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A preliminary prospective study of nutritional, psychological and combined therapies for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in a private care setting

Megan Anne Arroll, Alex Howard

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Department of Research, The Optimum Health Clinic, London, UK

Correspondence to
Dr Megan Arroll; drarroll@theoptimumhealthclinic.com

ABSTRACT

Background: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a condition characterised by severe and persistent fatigue, neurological disturbances, autonomic and endocrine dysfunctions and sleep difficulties that have a pronounced and significant impact on individuals' lives. Current National Institute for Health and Clinical Excellence guidelines within the UK suggest that this condition should be treated with cognitive behavioural therapy and/or graded exercise therapy, where appropriate. There is currently a lack of an evidence base concerning alternative techniques that may be beneficial to those with ME/CFS.

Objectives: This study aimed to investigate whether three modalities of psychology, nutrition and combined treatment influenced symptom report measures in those with ME/CFS over a 3-month time period and whether there were significant differences in these changes between groups.

Design and setting: This is a preliminary prospective study with one follow-up point conducted at a private secondary healthcare facility in London, UK.

Participants: 138 individuals (110 females, 79.7%; 42 participants in psychology, 44 in nutrition and 52 in combined) participated at baseline and 72 participants completed the battery of measures at follow-up (52.17% response rate; 14, 27 and 31 participants in each group, respectively).

Outcome measures: Self-reported measures of ME/CFS symptoms, functional ability, multidimensional fatigue and perceived control.

Results: Baseline comparisons showed those in the combined group had higher levels of fatigue. At follow-up, all groups saw improvements in fatigue, functional ability and symptomatology; those within the psychology group also experienced a shift in perceived control over time.

Conclusions: This study provides early evidence that psychological, nutritional and combined techniques for the treatment of ME/CFS may influence symptomatology,

ARTICLE SUMMARY

Article focus

- This preliminary prospective study investigated three (psychological, nutritional and combined) tailored interventions for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) over time.
- Differences between the reported changes over time between groups were also assessed.

Key messages

- Psychological, nutritional and combined approaches for the management of ME/CFS influenced symptomatology over time in some individuals with this disorder.
- Self-reported functional ability (physical and social) are influenced following tailored interventions lasting 3 months.
- This study provides preliminary evidence that tailored psychological, nutritional and combined interventions may influence self-reported symptomatology in some people with ME/CFS; however, due to the study's methodological limitations, it is important that these findings are investigated further in high-quality randomised controlled studies.

Strengths and limitations of this study

- The findings here are an initial step to fill the gap in the extant literature regarding the utility of tailored and multidisciplinary (psychological, nutritional and combined) treatments for ME/CFS.
- There is bias in this study as the participants were self-selected in the sense that they chose to attend the clinic and which treatment option they preferred (with advice), that is, the study was not randomised.
- There were low retention rates in this study which may constitute a bias in that those who remained in the study may have experienced benefits and those who experienced little or no benefits may have dropped out.

fatigue, function and perceived control. However, these results must be viewed with caution as the allocation to groups was not randomised, there was no control group and the study suffered from high drop-out rates.

INTRODUCTION

Myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS) is a condition characterised by a prolonged and debilitating fatigue, although the exact cause of this disorder is still under debate. Owing to the lack of a definitive biological marker, diagnosis is made on the basis of the exclusion of other explanatory conditions. The most widely used case definition by the Centers for Disease Control (CDC)[1] states that there must be at least 6 months severe fatigue of a new and definite onset, not the result of an ongoing exertion, not alleviated by rest and resulting in reduced levels of physical activity. The CDC definition also sets out a series of minor complaints that must accompany the fatigue (cognitive impairment, sore throat, tender cervical or axillary lymph nodes, muscle pain, multijoint pain, headaches of a new type, pattern or severity at onset, unrefreshing sleep and postexertion malaise), with individuals needing to have the occurrence of four or more symptoms to be diagnosed with ME/CFS. Estimates of the prevalence of ME/CFS have been made as low as 3 and as high as 2800/100 000.[2]

The most widely researched strategies for alleviating the symptoms of ME/CFS are the cognitive behaviour therapy (CBT) and graded exercise therapy (GET). Two reviews of studies on CBT[3 4] found that it significantly improved physical functioning in adult outpatients as compared with medical management, counselling, guided support, education and support or relaxation. Regarding GET, a systematic review illustrated that this form of therapy was potentially beneficial for people with ME/CFS, especially when combined with a patient education programme.[5] However, drop-out rates were higher in the GET groups than control groups suggesting that individuals with ME/CFS are averse to this type of therapy. Recently, a large-scale, longitudinal study investigating the CBT, GET, adaptive pacing therapy (APT) and specialist medical care (SMC) which had very low drop-out rates, found that CBT and GET (when added to SMC) were moderately effective outpatient treatments for this patient group as opposed to APT or SMC alone.[6]

Although CBT and GET studies have shown some promising outcomes, there is no known cure for ME/CFS. Therefore the National Institute for Health and Clinical Excellence (NICE)[7] recommends a number of symptom management strategies and interventions aimed at helping individuals to cope with their condition and reduce physical deconditioning brought about by the illness. Pharmacological interventions are, at times, suggested for patients with poor sleep or pain, for instance, low-dose antidepressants, as these have been shown to be effective.[8–14] However, patient expectations must be realistic as the drugs may help elevate mood and psychological outlook, but not reduce fatigue and other symptomatology associated with ME/CFS.[15] Numerous drugs such as thyroxin, hydrocortisone and antiviral agents are not advised by NICE due to contradictory findings.[16 17]

In terms of function and quality-of-life management, NICE offers general advice concerning sleep management, appropriate rest periods and pacing. Sleep hygiene instruction, together with pharmacological treatment tailored to the individual patient, can be beneficial in combating fatigue.[18] Dietary management may also reduce symptomatology for those with concurrent irritable bowel syndrome,[19] although this is not currently recommended by NICE. Dietary supplementation has been investigated in relation to ME/CFS. Fatty acids,[20] folic acid,[21] vitamin C,[22] co-enzyme Q10,[23] magnesium,[24] multivitamins[25] and minerals[26] have all been shown to reduce symptomatology in ME/CFS patients. However, other studies have shown conflicting findings with regard to nutritional supplementation, therefore it is perhaps wise to treat with supplements on a case-by-case basis.[27 28]

Owing to the lack of clear and definitive treatment strategies, individuals often seek out complementary and alternative medicines (CAM). Although NICE does not recommend the use of CAM they do acknowledge that many people with ME/CFS use such therapies and find them beneficial for symptom management. This view is due to the lack of published evidence for the effectiveness of these treatments. Examples of CAM treatments used by individuals with ME/CFS include religious healing, massage therapy, relaxation, meditation, homoeopathy, acupuncture, naturopathy and herbal therapies;[29 30] patient satisfaction with such approaches as CAM has been high, over 80% in some instances.[29] A recent systematic review of such interventions identified 70 controlled clinical trials (randomised and non-randomised) and found that 86% of these studies illustrated at least one positive effect, with 74% showing a decrease in illness-related symptomatology.[31] Meditative or mindfulness approaches warranted further investigation based on these results as did supplement programmes of magnesium, L-carnitine and *S*-adenosylmethionine. A subsequent review based solely on randomised controlled trials (RCTs) of CAM techniques identified 26 such studies and observed that qigong, massage and tuina (approaches based within the Chinese traditional medicine and based upon relaxation and connection with the body) illustrated positive effects as did supplementation studies utilising nicotinamide adenine dinucleotide and magnesium.[32] However, within both reviews it was noted that the methodological quality of reporting was poor and the sample sizes in these studies were small; hence ability to draw strong conclusions on the efficacy of CAM methods is limited. Porter *et al*[31] did note that individualised treatment protocols which include a range of

tailored strategies are a promising area for further investigation for this complex, multisystem illness.

Objectives

There is still much debate and uncertainty regarding alternative interventions for those with ME/CFS. A recent review of CAM techniques[31] highlight the need for further exploration of individually tailored interventions for the alleviation of the condition's often debilitating and an intrusive symptomatology. This study therefore aims to provide preliminary evidence for the utility of three types of approaches (psychological, nutritional and combined) to the management of ME/CFS over time (baseline and follow-up) offered at a private healthcare centre in the UK.

METHODS

Study design and setting

This preliminary prospective study aimed to investigate whether psychological, nutritional and combined approaches to the treatment of ME/CFS influenced symptom report measures over a 3-month time period and whether there were significant differences in these changes among groups. The research was conducted at a private secondary healthcare facility. All potential patients of the clinic were first asked to complete a comprehensive symptom profile and medical history, including questions relating to triggering factors, psychology subtypes and structural/biological subtypes (this is distinct from the research data collected). Subsequent to this, every individual received a 15 min screening with one of the practitioners (please note, this was neither of the authors of the current study) who recommended the best course of action for his/her needs; ie, the psychology-related intervention, nutritional advice and support or a combination of the two.

All individuals requesting treatment at the private care setting were offered the opportunity to participate in the study. Those who expressed an interest (N=145) were emailed a spreadsheet that contained the questionnaires and asked to complete it at their convenience. Informed consent was obtained prior to the completion of the questionnaires and the study was approved by the University of East London Ethics Committee. Participants were told that they could withdraw from the study at any time and that withdrawal would not affect their care at the clinic. Participants were allowed to ask questions at any point during the study and no deception was used as the participants were informed of the nature of the research programme before they agreed to participate. Subsequently, participants were requested to complete the questionnaire pack on a second occasion, 3 months from the baseline measures.

Psychology

The clinic offers a 3-month intervention which consists of a combination of neuro-linguistic programming (NLP), emotional freedom technique (EFT), life coaching and hypnotherapy/self-hypnosis constructed in a manner specific to the needs of those with ME/CFS. The primary aim of this approach is to reduce the anxiety that is associated with having a debilitating and unpredictable condition, improve emotional well-being and help individuals slowly manage and increase their activity within their own limits (ie, pacing). The programme is offered as a series of group sessions and the peer support is seen as an important component of the intervention, which is solidified via the use of moderated online support forums, narratives of previous clients' experiences and online materials that can be accessed as often as necessary. In addition to, or as an alternative to this course, individuals receive a series of one-to-one sessions and for the most severely affected ME/CFS patients, telephone sessions are arranged and support materials can be accessed in their own homes.

Over the 3-month period of this preliminary study, the participants experienced one of three treatment options. The first option included 13 h of practitioner contact time in a mix of group training in person, group telephone conference calls and one-to-one telephone sessions, the second option was 4 h of one-to-one telephone sessions and the final option was 3 h of in-person sessions. All participants had access to various support materials which included CDs and online resources. The amount of time spent on these was patient-led, but was in the region of a further 6 h. All the practitioners offering this option are qualified in hypnotherapy, NLP, life coaching and EFT and undergo an intensive period of training in the clinic's own integrative approach (please see Howard and Arroll[33] for more details of this approach) and ongoing supervision (individual and group supervision on a biweekly basis) from the department director, who is the only senior practitioner in the team.

Nutrition

Tailored nutritional therapy is achieved via one-to-one consultations with individuals. To begin, a very detailed history is taken based upon the information given in the aforementioned symptom profile. Qualified nutritional therapists (who have been given specialist training regarding ME/CFS from the clinic) then suggest tests consistent with symptomatology, for instance the Adrenal Stress Index Test, comprehensive stool analysis/gastrointestinal function, vitamin and mineral status, etc. Results from these tests are then used to compose an evidence-driven diet and supplement programme. As most cases of ME/CFS are complex involving multiple body systems, this process is often iterative and follow-up consultations are necessary to check progress and make alterations to the protocol. The nutritional therapy programme consists of an initial 1 h evaluation (which includes the tailored advice) and a follow-up approximately every 6 weeks; therefore, during the course of the present study, the participants received a minimum of two 1 h sessions with email support for any queries and

detailed nutritional guidance. All the nutritional therapists are qualified to the diploma level and members of (voluntary) regulatory bodies such as the British Association for Applied Nutrition and Nutritional Therapy and the Complementary and Natural Healthcare Council. Similar to the psychology department, the nutrition department is led by one senior practitioner who supervises the team with individual and group supervisory arrangements.

Combined

Within the combined programme, a multidisciplinary approach is taken with practitioners discussing the patients in case meetings to ensure that the psychological and nutritional aspects complement each other to achieve the best outcome. It should be noted that the interventions in the combined programme are phased-in as it was found that asking individuals to engage in numerous therapeutic activities at the same time resulted in high drop-out rates.

Primary outcome measures

Medical Outcomes Survey Short-Form 36 (SF-36)

This 36-item measure is the short form of the original Medical Outcomes Survey[34] to measure functional impairment and contains eight subsections: (1) physical activity limitations due to health problems; (2) social activity limitations due to physical or emotional problems; (3) usual role activity limitations due to physical health problems; (4) bodily pain; (5) general mental health; (6) role activity limitations due to emotional problems; (7) vitality (energy and fatigue) and (8) general health perceptions.[34] The items are scored so that higher scores indicate a greater functional ability. In terms of the psychometric properties of this measure, reliability estimates for all subscales are good, exceeding the Cronbach's α-coefficient value of 0.70.[35] In terms of validity, the Short-Form (SF-36) correlates amply, $r \geq 0.40$, with the frequency and severity of numerous symptoms and general health conditions.[36 37]

Multidimensional Fatigue Inventory

This 20-item measure contains five fatigue dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity.[38] Items such as 'I tire easily' are rated on a five-point scale (1=yes, that is true; 5=no, that is not true) with lower scores reflecting higher levels of fatigue. The Multidimensional Fatigue Inventory (MFI) has good internal consistency with average Cronbach's α-coefficient equalling 0.84 across the subscales. Convergent validity based on a sample of radiotherapy patients found correlations between the subscales and a visual analogue fatigue scale to be 0.77 for general fatigue, 0.70 for physical fatigue, 0.61 for reduced activity, 0.56 for reduced motivation ($p<0.001$) to 0.23 for mental fatigue ($p<0.01$).[38]

Secondary outcome measures

CDC CFS Symptom Inventory

CDC CFS Symptom Inventory[39] was used to measure specific ME/CFS symptoms and confirm diagnosis. This instrument is based upon the CDC case definition[1] and includes a fatigue item and the eight distinct symptoms are also included in the CDC guidelines with an additional 10 associated symptoms. The format of this self-report measure is a six-point scale of perceived frequency (0=absent, 5=all the time) and severity (0=none, 5=very severe). The psychometric properties of this instrument are good: the Cronbach's α-coefficient=0.88; r=0.74 convergent validity with the Chalder Fatigue Scale;[40] r −0.68 and −0.87 convergent validity with the SF-36 'vitality' and 'bodily pain' subscales, respectively.

Multidimensional Health Locus of Control Scale

Multidimensional Health Locus of Control Scale (MHLCS)[41–43] measures perceived control via three distinct subscales: 'internal', 'chance' and 'powerful others' which has two dimensions, that of 'doctors' and 'other people'. The instrument contains 18 items in total (six items each for the 'internal' and 'chance' scales and three items for both the 'powerful others' scales) and is scored on a 6-point Likert scale from 'strongly agree' to 'strongly disagree'. Internal reliability of the instrument is good with Cronbach's α-coefficients ranging from 0.67 for 'powerful others' to 0.77 for 'internal'. The measure correlates positively and significantly with associated scales from Levenson's[44] locus of control measure upon which the MHLOC was based, which demonstrates a good convergent validity.[41]

STATISTICAL METHODS

The data were initially screened for missing data. Four cases contained substantial amounts of missing data; therefore these were excluded from the analysis (one individual from the nutrition group and three from the combined group). Subsequent analyses were conducted on complete date only. The baseline data were subsequently of the quality for parametric tests, except for the variables CDC CFS swollen lymph nodes and glands, memory problems, abdominal pain and depression. However, the follow-up data suffered from high levels of skew and kurtosis which was not substantially alleviated by data transformation. This violated a key criterion for parametric testing, that of normality of distribution, so non-parametric tests were selected. In addition, as the sample sizes in each individual treatment group were small, the more conservative non-parametric tests were the preferred choice as even though tests such as analysis of variance are generally robust against non-normality, this does not hold true with small sample sizes. One-way analysis of variance tests and Kruskal-Wallis tests (the former for those variables that met the criteria for parametric tests, and the latter that did not) were used to investigate baseline variation and analysis of covariance

tests were used to account for this variation and test for differences among the three groups. Wilcoxon sign-rank tests were employed to look for differences over time (baseline and 3-month follow-up) and if differences were significant, percentage change was calculated. Please note, as this is an exploratory study with only one time-point and no control group, any significant findings do not infer clinical significance, rather statistical significance, and as such exact p values are presented.

RESULTS

Participants

Of the 145 individuals who expressed an interest in the study, 142 time-one questionnaires were returned, equating a 97.9% response rate at baseline (two participants from the psychology group and one from the combined group dropped out at this stage). Therefore, excluding the four cases deleted due to insufficient data, 138 cases were used for the baseline analysis; 42 participants in the psychology group, 44 in the nutrition group and 52 in the combined group. There was no significant association between gender and group (χ^2 (2)=0.179, p=0.915), all groups consisting of approximately one-fifth males (table 1). There was no significant difference in age (F(2, 135)=0.001, p=1.000); in fact group means for age were near identical at 42.881, 42.864 and 42.843 for psychology, nutrition and combined groups, respectively. There was also a non-significant result for illness duration (F(2, 135)=0.252, p=0.778). Therefore, in terms of demographics, the groups were comparable. With regard to the outcome measures, there were significant differences between the groups in terms of the MFI subscale 'general fatigue' (F(2, 135)=3.219, p=0.043), MFI 'physical fatigue' (F(2, 135)=3.343, p=0.038) and the CDC CFS symptom 'swollen lymph nodes and glands' (H(2)=7.161, p=0.028). To investigate the source of these differences, post hoc tests were conducted (unrelated t tests for the fatigue variables and Mann-Whitney tests for swollen lymph glands as the former did not meet criteria for parametric tests, all with Bonferroni correction for multiple comparisons). A significant difference was observed between the psychology and combined groups with regard to general fatigue (t(92)=−2.449, p=0.016) and physical fatigue (t(92)=−2.658, p=0.009) and also between the nutrition and psychology groups in terms of the degree of lymph node and gland swelling (U=635.00, p=0.009). Within the fatigue measures, the combined group reported significantly higher levels of both general and physical fatigue than the psychology group, whereas those undertaking nutritional support stated a higher occurrence of swollen lymph nodes and glands.

Retention analysis

Seventy-two of the original 138 participants (14 participants in the psychology group, 27 in the nutrition group and 31 in the combined group) completed the battery of measures at the 3-month follow-up, resulting in retention rates of 52.17% in the study overall, 33.33% in the psychology group, 61.36% in the nutrition group and 59.62% in the combined group. To investigate whether the individuals who did not complete the time-two measures were significantly different from those at baseline on demographic and outcome measures, a series of t tests and Mann-Whitney tests were performed. Those that dropped out of the research (although still receiving treatment at the clinic) differed significantly in terms of age (t(136)=−2.227, p=0.028) and illness duration (t(136)=−2.549, p=0.012). Those who remained in the study were of significantly older age (mean age of those that remained in the study=45.056, SD=11.535; mean age of drop-outs=40.400, SD=12.932) and longer illness duration than those who dropped out (mean age of those that remained in the study=10.836, SD=7.383; mean illness duration of drop-outs=7.571, SD=7.472). Individuals who did not remain in the study did not differ significantly in terms of gender (χ^2 (2)=1.222, p=0.269) or any of the outcome measures.

Table 1 Demographics for gender, age and illness duration across the three treatment groups

				95% CI for mean			
		Mean	SD	Lower	Upper	Test statistic	p Value
Gender	Psychology	9 (21.4%)[d]				0.179[c]	0.915
	Nutrition	8 (18.2%)[d]					
	Combined	11 (21.2%)[d]					
	Total	28 (20.3%)[d]					
Age	Psychology	42.881	13.986	38.523	47.239	0.000[a]	1.000
	Nutrition	42.864	12.504	39.062	46.665		
	Combined	42.843	11.125	39.714	45.972		
	Total	42.861	12.406	40.765	44.957		
Illness duration	Psychology	8.874	8.252	6.302	11.445	0.252[a]	0.778
	Nutrition	10.023	7.375	7.781	12.265		
	Combined	9.625	7.291	7.595	11.655		
	Total	9.523	7.580	8.247	10.800		

(a), c F statistic for one-way analysis of variance; (c), b χ^2 statistic; (d), a number of males.

Comparisons within groups across time

Overall sample

Primary outcomes

The following percentage change scores represent statistically significant changes, rather than clinically significant shifts, as this was an exploratory study. In the sample as a whole, there were improvements in all areas of the SF-36 (table 2), with a 5.80% improvement in physical functioning, a 68.98% improvement in role limitations due to physical difficulties, a 5.17% improvement in bodily pain, a 26.17% improvement in social functioning, a 5.77% improvement in general mental health, a 10.58% improvement in role limitations due to emotional difficulties, a 22.30% improvement in vitality, energy or fatigue and a 36.49% improvement in general health perception. When looking at the fatigue subscales of the MFI, all five subscales showed significant reductions in fatigue; 8.55% in general fatigue, 10.98% in physical fatigue, 8.81% in reduced activity, 12.96% in reduced motivation and 12.79% in mental fatigue.

Secondary outcomes

Within the CFS Symptom Inventory (table 3), there were improvements in occurrence of sore throats (34.48%), diarrhoea (42.47%), fatigue after exertion (16.32%), muscle aches or muscle pains (21.01%), pain in joints (34.55%), chills (37.00%), unrefreshing sleep (19.55%), sleeping problems (17.17%), headaches (24.94%), memory problems (17.86%), difficulty concentrating (26.66%), sinus and nasal symptoms (26.38%), shortness of breath (29.28%), sensitivity to light (28.62%) and depression (39.55%). There were no significant differences from time-one to time-two in the MHLCS subscale of 'chance', 'powerful others' and 'other people' (table 3); however, the MHLCS did illustrate significant increases in internal locus of control (30.67%) and that of doctors (47.49%).

Psychology group

Primary outcomes

Within the group of individuals who opted for a purely psychological intervention, improvements were seen in physical functioning (16.75%), role limitations due to physical problems (84.61%), social functioning (37.81%), general mental health (19.15%), vitality, energy or fatigue (49.57%) and general health perceptions (19.01%). Also, all the MFI fatigue scales decreased over a 3-month period, 13.58% in general fatigue, 17.74% in physical fatigue, 23.20% in reduced activity, 11.42% in reduced motivation and 29.66% in mental fatigue (table 4).

Secondary outcomes

Within those taking part in the psychology intervention, ratings of muscle aches or muscle pains (10.34%), chills (23.40%), memory problems (44.73%), difficulty concentrating (39.50%) and sensitivity to light (64.58%) decreased. A significant increase of 17.56% was observed in internal locus of control, a decrease of 4.67% in the perception that chance played an influential part in the individuals' lives (table 5).

Nutrition group

Primary outcomes

The nutrition group saw improvements in role limitations due to physical problems (75.28%), social functioning (24.93%), vitality, energy or fatigue (35.35%) and general health perceptions (29.73%). Once again,

Table 2 Comparisons across time within the primary outcome measures within the overall sample

	N	Baseline			3-Month follow-up			Comparisons	
		Percentiles			Percentiles			z Statistic	p Value
		Lower	Mdn	Upper	Lower	Mdn	Upper		
SF-36 physical functioning	72	18.075	41.644	66.667	25.694	47.222	77.583	−3.120	0.002**
SF-36 role limitations physical	71	0	0	0	0	25	50	−4.321	0.001***
SF-36 bodily pain	72	32.5	56.25	79.375	32.500	67.500	90	−2.240	0.025*
SF-36 social functioning	72	12.5	25	50	12.500	50	75	−4.504	0.001***
SF-36 general mental health	72	53	60	75	57	68	80	−2.665	0.008**
SF-36 role limitations emotional	72	0	33.317	100	41.667	66.670	100	−3.159	0.002**
SF-36 vitality energy or fatigue	72	10	15	35	11.250	30	45	−4.205	0.001***
SF-36 general health perceptions	72	20	30	40	25	40	50	−3.996	0.001***
MFI general fatigue	72	15	18	19	12	16	19	−3.692	0.001***
MFI physical fatigue	72	15	18	20	12	16	19	−4.591	0.001***
MFI reduced activity	72	11	15	18	9	14	17	−2.421	0.015*
MFI reduced motivation	72	8	10	13.750	7	9	12	−2.986	0.003**
MFI mental fatigue	72	11	14	18	8.250	12.500	15	−3.661	0.001***

*Significant at 0.05 level.
**Significant at 0.01 level.
***Significant at 0.001 level.
Mdn, median; MFI, Multidimensional Fatigue Inventory; SF-36, Short-Form 36.

Table 3 Comparisons across time within the secondary outcome measures within the overall sample

	N	Baseline			3-Month follow-up			Comparisons	
		Percentiles			Percentiles			z Statistic	p Value
		Lower	Mdn	Upper	Lower	Mdn	Upper		
CDC CFS sore throat	70	0	1.5	4	0	1	2	−2.257	0.024*
CDC CFS swollen lymph nodes/glands	71	0	2	6	0	1	4	−1.567	0.115
CDC CFS diarrhoea	72	0	1	4	0	0	2	−2.481	0.013*
CDC CFS fatigue after exertion	72	9	15	20	6.500	12	16	−3.574	0.001***
CDC CFS muscle aches/pains	72	4	9	12	1.250	6	12	−3.995	0.001***
CDC CFS pain in joints	70	0	4	9	0	1	6	−2.908	0.004**
CDC CFS fever	70	0	0	1	0	0	0	−1.667	0.095
CDC CFS chills	72	0	2	6	0	0	2.113	−4.206	0.001***
CDC CFS unrefreshing sleep	72	6	12	16	4	6	16	−2.295	0.022*
CDC CFS sleeping problems	72	2	8	12	2	4	12	−1.983	0.047*
CDC CFS headaches	71	1	6	9	1	6	11.250	−2.850	0.004**
CDC CFS memory problems	72	2	6	12	1	6	11.250	−2.053	0.040*
CDC CFS difficulty concentrating	72	2.500	8.500	12	1	6	12	−3.440	0.001***
CDC CFS nausea	71	0	1	4	0	2	6	−0.898	0.369
CDC CFS abdominal pain	71	0	2	6	0	2	6	−1.932	0.053
CDC CFS sinus nasal symptoms	71	1	4	6	0	1	6	−2.862	0.004**
CDC CFS shortness of breath	69	0	2	4	0	1	4	−2.402	0.016*
CDC CFS sensitivity to light	71	0	2	6	0	1	4	−2.388	0.017*
CDC CFS depression	72	0	2	6	0	1	4	−2.297	0.022*
MHLCS internal	72	0.528	0.681	0.799	0.611	0.722	0.889	−2.962	0.003**
MHLCS chance	72	0.222	0.344	0.417	0.201	0.320	0.444	−1.552	0.121
MHLCS powerful others	72	0.333	0.389	0.500	0.306	0.361	0.500	−1.601	0.109
MHLCS doctors	72	0.0833	0.139	0.222	0.083	0.111	0.194	−2.381	0.017*
MHLCS other people	72	0.194	0.250	0.3056	0.174	0.250	0.278	−1.186	0.236

*Significant at 0.05 level.
**Significant at 0.01 level.
***Significant at 0.001 level.
CDC CFS, Centers for Disease Control Chronic Fatigue Syndrome Inventory; CFS, chronic fatigue syndrome; Mdn, median; MHLCS, Multidimensional Health Locus of Control Scale.

all the MFI fatigue scales decreased over a 3-month period, 13.39% in general fatigue, 15.00% in physical fatigue, 13.28% in reduced activity, 14.64% in reduced motivation and 12.83% in mental fatigue (table 6).

Secondary outcomes

In the nutrition group, numerous symptom-related indices also showed improvements (table 7); sore throat (56.23%), swollen lymph glands (21.21%), fatigue after exertion

Table 4 Comparisons across time within the primary outcome measures within the psychology group

	N	Baseline			3-Month follow-up			Comparisons	
		Percentiles			Percentiles			z Statistic	p Value
		Lower	Mdn	Upper	Lower	Mdn	Upper		
SF-36 physical functioning	14	25.008	44.444	58.367	27.083	69.450	84.700	−2.707	0.007**
SF-36 role limitations physical	14	0	0	25	0	50	81.250	−2.379	0.017*
SF-36 bodily pain	14	39.375	57.500	80.625	32.500	72.500	90	−1.195	0.232
SF-36 social functioning	14	25	37.500	50	34.375	56.250	90.625	−2.689	0.007**
SF-36 general mental health	14	47	62	80	67	76	88	−2.497	0.013*
SF-36 role limitations emotional	14	24.974	100	100	58.336	100	100	−0.842	0.400
SF-36 vitality energy or fatigue	14	10	20	40	28.750	45	52.500	−3.066	0.002**
SF-36 general health perceptions	14	23.750	30	41.250	31.250	40	63.750	−2.561	0.010*
MFI general fatigue	14	14	16.500	18.500	9.750	13.500	18.500	−2.657	0.008**
MFI physical fatigue	14	13.750	16	19.250	8.750	13	16.750	−2.810	0.005**
MFI reduced activity	14	9.750	12.500	18.250	7	9	14.500	−2.142	0.032*
MFI reduced motivation	14	5.750	8	11.750	4.750	5.500	8.250	−2.131	0.033*
MFI mental fatigue	14	11.750	15.500	18	6.500	9.500	15	−2.950	0.003*

*Significant at 0.05 level.
**Significant at 0.01 level.
Mdn, median; MFI, Multidimensional Fatigue Inventory; SF-36, Short-Form 36.

Table 5 Comparisons across time within the secondary outcome measures within the psychology group

	N	Baseline Percentiles			3-Month follow-up Percentiles			Comparisons z Statistic	Comparisons p Value
		Lower	Mdn	Upper	Lower	Mdn	Upper		
CDC CFS sore throat	14	0	2	6	0	0	2.500	−1.365	0.172
CDC CFS swollen lymph nodes/glands	14	0	0.5	2.5	0	0	4	−0.341	0.733
CDC CFS diarrhoea	14	0	0	2	0	0	2.500	−0.730	0.465
CDC CFS fatigue after exertion	14	9	12	20	7.750	9	14	−1.550	0.121
CDC CFS muscle aches/pains	14	4	9	15.25	1.750	9	14	−2.145	0.032*
CDC CFS pain in joints	14	0	2.5	9	0	0.500	4.500	−1.778	0.075
CDC CFS fever	14	0	0	1.5	0	0	0.500	−0.135	0.892
CDC CFS chills	14	0	1	6.75	0	0	4.500	−1.970	0.049*
CDC CFS unrefreshing sleep	14	9	12	15.25	5.500	9	16	−0.802	0.422
CDC CFS sleeping problems	14	2.75	7	12	1	3	9.750	−1.738	0.082
CDC CFS headaches	14	1	2.5	6	0.750	1	6.750	−1.200	0.230
CDC CFS memory problems	14	1	6	9	0.750	1	6.750	−1.965	0.049*
CDC CFS difficulty concentrating	14	3.5	9	17	1	5	6.750	−2.809	0.005**
CDC CFS nausea	14	0	0	4.25	0	1	4.500	−0.213	0.832
CDC CFS abdominal pain	14	0	2	5.25	0	0	6	−0.343	0.732
CDC CFS sinus nasal symptoms	14	1	3.5	4.5	0	1.500	4.500	−0.724	0.469
CDC CFS shortness of breath	14	0	1.5	4.5	0	0.500	2.50	−1.556	0.120
CDC CFS sensitivity to light	14	0	1	4.5	0	0	1.250	−1.973	0.049*
CDC CFS depression	14	0	1.5	6	0	0	2	−1.614	0.106
MHLCS internal	14	0.556	0.653	0.840	0.611	0.872	0.923	−2.983	0.003**
MHLCS chance	14	0.326	0.417	0.535	0.167	0.361	0.451	−2.594	0.009**
MHLCS powerful others	14	0.319	0.375	0.451	0.299	0.356	0.431	0.000	1.000
MHLCS doctors	14	0.083	0.125	0.194	0.083	0.083	0.174	−1.122	0.262
MHLCS other people	14	0.194	0.236	0.285	0.194	0.222	0.257	−0.118	0.906

*Significant at 0.05 level.
**Significant at 0.01 level.
CDC CFS, Centers for Disease Control Chronic Fatigue Syndrome Inventory; CFS, chronic fatigue syndrome; Mdn, median; MHLCS, Multidimensional Health Locus of Control Scale.

(13.90%), muscle aches or muscle pains (20.56%), chills (40.74%), nausea (16.42%) and abdominal pain (20.16%). No significant differences were found from the baseline to follow-up in the perceived control (table 7).

Combined group

Primary outcomes

In terms of general health as gauged by the SF-36 measure, the group who received both psychological

Table 6 Comparisons across time within the primary outcome measures within the nutrition group

	N	Baseline Percentiles			3-Month follow-up Percentiles			Comparisons z Statistic	Comparisons p Value
		Lower	Mdn	Upper	Lower	Mdn	Upper		
SF-36 physical functioning	27	16.7	44.444	77.778	16.700	38.889	77.778	−1.136	0.256
SF-36 role limitations physical	26	0	0	0	0	25	25	−2.878	0.004**
SF-36 bodily pain	27	32.5	45	67.5	35.200	67.500	90	−1.800	0.072
SF-36 social functioning	27	0	25	50	12.500	37.500	75	−2.476	0.013*
SF-36 general mental health	27	52	60	72	52	64	80	−1.696	0.090
SF-36 role limitations emotional	27	0	0	100	0	66.670	100	−1.788	0.074
SF-36 vitality energy or fatigue	27	5	15	35	15	25	45	−2.734	0.006**
SF-36 general health perceptions	27	20	25	35	25	35	45	−2.157	0.031*
MFI general fatigue	27	15	18	19	12	15	19	−2.548	0.011*
MFI physical fatigue	27	14	18	19	11	16	19	−2.791	0.005**
MFI reduced activity	27	10	14	18	8	13	16	−2.164	0.030*
MFI reduced motivation	27	8	10	12	6	8	12	−1.985	0.047*
MFI mental fatigue	27	11	13	16	8	13	15	−2.082	0.037*

*Significant at 0.05 level.
**Significant at 0.01 level.
Mdn, median; MFI, Multidimensional Fatigue Inventory; SF-36, Short-Form 36.

Table 7 Comparisons across time within the secondary outcome measures within the nutrition group

	N	Baseline Percentiles			3-Month follow-up Percentiles			Comparisons z Statistic	Comparisons p Value
		Lower	Mdn	Upper	Lower	Mdn	Upper		
CDC CFS sore throat	27	8	1	2	0	1	2	–2.211	0.027*
CDC CFS swollen lymph nodes/glands	26	20	0	5	0	1	12	–2.051	0.040*
CDC CFS diarrhoea	27	16	0	1	0	0	1	–1.649	0.099
CDC CFS fatigue after exertion	27	25	9	16	4	12	20	–2.209	0.027*
CDC CFS muscle aches/pains	27	20	4	9	2	6	12	–2.901	0.004**
CDC CFS pain in joints	26	20	0.750	4	0	1	6	–1.827	0.068
CDC CFS fever	26	9	0	0	0	0	0	–1.254	0.210
CDC CFS chills	27	12	1	3	0	0	1	–3.401	0.001***
CDC CFS unrefreshing sleep	27	25	6	12	4	6	16	–1.421	0.155
CDC CFS sleeping problems	27	25	1	9	2	4	16	–0.190	0.849
CDC CFS headaches	26	25	0.750	6	1	3	6	–1.895	0.058
CDC CFS memory problems	27	25	2	6	2	6	12	–0.338	0.735
CDC CFS difficulty concentrating	27	25	2	6	4	6	12	–1.196	0.232
CDC CFS nausea	26	25	0	2	0	1	6	–2.407	0.016*
CDC CFS abdominal pain	26	16	0.750	3	0	3	6	–2.322	0.020*
CDC CFS sinus nasal symptoms	26	20	1	3.500	0	1	9	–1.244	0.213
CDC CFS shortness of breath	25	20	0	2	0	1	3	–1.651	0.099
CDC CFS sensitivity to light	26	25	0	4	0	2	6	–1.890	0.059
CDC CFS depression	27	20	0	4	0	2	4	–1.584	0.113
MHLCS internal	27	0.944	0.528	0.667	0.528	0.639	0.778	–0.687	0.492
MHLCS chance	27	0.694	0.222	0.333	0.222	0.333	0.472	–0.143	0.886
MHLCS powerful others	27	0.694	0.333	0.389	0.278	0.361	0.528	–1.843	0.065
MHLCS doctors	27	0.417	0.0833	0.139	0.083	0.139	0.222	–1.686	0.092
MHLCS other people	27	0.833	0.222	0.278	0.167	0.250	0.306	–1.697	0.090

*Significant at 0.05 level.
**Significant at 0.01 level.
***Significant at 0.001 level.
CDC CFS, Centers for Disease Control Chronic Fatigue Syndrome Inventory; CFS, chronic fatigue syndrome; Mdn, median; MHLCS, Multidimensional Health Locus of Control Scale.

and nutritional intervention reported reductions in role limitations due to physical difficulties (57.02%), social functioning (22.61%), role limitations due to emotional difficulties (29.47%) and general health perceptions (26.45%). Only one measure of fatigue, that of physical fatigue, saw significant improvements over time (6.42%) in the combined group (table 8).

Table 8 Comparisons across time within the primary outcome measures within the combined group

	N	Baseline Percentiles			3-Month follow-up Percentiles			Comparisons z Statistic	Comparisons p Value
		Lower	Mdn	Upper	Lower	Mdn	Upper		
SF-36 physical functioning	31	22.200	33.333	61.111	27.778	55.556	72.222	–1.850	0.064
SF-36 role limitations physical	31	0	0	0	0	25	25	–2.225	0.026*
SF-36 bodily pain	31	32.500	45	80	32.500	57.500	80	–1.048	0.294
SF-36 social functioning	31	12.500	25	37.500	12.500	37.500	62.500	–2.426	0.015*
SF-36 general mental health	31	56	60	72	56	68	76	–0.524	0.600
SF-36 role limitations emotional	31	0	33.333	100	66.667	66.670	100	–2.313	0.021*
SF-36 vitality energy or fatigue	31	10	15	30	10	25	40	–1.558	0.119
SF-36 general health perceptions	31	20	30	40	25	40	55	–2.423	0.015*
MFI general fatigue	31	16	18	19	14	17	19	–0.854	0.393
MFI physical fatigue	31	15	19	20	13	17	20	–2.364	0.018*
MFI reduced activity	31	12	16	18	11	16	18	–0.070	0.944
MFI reduced motivation	31	9	11	14	8	10	13	–1.082	0.279
MFI mental fatigue	31	10	14	18	11	13	16	–1.586	0.113

*Significant at 0.05 level.
Mdn, median; MFI, Multidimensional Fatigue Inventory; SF-36, Short-Form 36.

Secondary outcomes

Those in the combined group saw significant reductions over the 3-month interval in diarrhoea (47.97%), fatigue after exertion (19.20%), chills (40.23%), headaches (36.18%) and sinus and nasal symptoms (20.56%; table 9). No significant differences were found from the baseline to follow-up in the perceived control as measured by the MHLCS in the combined treatment group (table 9).

Comparisons across groups

With correction for baseline variation, there were no significant differences between the three groups in terms of change scores.

DISCUSSION

Key results

There were statistically significant (rather than known clinically significant) changes over time of numerous measures in all groups investigated. However, this is not to say that these changes were due to the interventions as the design of this study was exploratory, rather than experimental (please see the following sections for a further critique of the design). The psychology group contained the most significant findings, including those concerned with daily functioning, fatigue, locus of control and cognitive CDC CFS-specific symptoms. These findings appear consistent with outcomes from other psychological interventions.[3 4 6] As expected, changes in the perceived control were not observed in the nutrition group as this is not an area that is targeted in this programme. However, the more immune-type symptoms such as sore throat and swollen lymph nodes or glands did see significant reductions over time as would be envisaged in treatment protocols based upon nutritional expertise. The group that exhibited the least significant findings was the combined group and, as noted below, this may be due to the greater general severity of symptoms in this group and the need for a more lengthy intervention. Nevertheless, considering the small sample sizes in the groups at the follow-up, these results are very promising and warrant further attention.

Interpretation

As noted previously[31] individualised treatment protocols which include a range of tailored strategies are a favourable direction for dealing with a complex and multisystem disorder such as ME/CFS. The present study has demonstrated that such interventions may be useful in

Table 9 Comparisons across time within the secondary outcome measures within the combined group

	N	Baseline Percentiles			3-Month follow-up Percentiles			Comparisons	
		Lower	Mdn	Upper	Lower	Mdn	Upper	z Statistic	p Value
CDC CFS sore throat	29	0	0	3.500	0	1	2.030	−0.567	0.571
CDC CFS swollen lymph nodes/glands	31	0	2	4	0	1	3	−0.725	0.046
CDC CFS diarrhoea	31	0	2	4	0	0	2	−1.996	0.046*
CDC CFS fatigue after exertion	31	8	15	20	6	12	16	−2.392	0.017*
CDC CFS muscle aches/pains	31	2	6	12	1	6	9	−1.908	0.056
CDC CFS pain in joints	30	0	1.500	8	0	1	4	−1.680	0.093
CDC CFS fever	30	0	0	1	0	0	0.720	−1.383	0.167
CDC CFS chills	31	0	2	6	0	1	2.150	−2.049	0.040*
CDC CFS unrefreshing sleep	31	6	12	16	4	9	16	−1.513	0.130
CDC CFS sleeping problems	31	1	6	12	2	4	9	−1.794	0.073
CDC CFS headaches	31	2	6	9	1	3	6	−2.807	0.005**
CDC CFS memory problems	31	2	6	12	1	3	9	−1.446	0.148
CDC CFS difficulty concentrating	31	2	8	12	1	6	12	−1.899	0.058
CDC CFS nausea	31	0	1	6	0	2	6	−0.855	0.392
CDC CFS abdominal pain	31	0	1	6	0	2	4	−0.598	0.550
CDC CFS sinus nasal symptoms	31	0	5	8	0	1	4	−2.482	0.013*
CDC CFS shortness of breath	30	0	2	6	0	1	4	−0.976	0.329
CDC CFS sensitivity to light	31	0	1	6	0	1	4	−0.787	0.431
CDC CFS depression	31	0	2	6	0	1	6	−1.304	0.192
MHLCS internal	31	0.556	0.694	0.861	0.639	0.750	0.889	−1.755	0.079
MHLCS chance	31	0.222	0.333	0.361	0.167	0.306	0.417	−0.672	0.501
MHLCS powerful others	31	0.333	0.389	0.500	0.333	0.389	0.500	−0.577	0.564
MHLCS doctors	31	0.111	0.167	0.222	0.083	0.139	0.500	−1.384	0.166
MHLCS other people	31	0.167	0.250	0.278	0.194	0.250	0.306	−0.213	0.831

*Significant at 0.05 level.
**Significant at 0.01 level.
***Significant at 0.001 level.
CFS, chronic fatigue syndrome; Mdn, median; MHLCS, Multidimensional Health Locus of Control Scale.

lowering symptomatology, improving functioning and helping individuals gain a greater sense of control over their health status.

Limitations and generalisability

This study was a preliminary study in a naturalistic setting and as such did not have a robust design. There was not a control group and the participants were not randomly assigned to groups, therefore the results should be treated with caution. To ascertain whether the changes in symptom and functional reports were due to the interventions, an RCT should be conducted. Also, there was a high drop-out rate from time-one to time-two and this rate differed across groups. The highest drop-out rate was in the psychology group; while we cannot be sure why this occurred, it is postulated that the retention was poor in the group as the individuals in the psychology programme had more activities to engage in and may have felt overburdened with the research questionnaires in addition to their sessions and homework (this would not be the case in the combined group as the therapeutic activities are phased-in as mentioned hereinbefore).

In this study, each individual was guided to an appropriate treatment within an initial screening with clinic staff; therefore the group was dependent on the nature of the individual's symptoms and their personal choice as the programmes on offer were privately funded. Notably, the groups did differ in general and physical fatigue with participants in the combined groups reporting greater fatigue than those in the psychology group which suggests that this group's general symptomatology was more severe. The combined group illustrated less change over time compared to the psychology and nutrition groups and it is feasible to infer that individuals with a greater number and degree of complaints are referred to the combined group within the clinic. Also, those in the combined group will not experience the intensity of each intervention as this has been demonstrated to result in non-compliance; therefore, changes in outcome measures in this group may not be noted at an interval of 3 months. Further studies underway presently will investigate follow-ups at 6 and 12 months to identify whether the findings here are maintained over time and also whether those with a greater symptom severity benefit with a longer intervention. The results from this study will then inform plans for an RCT of the clinic's practices. As the participants were self-selected onto these programmes, the findings lack generalisability; future work should sample from the overall ME/CFS population and be randomly assigned to groups to make valid assumptions regarding the illness group as a whole.

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