

A placebo-controlled, double-blind, randomized controlled trial of a natural killer cell stimulant (BioBran MGN-3) in chronic fatigue syndrome

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Received 27 November 2005 and in revised form 8 April 2006

Summary

Background: Previous research has suggested that natural killer (NK) cell activity may be reduced in patients with chronic fatigue syndrome (CFS).

Aim: To evaluate the effectiveness of a putative NK cell stimulant, BioBran MGN-3, in reducing fatigue in CFS patients.

Design: Randomized, double-blind, placebo-controlled trial.

Methods: We recruited 71 patients with CFS (according to the Centers for Disease Control 1994 criteria) attending an out-patient specialist CFS service. Participants were given oral BioBran MGN-3 for 8 weeks (2 g three times per day) or placebo equivalent. The primary outcome measure was the Chalder physical fatigue score.

Self-reported fatigue measures, self-assessment of improvement, change in key symptoms, quality of life, anxiety and depression measures were also included.

Results: Data were complete in 64/71 patients. Both groups showed marked improvement over the study duration, but without significant differences. Mean improvement in the Chalder fatigue score (physical scale) was 0.3 (95%CI -2.6 to 3.2) lower in the BioBran group.

Discussion: The findings do not support a specific therapeutic effect for BioBran in CFS. The improvement showed by both groups over time highlights the importance of placebo controls when evaluating interventions in CFS.

Introduction

Chronic fatigue syndrome (CFS) is a medically unexplained syndrome in which severe physical and mental fatigue is often accompanied by musculoskeletal pain and other symptoms. Community-based studies have reported prevalences of CFS ranging from 0.007% to 2.8%, depending on the diagnostic criteria used.¹ While systematic reviews suggest that cognitive behavioural therapy and graded exercise have some clinical benefits,¹ no single intervention

(or combination of interventions) has been proven to prevent long-term disability in all patients. The aetiology of CFS is unknown. However, some studies have suggested an association between CFS and decreased natural killer cell activity.^{2,3} Many patients report symptoms that might suggest an ongoing immune response, such as sore throat or tender lymph nodes.⁴

We tested a novel approach to treating the condition using BioBranTM MGN-3 (hereafter referred

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to as BioBran). The active ingredient of BioBran is arabinoxylane. Previous research has suggested that the product may enhance natural killer (NK) cell activity.⁵ In 2001, the results of an uncontrolled observational study of BioBran in CFS patients suggested that it might improve symptoms in CFS.⁶ The aim of this study was to test whether BioBran was effective in improving fatigue in CFS patients.

Methods

This study was a double-blind, randomized, placebo-controlled trial with a total duration per participant of 10 weeks (2 weeks pre-randomization assessment, 8 weeks treatment and follow-up). The study was approved by East Dorset Local Research Ethics Committee (Application number 810/02/B). Written informed consent was obtained from all patients prior to enrolment. We obtained a clinical trial exemption certificate from the Medicines and Healthcare products Regulatory Agency (MHRA) (2002).

Participants

All patients enrolled between March 2003 and March 2004, and follow-up was completed by May 2004. Participants were recruited from out-patients attending a specialist CFS rehabilitation service that serves a single English county: the Dorset CFS clinic at Wareham Community Hospital. We included male and female patients with a diagnosis of CFS according to the Centers for Disease Control 1994 criteria.⁷ Other inclusion criteria were an illness duration of between 6 and 60 months, age >18 years and two or more of the following symptoms suggestive of immune activation: tender lymph nodes, sore throat or poor temperature control. Patients were excluded if they were taking immunomodulatory medication, had serious illnesses other than CFS, were unable to attend for out-patient appointments, or were pregnant or breast-feeding.

We identified potential participants by database searching of existing CFS service patients and by screening all new patients referred to the clinic for eligibility.

Interventions

BioBran is defined by the Medicines and Healthcare products Regulatory Agency (MHRA) as a food supplement. Its active ingredient is arabinoxylane, a hemi-cellulose compound that is released from rice bran when it is incubated with an enzyme obtained from *Lentius edodes mycelia* (Shitake mushrooms). In this study, we used 2000 mg sachets of BioBran, each containing 1000 mg of the active ingredient

and 1000 mg excipient (500 mg microcrystalline cellulose, 260 mg corn starch, 200 mg dextrin and 40 mg tricalcium phosphate). This preparation is identical to that sold over the counter by the manufacturer in both the UK and USA. The product received its Japan Health Food Authorization (JHFA) Mark from the Japan Health Food and Nutrition Food Association in 1999.

Trial procedure (design, randomization and blinding)

The trial was double-blind, randomized and placebo-controlled. Patient flow is shown in Figure 1. Following the measurement of baseline parameters in the 2 weeks prior to treatment (weeks -2 and 0), patients were randomly allocated in equal proportions to receive oral BioBran or placebo. To maintain balance over time, randomization was blocked. Randomization and allocation to study group was based on study number. Patients were enrolled by blinded research personnel, who assigned the lowest study number available to each new participant. The manufacturer provided a computer-generated random number list that linked the study number with numbered treatment packs containing either BioBran or placebo. This list was held by an independent organization (Dorset Research and Development Support Unit).

Study packs contained sachets of BioBran or placebo, and were identical in every way other than the study number marked on the outside. The contents of the placebo sachets were indistinguishable in taste and appearance from the BioBran sachets. The study team evaluated both placebo and BioBran blind to confirm equivalence. Patients commenced treatment immediately after randomization (week 0). All patients were asked to take a dose of 2 g three times per day dissolved in water or milk for eight weeks, (the dose recommended by the manufacturer as being clinically effective). Patients were followed up 4 weeks after treatment commenced (week 4) and at the end of treatment (week 8). Patients who dropped out before completing treatment were asked to complete all outcome measures on exiting the trial. In addition to researchers and participants, the database manager and statistician remained blinded until the analysis was completed.

All patients attending the Dorset CFS/ME Service are advised to maintain a natural healthy diet with an adequate intake of fruit and vegetables. No additional instructions on diet were given to participants in this study, and food intake was not monitored.

NK cell activity was not measured directly by laboratory testing, as this was felt to be a costly

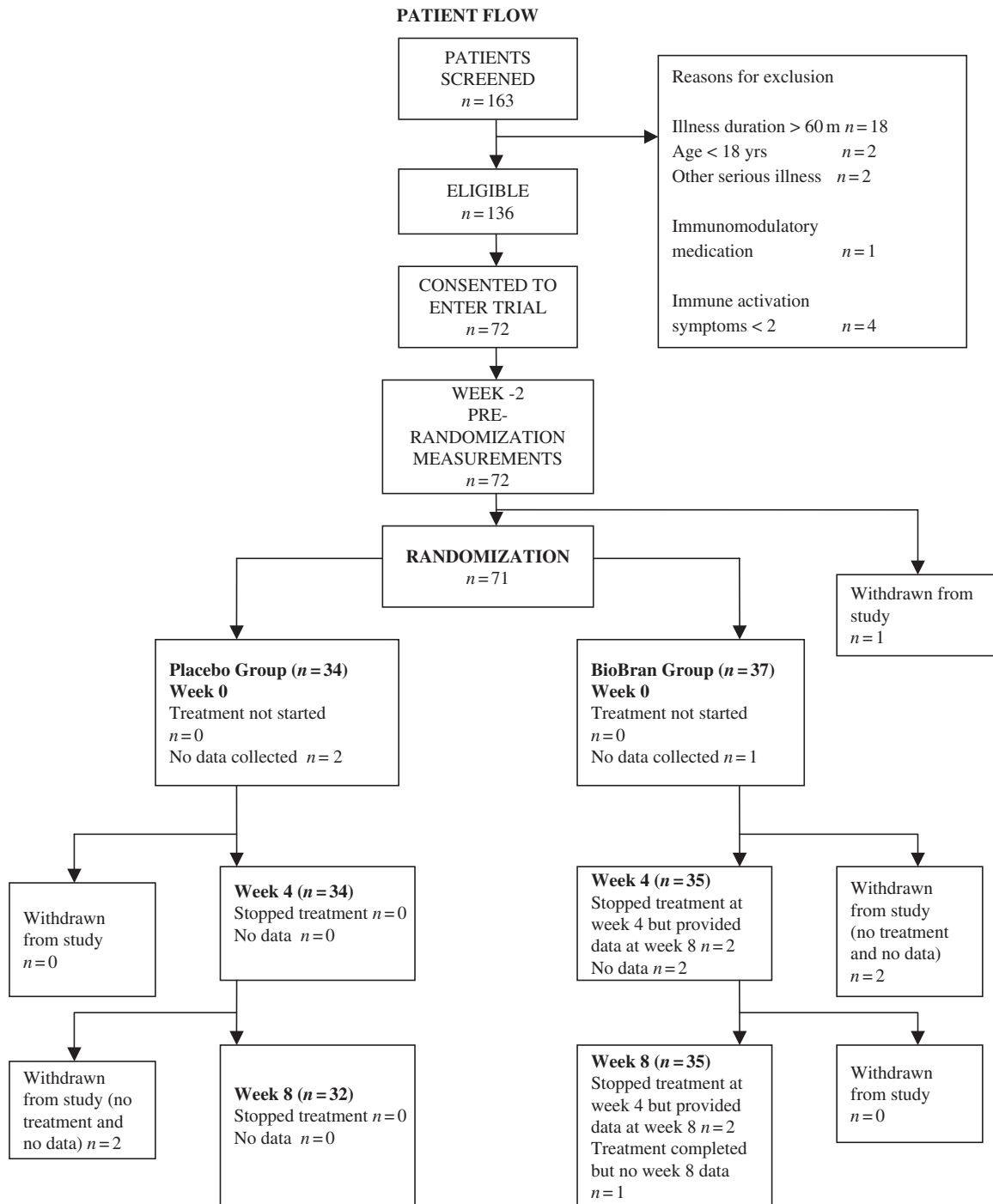


Figure 1. Patient flow.

addition to this trial that would not directly contribute to the main research objective of ascertaining whether BioBran was effective in improving the symptoms of CFS.

Administration of outcome measures

The written instructions at the start of each self-report questionnaire instructed participants to

report on the current impact of their condition. Participants were allowed to complete the questionnaires in private in order to reduce the influence of researcher expectations on the answers given.

Primary outcome measure

Our primary outcome measure was the physical fatigue subscale of the Chalder Fatigue Scale,⁸

a validated self-report questionnaire recommended for use by the Centers for Disease Control 2003 guidelines on CFS Research.⁹ We used the 11-item Chalder Scale with seven items for physical fatigue (maximum score 21) and four items for mental fatigue (maximum score 12). A bimodal score was also calculated from all 11 questions (maximum score 11). The primary end-point of the study was the physical fatigue score at week 8 (end of treatment).

Secondary outcome measures

The mental fatigue subscale and the bimodal fatigue score of the Chalder Fatigue Scale were used as secondary outcome measures. To detect overall changes in condition, we asked participants to complete the Patient Global Impression of Change (PGIC) questionnaire, in which they rated change in their condition on a seven point scale ranging from 'very much better' to 'very much worse'. This measure has been used in a number of randomized trials on CFS.^{10,11} To detect changes individual to each patient, we used the Measure Yourself Medical Outcomes Profile 2 (MYMOP 2) questionnaire.¹² We measured change in quality of life using the WHOQOL-BREF questionnaire,¹³ and change in psychological well-being using the Hospital Anxiety and Depression Scale (HADS).¹⁴ All these measures are validated, and the HADS Scale has been widely used in CFS research.

Sample size

As this is the first blinded and randomized placebo-controlled clinical trial to evaluate the use of BioBran in patients with CFS, sample size was based upon previous research that evaluated other food supplements for CFS.¹⁵ With a total sample size of 71 participants, the study has 80% power to detect effect sizes of 0.68 SD at the 5% significance level and 90% power to detect effect sizes of 0.78 SD.

Statistical analysis

All analyses were on an intention-to-treat basis, using the Statistical Package for Social Sciences (SPSS 11.5), a 5% significance level and two-tailed tests. Follow-up data were collected from patients who discontinued treatment wherever possible. As there were statistically significant improvements in the Chalder Fatigue Scale between pre-randomization measures (week -2) and baseline (week 0), analysis of outcomes focussed on change between measures at baseline and 8 weeks. Independent-samples t-tests on change between

baseline and 8 weeks were performed for all variables satisfying parametric assumptions. If the data had not satisfied parametric assumptions, the Mann-Whitney U test would have been used instead, but proved unnecessary. We also repeated the analysis using analysis of covariance to adjust for baseline values. These results are not reported, but were essentially the same. The percentage of participants defined as improved by the Patient Global Impression of Change (i.e. those participants reporting that they were either 'much better' or 'very much better') was compared using Fisher's exact test.

Results

Participant flow

A total of 72 patients consented to enter the trial. Figure 1 illustrates participant flow. One patient dropped out prior to randomization. Of the 71 randomized patients, 65 completed treatment and six (four in the BioBran group, two in the placebo group) stopped before the end of the trial. Of these six patients, four stopped because of possible side-effects, one because of elective surgery and one was lost to study. Exit data (8 weeks after treatment began) were collected for two of these six patients, and are included in the analyses.

Baseline characteristics

Table 1 shows the baseline characteristics for the placebo and treatment groups taken at baseline. The groups did not differ significantly with respect to any baseline variable.

Outcome

There were statistically significant improvements in the Chalder Fatigue Scale between pre-randomization measures and baseline: mean improvement (95%CI) 1.2 (0.2, 2.1) for physical fatigue, 0.8 (0.1, 1.4) for mental fatigue and 1.2 (0.4, 2.0) for total fatigue. Therefore, our analysis of outcomes focussed on change between measures at baseline and 8 weeks.

Mean Chalder physical fatigue scores over the course of the study can be seen in Figure 2. The results for change in outcome measurements between baseline and end of treatment (week 8) are shown in Table 2.

We found no significant differences between groups for the primary outcome measure, nor for any of the secondary outcome measures, except for the social well-being subscale of the

Table 1 Baseline characteristics of study population (n=71)

Group	Placebo (n=34)	BioBran (n=37)	p
Female	23 (68%)	28 (76%)	0.63 ^a
Mean (SD) age (years)	43 (12)	42 (15)	0.75 ^b
Sore throat	26 (77%)	30 (81%)	0.85 ^a
Tender lymph nodes	30 (88%)	31 (84%)	0.84 ^a
Poor temperature control	29 (85%)	34 (92%)	0.62 ^a
<i>Chalder fatigue scores</i>			
Mean (SD) physical fatigue (Likert score)	14.6 (4.4)	15.5 (4.6)	0.43 ^b
Mean (SD) mental fatigue (Likert score)	7.6 (3.2)	7.8 (2.5)	0.76 ^b
Mean (SD) total fatigue (bimodal score)	7.7 (3.9)	8.5 (3.5)	0.35 ^b
<i>HAD scores</i>			
Mean (SD) anxiety	10.2 (4.4)	10.9 (4.6)	0.53 ^b
Mean (SD) depression	9.7 (5.2)	8.9 (3.6)	0.48 ^b
<i>WHOQOL-BREF scores</i>			
Mean (SD) physical wellbeing	35.6 (15.6)	37.7 (16.1)	0.59 ^b
Mean (SD) psychological well-being	45.2 (18.1)	48.4 (14.3)	0.42 ^b
Mean (SD) social well-being	53.9 (22.2)	60.3 (21.0)	0.23 ^b
Mean (SD) environmental well-being	61.4 (18.1)	68.0 (14.2)	0.10 ^b

Values are numbers (percentage) unless stated otherwise. ^a χ^2 test for association, with Yates' correction. ^bIndependent-samples t-test.

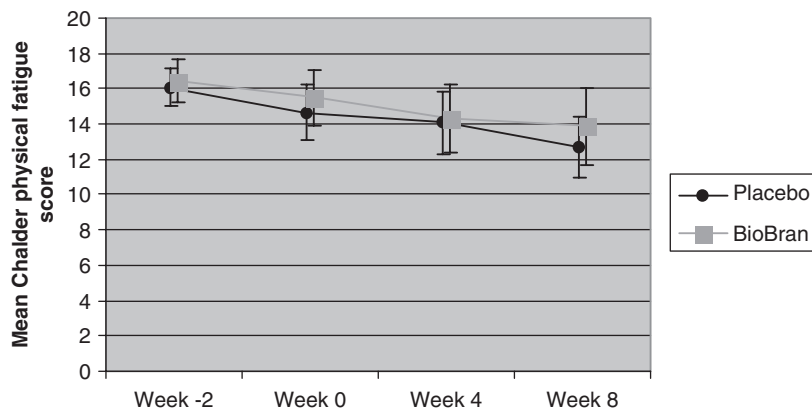


Figure 2. Mean physical fatigue scores during trial. Bars represent 95% CIs. High scores indicate worse fatigue.

WHOQOL-BREF, where improvement was significantly better in the placebo group. While there was a small, non-significant difference between groups for the primary outcome measure, the placebo group improved more than the BioBran treatment group. For the Patient Global Impression of Change, four of the BioBran group and four of the placebo group felt that they were ‘much better’. No patient felt that they were ‘very much better’.

When asked to guess their treatment at the end of the study, 68% of participants believed that they had been taking the placebo.

No serious adverse effects were reported. Three participants dropped out in the active treatment group because of minor side-effects (mild nausea,

exacerbation of CFS symptoms and exacerbation of irritable bowel symptoms, respectively). One participant dropped out in the placebo group because of exacerbated fatigue and anxiety.

Discussion

We investigated whether BioBran could improve the symptoms of CFS among patients with symptoms suggesting immune involvement, using a double-blind, placebo-controlled RCT design. We believe that the use of this methodology has minimized the possibility of bias in the results. Our findings do not support the use of BioBran

Table 2 Independent-samples t-tests comparing mean change in scores between baseline and week 8 for placebo and BioBran groups

Outcome measure	Mean (SD) change in scores (week 8–week 0)		Difference in mean change (Placebo–BioBran)	95%CI	<i>p</i> ^a
	Placebo (<i>n</i> = 30)	BioBran (<i>n</i> = 34)			
<i>Chalder fatigue scores</i> ^b					
Physical fatigue	–1.8 (5.7)	–1.5 (5.9)	–0.3	–3.2 to 2.6	0.84
Mental fatigue	–1.4 (3.0)	–0.5 (2.3)	–0.9	–2.3 to 0.4	0.16
Total fatigue (bimodal scoring)	–1.4 (3.8)	–1.1 (4.4)	–0.2	–2.3 to 1.8	0.81
<i>HAD scores</i> ^b					
Anxiety	–0.1 (2.2)	–1.0 (2.4)	0.8	–0.3 to 2.0	0.15
Depression	–1.0 (1.8)	–0.4 (2.9)	–0.6	–1.8 to 0.7	0.35
<i>WHOQOL-BREF scores</i> ^c					
Physical well-being	5.0 (15.2)	3.1 (14.6)	1.9	–5.7 to 9.4	0.62
Psychological well-being	–1.0 (12.9)	1.4 (9.8)	–2.4	–8.2 to 3.4	0.41
Social well-being	6.9 (14.0)	–1.3 (12.7)	8.2	1.5 to 14.9	0.02
Environmental well-being	1.6 (10.7)	–0.6 (10.0)	2.2	–3.1 to 7.5	0.41
<i>MYMOP 2</i> ^b					
Primary symptom	–0.5 (1.4)	–0.3 (1.6)	–0.2	–0.9 to 0.6	0.65
Activity	–0.6 (1.4)	–0.4 (1.7)	–0.2	–0.9 to 0.6	0.69
Overall well-being	–0.5 (1.2)	–0.1 (1.6)	–0.3	–1.1 to 0.4	0.37

^aTwo-tailed independent-samples t-test, equal variances assumed. ^bNegative change scores indicate improvement. ^cPositive change scores indicate improvement.

as a symptomatic treatment for CFS. Nevertheless, the study was small and interpretation of the results should consider the possibility of a type II error (false negative). The upper confidence interval for between group comparisons on the Chalder Fatigue Scale suggests that differences of magnitude of more than 2.6 in favour of BioBran are unlikely. To conduct a study with 90% power to detect a difference of this magnitude would require a sample size of at least 200 participants. As most of the differences between the two groups were in favour of placebo, the need for further trials appears doubtful.

The rationale for this trial was based on previous published studies in CFS patients that appeared to demonstrate reduced levels of NK cell activity, and speculation that there might be an underlying immunological cause for CFS.^{2,3,16–19} In previous studies, BioBran had stimulated NK activity *in vitro*⁵ and *in vivo*,²⁰ and so we hypothesized that this product might prove therapeutic in some CFS patients.

We did not measure NK cell activity directly, but instead focused on measuring symptomatic improvement in participants. While laboratory assessment of NK cells might have provided interesting data, this costly addition to this trial would not have contributed directly to the main

research objective of ascertaining whether BioBran was effective in treating CFS symptoms.

The difficulties inherent in investigating NK cell activity in this condition were highlighted in 2003 by a systematic review of immunological studies in CFS. Lyall *et al.* found an inverse association between study quality and results indicating low levels of natural killer cells, suggesting that the association may be related to study methodology.²¹ If this is the case, a natural killer stimulant may not be a relevant intervention for CFS patients, although this was not apparent when the study was designed.

A randomized controlled trial of 16 participants in 2003 (Diaz-Mitoma *et al.*) found some correlation between improvement in CFS symptoms and increased NK cell activity in participants allocated to treatment with the immuno-pharmacological agent isoprinosine.²² Nevertheless, the authors noted, there are frequent inconsistencies in observed immune function changes among CFS patients and the only outcome that is likely to matter to patients is how they feel.²² While there may be an association between increased NK cell activity and improved CFS symptoms, no underlying mechanism for this has yet been defined, and the relationship remains unclear.

In this study, we used the dosage of BioBran recommended by the manufacturer for

'over the counter' sale of this product. No Phase II study has yet been carried out to evaluate dosage effects for this product in CFS patients and thus we do not know whether a higher dosage might have produced different results. Further research could clarify this issue.

This study evaluated the effect of BioBran on a subgroup of CFS patients whose symptoms suggested possible immune activation. It is possible that other subgroups of CFS patients (such as those without sore throat or tender lymph nodes) might have responded differently. The choice of the subgroup used in this trial was based on the findings of an observational study of 10 CFS patients by Kenyon *et al.*, in which all those who improved after taking BioBran had symptoms prior to treatment suggestive of a 'viral aetiology'.⁶

All the patients in this study were attending a specialist CFS service that provides support and advice on CFS management. This advice is offered to increasing numbers of patients in Britain as standard clinical care. It would therefore have been unethical for the service to withhold this advice from patients participating in this study.

Both groups improved markedly not only during treatment but also during the pre-treatment observation period. We do not know whether the improvement was due to natural illness trajectory, CFS management advice or non-specific treatment effects, such as the therapeutic benefit of contact with trial staff. During the treatment period, a placebo effect may also have been a factor. Both groups improved in social well-being as measured by the WHOQOL-BREF, with the placebo group improving most. This may relate to the positive effect of contact with trial staff and perceptions of support.

The marked improvement in the primary outcome measure for both groups highlights the importance of using a control group in any study evaluating an intervention in CFS. Without this, the data might have appeared to support the efficacy of this intervention.

All outcome measures in this study were based on self-report questionnaires. It is not possible to ascertain whether patients reported their real feelings or what they felt they should feel. The research staff ensured that the participants were able to complete the questionnaires in privacy, but although this may have reduced the effect of investigator expectations, it is unlikely to have eliminated it. However, randomization and double-blinding procedures should balance the effects of this potential bias between the two groups.

This trial was investigator-initiated. The manufacturers of BioBran funded the trial, but placed no

restrictions on the design of the trial or on the publication of results. We encourage all manufacturers, clinicians and patients to appraise complementary therapies with the same rigor that is applied to conventional medical therapies.

Acknowledgements

We would like to thank the patients of the Dorset CFS/ME Service for their participation in this study. The trial was funded by Daiwa Pharmaceutical Company. Dr George Lewith's post is funded by a grant from the Rufford Maurice Laing Foundation.

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