systematic and rigorous methods of investigation, analysis, and interpretation that are entirely replicable. The standards recommended in the CONSORT statement are met. Methodological standards exceeded those of some trials of conventional medicine, which although desirable, are not usually met in RCTs; for example, triple blinding (where data analysis is done blind to group membership).

For one of the primary measures, MFI general fatigue, this trial found that the mean improvement in score for those who had homeopathic medicine is significantly greater than for those who received placebo. For the other primary outcome measures (the other subscales of the MFI), differences between treatment and placebo arms in mean improvement from baseline to posttreatment scores were not statistically significant. Differences between treatment and placebo arms in the proportion of people showing clinically significant improvement on each of the five primary outcome measures were not statistically significant.

Of the secondary outcome measures, there are statistically significant differences between groups in improvement on the FLP physical limitations dimension. Other secondary outcome measures do not show statistical significance. Thus, for 2 of the 10 outcome measures, differences between treatment and placebo arms show statistically significant differences in the direction of more improvement in the homeopathic treatment arm.

Multiple testing

Testing of five subscales independently inevitably leads to some exaggeration of the significance of the results. Given the rigorous trial design, these equivocal results are unlikely to be due to methodological bias. It is possible that multiple testing has resulted in two of many outcomes showing statistical significance. However, 1 in 20 results could be expected to be significant by chance; here, 2 out of 10 are statistically significant. Thus, it is likely that these results are weak evidence of a specific treatment effect due to the homeopathic medicine.

The randomisation method effectively means that for each homeopath, a small trial has been done. No heterogeneity between homeopaths was found. However, tests of interaction have low power and the small numbers of patients per homeopath in this trial means that this finding should not be taken as indicating that any effects are consistent over all homeopaths.

Shortcomings in the trial have probably contributed to the problem of interpretation of these results. Outcome measures were carefully selected to reflect the multidimensional diagnostic features of CFS. In retrospect, it may have been appropriate to identify a single outcome as defining clinical improvement before commencing the trial. Sample size was disappointing. Recruitment of patients dramatically decreased in the latter stages of the trial, and the trial was underpowered. We have assumed that missing outcomes were the same for patients in both groups and there are good reasons for this. Nevertheless, it is an assumption and should be borne in mind when interpreting the results. We believe this was a methodologically sound trial, which was underpowered to show a statistically significant difference. A post hoc power calculation shows that for the MFI general fatigue scale,the trial shows only 49% power at $P = .05$. Larger studies are needed to verify the results of the current trial. Results obtained for the proportion of people showing clinically significant improvement on the general fatigue subscale suggest that follow-up data for 112 patients in each arm would be needed for the study to have 80% power.

Historical controls

The trial design did not include a ‘‘no-treatment’’ group. The depth of enquiry in both the screening interview and the outcome measures makes it difficult to envisage how an appropriate comparison group could have been used without a significant ‘‘Hawthorne effect.’’ Comparisons with historical controls, despite their limitations, give some indication of how the results of this trial compare with the natural course of disease. In a study of CBT versus medical care for CFS [8], 60% of patients in a CBT programme showed an improvement of at least 10% on the Karnofksy Scale (a physician-rated scale of disability or functional impairment) at 8 months after starting treatment compared to 20% of medical care patients. A systematic review of the prognosis in CFS and chronic fatigue [35] showed that chronic fatigue and CFS appear to run a chronic course in many sufferers with most patients reporting symptoms and disability at follow-up. A comparison among CBT, support groups, and the natural course of disease [11] showed that at 8 months after baseline, 13% of untreated patients showed some improvement on a fatigue severity scale. A study that controlled for factors such as therapist time and attention comparing CBT with relaxation therapy [8] showed 31% of patients in the relaxation group, and 70% of patients in the CBT group reported being better or much better on a global improvement scale at 6 months after treatment. In the

present trial, 47% of people in the treatment group and 28% of people in the placebo group showed clinically significant improvement (15% change in subscale score) on the general fatigue subscale. It is common in studies of treatments for CFS to find a high rate of placebo responders (for example, [36]). Some aspect(s) of taking part in a study must account for the observed improvements in placebo responders. It is worth considering whether the mechanisms by which improvements occur in people in a placebo arm of a trial could be harnessed therapeutically. Perhaps there is a role for the nonspecific effects of the homeopathic consultation in contributing to improvements for people with CFS.

Conclusions

These results inform two questions: Is there is evidence that the effects of homeopathic medicine are more than placebo and is there evidence of efficacy of homeopathic treatment for patients with CFS? There is weak, probably unpersuasive, evidence that the effects of homeopathic medicine are other than placebo effects. The finding of significant differences between the effects of homeopathic remedies and placebo is consistent with a recent meta-analysis of placebo-controlled clinical trials in homeopathy [34] in which the authors concluded that their results were incompatible with the hypothesis that clinical effects of homeopathy are completely due to placebo.

Information about the natural course of CFS and the benefits of CBT from historical comparisons gives a context for the interpretation of the results of this trial. On the basis of this trial, we suggest that there may be benefit for CFS patients in the nonspecific effects of a homeopathic consultation. If there is such a nonspecific effect of the consultation, further research designed to describe the mechanisms of this effect and to establish its comparative effectiveness with proven treatments for CFS is potentially of interest to CFS patients and physicians.

CFS is a syndrome in which treatment seldom produces spectacular effects, and patients disaffected with orthodox medicine may pursue treatments in CAM. In the context of other CFS research, the results of this trial suggest that professional homeopathic consultations may for certain patients be a useful addition to clinicians' resources for managing patients with CFS.

Acknowledgments

The research was supported by a grant from the Linbury Trust. The authors would like to thank Mark Pickin, Medical Care Research Unit, for comments on the paper.

The Homeopathic Trials Group: Homeopaths — Gill de Boer, MBChB, MFHom, Maryjoan Foster, RSHom, Susanne Hartley, RSHom, Jane Howarth, BRCPHom, Pat Mayborne RSHom, Georgina Ramsayer RSHom, Clare Relton, RSHom, Pat Strong, MBBS, MFHom, Angela Zajac, BSc, RSHom, BRCPHom; Homeopathic pharmacists — John Morgan, RSHom, Roger Haddon, RSHom.

References

[1] A Report of the CFS/ME Working Group. Report to the chief medical officer of an independent working group: Department of Health, 2002.
[2] Wessely S, Chalder T, Hirsch S, Wallace P, Wright D. The prevalence and morbidity of chronic fatigue and chronic fatigue syndrome: a prospective primary care study. Am J Public Health 1997;87(9): 1449–55.
[3] Sharpe M, Archard L, Banatvala J, Borysiewicz LK, Clare AW, David A, Edwards RHT, Hawton KEH, Lambert HP, Lane RJM, McDonald EM, Mowbray JF, Pearson DJ, Peto TEA, Preedy VR, Smith AP, Smith DG, Taylor DJ, Tyrrell DAJ, Wessely S, White PD, Behan PO, Rose FC, Peters TJ, Wallace PG, Warrell DA, Wright DJM. Chronic fatigue syndrome: guidelines for research. J R Soc Med 1991;84:118–21.
[4] Fukuda K, Straus S, Hickie I, Sharpe MC, Dobbins JG, Komaroff A, International Chronic Fatigue Syndrome Study Group. Chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1994;121(12):953–9.
[5] Reid S, Chalder T, Cleare A, Hotopf A, Wessely S. Chronic fatigue syndrome. In: Clinical evidence reproduced in BMJ, vol. 320, 2000. pp. 292–6.
[6] Whiting PM, Bagnall AMP, Sowden AJP, Cornell JEP, Mulrow CDM, Ramirez GD. Interventions for the treatment and management of chronic fatigue syndrome: a systematic review. JAMA 2001;286: 1360–8.
[7] Price JR, Couper J. Cognitive behaviour therapy for adults with chronic fatigue syndrome (Cochrane review). The Cochrane Library Issue 4. Oxford: Update Software, 2000.
[8] Deale A, Chalder T, Marks I, Wessely S. Cognitive behavior therapy for chronic fatigue syndrome: a randomized controlled trial. Am J Psychiatr 1997;154(3):408–14.
[9] Sharpe M, Hawton K, Sumkin S, Surawy C, Hackmann A, Klimes I, Peto T, Warrell D, Seagroatt V. Cognitive behaviour therapy for the chronic fatigue syndrome: a randomised controlled trial. BMJ 1996;312:22–6.
[10] Lloyd AR, Hickie K, Simkin S, Surawy C, Hackmann A, Klimes I, Peto T, Warrell D, Seagroatt V. Immunologic and psychologic therapy for patients with chronic fatigue syndrome: a double-blind placebo controlled trial. Am J Med 1993;94:197–203.
[11] Prins JB, Bleijenberg G, Bazelmans E, Elving LD, de Boo TM, Severens JL, van der Wilt GJ, Spinhoven P, van der Meer JWM. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. Lancet 2001;357:841–7.
[12] Powell P, Bentall RP, Nye FJ, Edwards RHT. Randomised controlled trial of patient education to encourage graded exercise in chronic fatigue syndrome. Br Med J 2001;322:387–90.
[13] Wearden AJ, Morriss RK, Mullis R, Strickland PL, Pearson DJ, Appleby L, Campbell IT, Morris JA. Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. Br J Psychiatry 1998;172: 485–90.
[14] Lloyd AR, Pender H. The economic impact of chronic fatigue syndrome. Med J Aust 1992;157(9):599–601.
[15] Campion PD, Lynch SPJ, Blenkiron P. Chronic fatigue syndrome: a UK primary care perspective. Prim Care Psychiatry 1999;5(1):31–6.
[16] Thomas KJ, Nicholl JP, Coleman P. Use and expenditure on complementary medicine in England: a population based study. Complement Ther Med 2001;9:2–11.
[17] Awdry R. Homœopathy and chronic fatigue — the search for proof. Int J Altern Complement Med 1996;14(2):19–22.

[18] Gibson SLM, Gibson RG. A multidimensional treatment plan for chronic fatigue syndrome. J Nutr Environ Med 1999;9:47–54.
[19] Chronic fatigue syndrome: report of a joint working group of the Royal College of Physicians, Psychiatrists and General Practitioners. Royal College of Physicians, 1996.
[20] Euba R, Chalder T, Deale A, Wessely S. A comparison of the characteristics of chronic fatigue syndrome in primary and tertiary care. Br J Psychiatry 1996;168:121–6.
[21] American Psychiatric Association S. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association, 1994.
[22] First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for DSM-IV patient edition version 2.0. Feb 1996 (revised April 1997).
[23] Blenkiron P, Edwards R, Lynch S. Associations between perfectionism, mood and fatigue in chronic fatigue syndrome: a pilot study. J Nerv Ment Dis 1999;187(9):566–70.
[24] Edwards R, Suresh R, Clarkson P, Lynch S, Stanley P. Illness perceptions and mood in chronic fatigue syndrome. J Psychosom Res 2001; 50(2):65–8.
[25] Morrison B, Lilford RJ, Ernst E. Methodological rigour and results of clinical trials of homeopathic remedies. Perfusion 2000;13:132–8.
[26] Hahnemann SC. Organon of Medicine 6th. London: Victor Gollancz, 1983 (German edition).
[27] Close S. The genius of homeopathy. Lectures and essays on homeopathic philosophy. Philadelphia: Boericke and Tafel, 1924.
[28] Smets EMA, Garrson B, Bonke B, de Haes JCJM. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995;39:315–25.
[29] Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. Clin Infect Dis 1994;18(Suppl 1):S79–83.
[30] Patrick DL, Peach H. Disablement in the community Oxford: OUP questionnaire. In: Johnston M, Wright S, Weinman J. Measures in Health Psychology: Illness, Symptoms, Disability and Recovery. NFER-Nelson, 1995.
[31] Goldberg DP, Hiller VF. A scaled version of the general health questionnaire. Psychol Med 1979;9:139–45.
[32] Machin D, Fayers PM. Quality of life: assessment, analysis and interpretation. Chichester: Wiley, 2000.
[33] SPSS for Windows release 9.0.0. [computer software package].
[34] Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges LV, Jonas WB. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. Lancet 1997;350: 834–43.
[35] Joyce J, Hotopf M, Wessely S. The prognosis of chronic fatigue and chronic fatigue syndrome: a systematic review. QJM 1997;90(3): 223–33.
[36] Lloyd AR, Hickie I, Brockman A, Hickie C, Wilson A, Dwyer J, Wakefield D. Immunologic and psychologic therapy for patients with chronic fatigue syndrome: a double-blind, placebo-controlled trial. Am J Med 1993;94:197–203.