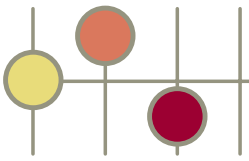

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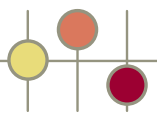

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REPORT 35

The treatment and management of chronic fatigue syndrome (CFS) / myalgic encephalomyelitis (ME) in adults and children

Update of CRD Report 22

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EXECUTIVE SUMMARY

Background

Chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME) is a debilitating condition characterised by fatigue on minimal exertion accompanied by a range of other symptoms such as headaches, sleep disturbance, cognitive difficulties and muscle pain. Many different interventions have been used for the treatment, management and rehabilitation of patients with CFS/ME. A systematic review covering all available interventions was performed by CRD in 2001, but since that time many new studies have been published and there is a need for the report to be updated.

Objective

Our objective was to determine whether any particular intervention or combination of interventions is effective in the treatment, management and rehabilitation of adults and children with a diagnosis of CFS/ME.

Methods

We searched eleven electronic databases, reference lists of articles and reviews, and textbooks on CFS/ME. Additional references were sought by contact with experts. Randomised (RCTs) and non-randomised controlled trials of any intervention or combination of interventions were eligible for inclusion. Study participants could be adults or children with a diagnosis of CFS/ME based on any criteria. Decisions on inclusion and assessment of study quality were performed by two reviewers independently. Disagreements were resolved by discussion, with reference to a third reviewer if necessary. Data were extracted from study reports by one reviewer and checked by another. Any discrepancies were resolved by reference to the original study, with a third reviewer being consulted if necessary. Only between-group comparisons were considered.

Data were grouped by intervention into pre-specified broad categories and synthesised qualitatively. A study was classified as showing some effect (positive or negative) of an intervention if any of the outcomes measured showed a significant ($p < 0.05$) difference between the treatment and control groups. Studies were classified as showing an overall effect of the intervention if there was a significant difference between the treatment and control groups for more than one clinical outcome. Studies of pre-specified subgroups (children and those with severe CFS/ME) were considered separately.

Results

The overall literature search identified 10,768 items, of which 70 met the inclusion criteria for the review. Two studies included in the review by Bagnall et al. were excluded from the updated review, one because it included patients with chronic mononucleosis and one because a full report was subsequently published. Fifteen papers that were ordered as potentially meeting inclusion criteria had not arrived at the time of writing. One paper in the Russian language was identified as potentially meeting inclusion criteria but has not been translated. The paper is about a yeast extract supplement but it is unclear whether patients all had CFS.

Of the studies included in the review, 59 were RCTs and the remainder non-randomised controlled trials. Of the newly included studies, 15 showed some beneficial effect of the intervention and eight showed an overall beneficial effect. Validity scores ranged from 2 to 19 for the included RCTs and from 0 to 14 for the controlled trials. Controlled trials generally scored less well than RCTs on all validity criteria. A high degree of heterogeneity in interventions and outcomes was evident.

Behavioural

The evidence supporting the effectiveness of cognitive behaviour therapy (CBT) has been strengthened by one recent good quality RCT in children and adolescents, which found an overall positive effect of the intervention. CBT was associated with a significant positive effect on fatigue, symptoms, physical functioning and school attendance. Most other new studies of CBT and modified CBT have also favoured the treatment for one or more outcomes but these were either lower quality RCTs or non-randomised studies. Graded exercise therapy (GET) has recently been studied in two moderate quality RCTs. As with CBT, the overall results of studies to date suggest that GET may have positive effects on the symptoms of CFS/ME and on physical functioning.

Immunological
Two new studies of immunological therapies (a controlled trial of inosine pranobex and a relatively low quality RCT of staphylococcus toxoid) were added to the updated review. Both treatments showed benefits for some outcomes but were also associated with relatively high levels of adverse events. Overall there is still insufficient evidence about the effectiveness of therapies of this type.

Pharmacological
Treatment of CFS/ME with pharmacological therapies has given disappointing results in most cases. A recent large RCT of the acetylcholinesterase inhibitor galantamine hydrobromide found no significant differences between groups. An RCT of hydrocortisone published in 2002 found a significant difference between groups for fatigue, but this study scored poorly for validity. Two other recent studies of steroid treatment found no significant effect, in line with the mixed results reported in 2002.

Complementary/alternative
The only new study of complementary/alternative therapies was an RCT of homeopathic treatment that showed significant differences favouring the treatment group for one of five measures of fatigue and one of five measures of functional limitations.

Supplements
A supplement of acetyl-L-carnitine and propionyl-L-carnitine showed an overall positive effect in one moderate quality RCT published in 2004. Other supplements (essential fatty acids and magnesium) have also given promising results in single studies. The evidence base for supplements and miscellaneous interventions for CFS/ME remains very limited.

Safety
There is limited evidence about adverse effects associated with behavioural interventions. Withdrawals from treatment in RCTs suggest that there may be an issue but the evidence is often difficult to interpret because of poor reporting. New studies of behavioural interventions included in the update did not report any withdrawals caused by adverse events, although again the reasons for withdrawal were often not reported.

Several studies of immunological/antiviral, pharmacological and nutritional interventions have reported withdrawals because of adverse effects, including recent studies of Staphylococcus toxoid, galanthamine hydrobromide, and hydrocortisone/fludrocortisone.

Subgroups
Recent studies of CBT and modified CBT in children and young people both reported that school attendance was significantly better in the treatment group compared with controls. One study supports the effectiveness of immunoglobulin treatment in children but this intervention may also have harmful effects. There is a lack of new studies evaluating interventions for patients severely affected by CFS/ME.

Conclusions
Over the last 5 years, there has been a marked increase in the size and quality of the evidence base on interventions for CFS/ME. CBT and GET have shown promising results in reducing the symptoms of CFS/ME and improving physical functioning. There is a need for research to define the characteristics of patients who would benefit from specific interventions and to develop clinically relevant objective outcome measures**.**

INTRODUCTION

We have undertaken a systematic review to update the previous review on interventions for the management/ treatment/ rehabilitation of people with CFS/ME.[1] This report of the updated review should be read in conjunction with the original CRD Report 22, which provides background information on the condition, interventions and outcomes and a fuller discussion of studies published up to 2001.

The project was funded by the National Institute for Health and Clinical Excellence (NICE), which commissioned the National Collaborating Centre for Primary Care (part of the Royal College of General Practitioners) to produce guidelines for 'The diagnosis and management of chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy) in adults and children'. The review formed part of the independent synthesis of research evidence to support the development of these guidelines. The views expressed in this report are those of the authors and not necessarily those of the NCC-PC, RCGP or NICE.

Review question

Does the evidence show that any particular intervention or combination of interventions is effective in treatment, management or rehabilitation of adults and children with a diagnosis of CFS/ME?

Review methods

Literature search

The literature search was updated form 2001 to 2005. The search was broad and not restricted by intervention or outcome. The search aimed to pick up all studies of CFS/ME and related synonyms.

Individual search strategies were developed for each electronic database searched. The following databases were searched: MEDLINE (1966 to May 2005), EMBASE (1980 to May 2005), PSYCINFO (1887 to May 2005), CCTR (March 2005), Social Science Citation Index (1981-2005), Science Citation Index (1981-2005), Index to Scientific and Technical Proceedings (1982-2005), PASCAL (1973–2005), MANTIS (1880 – January 2005), JICST (1985 – 2005), Conference Proceedings Index (1973 – January 2005), AMED (1984 – January 2005).

The full search strategies are listed in Appendix 1.

Via the NICE Guideline Development Group (GDG) consultation process, we attempted to make contact with individuals who are experts in the field to identify any unpublished literature or ongoing studies. The bibliographies of included studies were also scanned for any additional references.

Study selection

Two reviewers independently assessed all titles and abstracts identified from the searches of electronic databases for potential relevance to the review question. All papers that looked potentially relevant were retrieved in full. Two reviewers independently assessed all retrieved studies for possible inclusion, using the inclusion criteria listed below. The use of two reviewers is a method which is commonly employed in systematic reviews, to minimise the risk of introducing bias to the results of the review. If the two reviewers cannot agree, a third reviewer is consulted to resolve the differences.

Inclusion criteria

Intervention – any intervention or combination of interventions used in the treatment, management or rehabilitation of people with CFS/ME
Population – adults or children aged 5 years or more with a diagnosis of CFS/ME based on any criteria
Outcomes – all outcomes reported in included studies were considered.
Study design – only randomised or controlled clinical trials were included.

Data extraction, validity assessment and data synthesis

For all review questions, data were extracted by one reviewer and checked by a second reviewer. Discrepancies were resolved by referral to the original studies. If necessary, arbitration was by a third

reviewer. Duplicate publications were actively screened for and where found the latest or most complete report was used.

The following categories of data were extracted: study author; year of publication; country study was carried out in; number of study participants; participant details paying particular attention to the following - inclusion/ exclusion criteria (if any), information relating to subgroups (age/ severity) if reported, baseline functioning and diagnostic criteria used; setting; study design; level of evidence; intervention details (according to whether the intervention is pharmacological or non-pharmacological e.g. drug dose, frequency, duration, content, persons delivering the intervention, setting of intervention (e.g. Group or Individual CBT), co-interventions); comparators (if any, details as for interventions); outcomes measured; results.

Validity assessment was carried out, using an existing validity assessment tool, by two reviewers independently, using predefined criteria. Discrepancies were resolved by discussion or, when agreement could not be reached, by consultation with a third reviewer.

The information was tabulated and summarised narratively, grouped by intervention. Interventions were broadly grouped into the following categories:

- pharmacological
- immunological
- behavioural (including graded exercise, graded activity, pacing, CBT, psychotherapy, counselling, family therapy, rehabilitation)
- complementary
- other (e.g. multicomponent interventions tailored to symptoms of the individual; buddy programmes, dietary)
- supplements

In evaluating the effects of interventions, a study was classified as showing some effect of treatment if any of the outcomes measured showed a significant ($p < 0.05$) difference between the treatment and control groups. Studies were classified as showing an overall effect of treatment if there was a significant difference between the treatment and control groups for more than one clinical outcome. Information from stronger study designs (with higher validity scores) was emphasised. In addition, where information was presented regarding subgroups (children or severely affected) this was summarised separately.

The homogeneity/heterogeneity in terms of participants, interventions and outcomes in included studies was assessed in a qualitative manner based on the judgment of the reviewers.

RESULTS

Seventy trials are included in this section. Detailed data extraction and validity assessment tables are presented in Appendix 2 and 3. Additionally, four ongoing trials that have not yet been published were identified.[2-5]

Fifteen papers that were ordered as potentially meeting inclusion criteria had not arrived at the time of writing this report.[6-20] One paper in the Russian language was identified as potentially meeting inclusion criteria but has not been translated.[21] The paper is about a yeast extract supplement but it is unclear whether patients all had CFS.

No RCTs, controlled trials, or good quality cohort studies, case-control studies before-and-after studies or interrupted time series were found for the following treatments which the GDG had identified a priori as being of interest: expert patient programme; amitriptyline; gabapentin; baclofen; vitamin B12 injections.

Evidence relating to adults with CFS/ME

Main results of behavioural treatment trials (Table 1)

CBT, given in weekly or biweekly sessions with the aim to increase activity and reduce rest time in a systematic manner, independent of symptoms, was evaluated in adults in four RCTs.[22-26] A controlled trial of "modified CBT" used a different form of treatment without graded activity, which is normally considered an integral part of CBT for CFS/ME. The intervention used in this study aimed to promote shared coping through relaxation training and guided imagery, cognitive therapy techniques and behavioural prescription involving activity limitations.[27] Other types of modified CBT, with occupational therapy/rehabilitation aspects, were examined in another RCT[28] and two controlled trials.[29, 30] All studies included people diagnosed with CFS according to one of the recognised case definitions, except one which included people with post viral fatigue syndrome.[31] CBT was compared to routine medical care in two RCTs,[25, 28] and two controlled trials,[29, 30] to relaxation in one RCT,[22, 23] to natural course (control) in another RCT,[26] and to guided support in one controlled trial of "modified CBT".[27] A further RCT compared CBT plus placebo injections to CBT plus leukocyte extract, a control clinic plus leukocyte extract and to a control clinic plus placebo injections.[24]

The RCT which investigated the effects of both leukocyte extract and CBT showed a significantly greater effect on general health in the group receiving both leukocyte extract and CBT compared to the other groups. No differences were found between groups (including CBT alone) for the other outcomes investigated.[24] The controlled trial of modified CBT found no difference between intervention and control groups for fatigue, depression or symptom scores.[27] This study scored very poorly on the validity assessment, scoring only 1 out of a possible 20.

The remaining three RCTs reported a beneficial effect of CBT when compared to controls.[22, 25, 26] All three RCTs found a significant short term improvement in physical functioning, fatigue, and global improvement, but neither of the two studies that assessed depression found any differences between groups.[22, 25] One of these RCTs also followed patients for five years after the intervention. At the five year follow-up assessment global improvement was greater in the intervention group, as was the proportion of participants who completely recovered,[23] however, no differences were reported between the groups in terms of physical functioning, fatigue, general health, symptoms, relapses or the proportion of participants that no longer met the UK criteria for CFS.

The three studies of modified CBT with rehabilitation[28-30] found significant differences between groups for symptoms (one RCT, one controlled trial), emotional distress (one controlled trial) and global health/ quality of life (3 controlled trials).

In one RCT two participants dropped out of the CBT group because they felt a deterioration in their symptoms was due to the intervention.[25] A second RCT showed very high drop out rates of between 20 and 40% in all three treatment groups.[26] Drop out rates were highest in the CBT group and lowest in the control group, reasons for drop-outs were not stated and no adverse effects from treatment were reported.

The effects of graded exercise therapy (GET) were investigated in five fairly large RCTs of patients with CFS, all of which found significant improvements in the intervention compared to the control groups. Improvements in measures of fatigue and physical function were found in all five RCTs.[32-36] Two also showed improvement in general health[32, 34] and one in physiological measurements and symptoms.[33] When exercise was combined with fluoxetine there was no additional effect.[33] One RCT assessed different interventions to encourage graded exercise and found benefits of GET compared to standardised medical care for all outcomes investigated. However, there were no differences between the different intervention groups for any of the outcomes investigated. [34, 37]

In one of the RCTs evaluating GET, one participant dropped out from each group due to worsening of symptoms.[32] In another RCT of exercise (and exercise plus fluoxetine), 11 participants dropped out due to side effects but it is unclear which intervention group they were in.[33]

Table 1 Results of behavioural treatment trials in adults

Results in bold indicate statistically significant differences between treatment groups (p<0.05)

Intervention	Author (Year), number of participants	Results					Drop-outs/Adverse effects	Validity score
		Resource use	Physical	Psychological	Physiological	Quality of life and general health		
CBT	Deale (1997)[22] n=60		***Physical functioning and fatigue (assessor and patient rating):*** **greater improvement in treatment than control (p<0.01)**	*Depression:* No significant differences in change between groups		***Work and social adjustment, long term goals, self-rating of global improvement, patient satisfaction with treatment outcome and proportion employed:*** **greater improvement in treatment than control (p<0.05)** *General health questionnaire, patient assessment of usefulness of treatment:* no significant differences in change between groups	7 dropped out, 3 from CBT, no adverse effects reported	18
	Results at 5 year follow-up[23] n=53		*Physical functioning and fatigue:* no significant difference between two groups			***Global improvement and proportion completely recovered:*** **greater improvement in treatment than control (p<0.001)** *General health and proportion that no longer meet UK CFS criteria:* no significant differences between groups ***Symptoms and relapses:*** **suggestion of greater improvement in treatment than control (p=0.05)**		
	Lloyd (1993)[24] n=49		*Physical capacity & functional measure*: no significant differences between groups	*Mood*: no significant differences between groups	*Immune outcomes*: no significant differences between groups	***General health*****: group in which DLE combined with CBT showed greater improvement than other intervention groups (p<0.05)**	2 participants dropped, however, no participants dropped out due to adverse effects	13
	Sharpe (1998)[25] n=60		***Physical functioning, interference with activities, number of days in bed, exercise and fatigue:*** **greater improvement in treatment than control (p<0.05)**	*Depression and anxiety:* no significant differences between groups (p>0.05)		***Improvement in work status, global improvement:*** **greater improvement in treatment than control (p<0.001)** ***Illness beliefs:*** **greater proportion of patients in treatment group reported reduction in strength of illness beliefs (p<0.05).**	Complete data not available for one patient, 2 in CBT group attributed deterioration in symptoms to treatment	15
	Prins (2001)[26] n=270		***Fatigue, functional impairment:*** **greater improvement in treatment than control (p<0.01)**	***Psychological well-being:*** **greater improvement in treatment than control (p<0.01)**		***QOL, work, general improvement:*** **greater improvement in treatment than control (p<0.05)**	37 in CBT group, 29 in support group and 18 in control group. 10 in CBT and 8 in support group did not start treatment. No adverse effects reported	16

	Whitehead (2002)[38]		*Fatigue:* no significant difference between groups	*Anxiety and Depression:* no significant differences between groups		*Disability:* no significant differences between groups	At 6 months, 8 in treatment group and 11 in control group were lost to follow-up	3
Modified CBT	Cox (2002)[29]		*Physical functioning and fatigue:* no significant differences between groups	*Emotional distress:* no significant differences between groups		*Maintaining activity and accommodating to illness:* **significant difference in favour of treatment group (p<0.03)**	6 months after discharge, 14 in treatment group and 16 in control group did not return questionnaires	7 (NB controlled trial)
	Cox (2002)[30]		*Physical / functional status, fatigue, pain, symptoms:* **significant difference between groups for fatigue symptoms (p<0.02) and pain (p<0.05)**	*Perceived ability, anxiety, depression, emotional distress:* **significant difference between groups for emotional distress (p<0.03)**		*Illness management:* **significant difference in favour of treatment group (p<0.03)**	5 withdrew from experimental group, 18 from control group	8 (NB controlled trial)
	Friedberg (1994)[27] n=44		*Fatigue:* significant decrease within treatment group, not control, difference between groups not discussed	*Depression:* no significant difference between groups		*Stress symptom score:* no significant difference between groups	2 patients who did not want CBT refused to participate in control group	1 (NB controlled trial)
	Taylor (2004)[28]		*Symptoms:* **significant interaction (p<0.05)**			*Quality of life:* **significant interaction (p<0.05)**	No withdrawals	9
GET	Fulcher (1997)[32] n=66		*Fatigue & function:* **Chalder fatigue score, total fatigue score, physical fatigue score, physical function score were significantly better in treatment group (p<0.05)** Mental fatigue and sleep: no difference between groups	*Depression and anxiety:* no difference between groups	*Physiological*: **treatment group showed significant increase in peak oxygen consumption and maximum ventilation but not other measures compared to controls (p<0.05)**	*General health:* **Greater improvement in treatment group (p=0.04)** *Symptom score:* **symptom score and general health score significantly greater in treatment group (p<0.05)**	7 participants dropped out, 4 in exercise group and 3 in control, 1 from each group dropped out due to worsening of symptoms	17
	Moss-Morris (2005)[35] n=49		*CGI, fatigue:* **significant difference in favour of treatment group (p<0.03)**				3/25 dropped out of treatment and 3/24 did not return questionnaires at 12 weeks	9

	Powell (2000)[37] n=148		*Physical functioning, fatigue:* **greater improvement in all intervention groups than control (p<0.001)**, no difference between intervention groups *Sleep problems:* greater improvement in all intervention groups than control (no measure of significance), no difference between intervention groups	*Depression and anxiety:* greater improvement in all intervention groups than control (no measure of significance), no difference between intervention groups		*Improvement, and patients report of improvement*: **greater improvement in all intervention groups than control (p<0.01),** no difference between intervention groups	21 dropped out, 19 in intervention groups, dropped out during treatment: 8 for medical reasons, 7 for psychiatric reasons, 4 gave no reason, 1 emigrated, 1 was dissatisfied with treatment	17
	Wallman (2004)[36] n=61		*Fatigue:* **significantly better in treatment group (p=0.027)**	*Depression, anxiety:* **significantly better in treatment group (p=0.027)**	*Resting and target heart rate and blood pressure, exercise test values:* comparisons not made between groups		One excluded after randomisation because BMI too high to participate in exercise test. None reported during the study	9
GET & fluoxetine	Wearden (1998)[33] n=136		*Fatigue:* Trends for exercise to improve fatigue in exercise group (p=0.07) and exercise + placebo group, fluoxetine had no effect on fatigue *Functional work capacity:* **significant effect of exercise on functional work capacity (p=0.03),** fluoxetine had no effect		*Depression:* no significant differences between groups	*General health:* no significant differences between groups	22 drop outs at 3 months, 40 at 6 months. More drop-outs in exercise than control (25/68 v 15/69), no difference in drop-outs between fluoxetine and placebo. 11 dropped out due to side effects, 16 due to lack of efficacy	17

Main results of immunological/ antiviral treatment trials (Table 2)

Three RCTs of participants diagnosed with CFS investigated the effects of immunoglobulin in adults; two found some positive effect, and the third found no effect of treatment. One RCT found greater improvements in the intervention group on symptom scores and functional capacity but not in depression, immune outcomes or quality of life.[39] A second smaller RCT found improved immune measurements (physiological outcome) but not functional or symptom measures.[40] A third RCT, which was the largest in the immunoglobulin category, found no improvement in any of the outcomes investigated (functional status, mood, immune outcomes and quality of life).[41]

Other immunomodulators were investigated in four RCTs, all of which included participants with CFS. Two of these evaluated interferon, one of which suggested some positive effect. In one very small RCT, treatment led to increased physical activity and recovery which remained after 8 months follow-up, however it is not reported whether this was statistically significant.[42] In the other RCT, alpha-interferon led to an improvement in immune measurements (one outcome) but not in quality of life measurements.[43] The effects of ampligen were investigated in one relatively large (n=92) RCT, which found an improvement in functional ability, activity, exercise, cognitive function and work measures but not in depression scores.[44] In the same RCT, elective use of other medications by participants was reported to have increased significantly in the placebo group compared to the intervention group. One RCT assessed the combined effect of leukocyte extract and cognitive behavioural therapy using a factorial design.[24] A significant improvement in general health was reported for the group which received both interventions, compared to the other groups. No beneficial effects were reported for physical and functional capacity, mood or immune outcomes for any of the groups in this study.

The effect of acyclovir, an antiviral, was investigated in one small RCT in those who fulfilled criteria for CFS and additionally had prior infection with Epstein Barr virus confirmed.[45] A significant negative effect was reported for anxiety, depression and confusion with the control group showing a greater improvement in symptoms than the treatment group, but not for the other outcomes investigated (rest, anger, vigour, fatigue, oral temperature and personal well-being). A very small trial of gancyclovir (n=11) found no beneficial effects, and the trial had to be stopped early due to bleeding during invasive investigations.[46] A small trial of inosine pranobex (n=16) found significant improvements in immune function in the treatment group, but no differences between groups for other outcomes (symptoms, cognitive function, global severity, activity).[47]

One RCT of patients with CFS evaluated the antihistamine terfenadine.[48] This study found no differences between the groups for any of the outcomes investigated (functional status and symptoms).

The effects of vaccination with staphylococcus toxoid were investigated in one small controlled trial of patients with CFS[49] and one fairly large RCT.[50] In the controlled trial, no differences were reported in depression, pain or psychological outcomes between the intervention and control group. However, a greater improvement in the clinical global impression in the treatment group was found. In the RCT, the treatment group had a significantly better outcome than the control group for global impression and one item on the fibromyalgia impact questionnaire.

Some severe adverse effects were noted in participants in the immunological intervention groups. Three people had to withdraw from acyclovir treatment due to reversible renal failure[45] and two people from immunoglobulin treatment due to severe constitutional symptom reactions.[41] One recipient of immunoglobulin therapy also withdrew due to mild but transient liver failure[39] and phlebitis has also been noted with immunoglobulin infusions.[39] Transient elevation of serum uric acid was noted in the trial of inosine pranobex.[47] In the RCT of staphylococcus toxoid, 13 patients in the treatment group and 7 in the placebo group experienced side effects.[50] It should be noted that immunoglobulins and leukocyte extract are blood products. There are known risks associated with the use of blood products such as the possible transfer of infectious diseases.

Table 2 Results of immunological treatment trials

Results in bold indicate statistically significant differences between treatment groups (p<0.05)

Intervention		Author (Year), number of participants	Results						
			Resource Use	Physical	Psychological	Physiological	Quality of life and general health	Drop-outs/Adverse effects	Validity score
Antihistamine	Terfenadine	Steinberg (1996)[48] n=30		*Functional*: no significant differences between groups			*Symptoms*: no significant differences between groups	1 participant from each group withdrew due to non-improvement	12
Antiviral	Acyclovir	Straus (1988)[45] n=27		*Rest*: no significant differences between groups	***Mood*: greater improvement in control group for anxiety, depression and confusion (p<0.05).** No difference for anger, vigour or fatigue	*Oral temperature*: no significant differences between groups	*Personal well-being*: no significant differences between groups	3 participants had reversible renal failure during acyclovir infusions and were withdrawn from the study	15
	Gancyclovir	Lerner (2001)[46] n=11		*Symptoms, energy:* no significant differences between groups		*Antibody titres:* no significant differences between groups		2 patients had serious pericardial bleeding during ventricular endomyocardial biopsies. Study was ended prematurely.	1
	Inosine pranobex	Diaz-Mitoma (2003)[47] n=16		*Symptoms, fibromyalgia tender points:* no significant difference between groups	*Cognitive function:* no significant differences between groups	*Immune function:* **significant improvements in treatment group (p<0.03)**	*Global severity, activities of daily living, Karnofsky Performance Scale:* no significant differences between groups	1 withdrawal in each group. Transient elevation of serum uric acid (presumably in treatment group)	6
Immuno-modulators	Immunoglobulin	Lloyd (1990)[39] n=49			*Depression*: no significant differences between groups		***Symptom measure*: greater improvement in treatment group for symptom scores and functional capacity (p=0.03)** *QOL*: no significant differences between groups	2 immunoglobulin recipients withdrew from the study, one because of mild but transient abnormal liver function tests, the other withdrew voluntarily after phlebitis had occurred with the first infusion	13
	Immunoglobulin	Peterson (1990)[40] n=30		*Functional*: no significant differences between groups		***Immune outcomes*: IgG levels of all participants receiving IgG fell within normal range, not observed in placebo group.**	*Symptom measure*: no significant differences between groups	2 participants dropped out due to adverse effects, 1 from each treatment group	15
	Immunoglobulin	Vollmer Conna (1997)[41] n=99		*Functional*: no significant differences between groups	*Mood*: no significant differences between groups	*Immune outcomes*: no significant differences between groups	*QOL*: no significant differences between groups	2 immunoglobulin recipients withdrew from study after severe constitutional reaction to infusion. One participant was withdrawn after developing skin eruption.	13

Intervention		Author (Year), number of participants	Results						
			Resource Use	**Physical**	**Psychological**	**Physiological**	**Quality of life and general health**	**Drop-outs/Adverse effects**	**Validity score**
Immunomodulators (continued)	Interferon	Brook (1993)[42] n=20		*Activity:* 3 participants recovered completely, 2 participants improved in treatment group, none of the participants in the control group recovered significantly. Improvement remained after 8 months follow up**.**				1 participant in the treatment group withdrew after 3 weeks therapy because of increased fatigue, 1 participant in control group decided not to be treated	6
	Alpha interferon	See (1996)[43] n=30				***Immune outcomes*: NK function increased significantly (p<0.05) in treatment group but not in control.** No differences in %NLP, CD4 or CD8 counts	*QOL*: no significant changes in either group	4 participants on interferon treatment withdrew: 2 had neutropenia, one palpitations and one worsened fatigue	11
	Leukocyte extract	Lloyd (1993)[24] n=49		*Physical capacity & functional measure*: no significant differences between groups	*Mood*: no significant differences between groups	*Immune outcomes*: no significant differences between groups	***General health*: group in which DLE combined with CBT showed greater improvement than other intervention groups**	2 participants dropped out, however, no participants dropped out due to adverse effects, although 1 participant developed puritic skin eruption that did not necessitate discontinuation of therapy	13
	Ampligen	Strayer (1994)[44] n=92	***Medication use*: use of 3 classes of drugs & all medications increased 'significantly' in placebo group compared to treatment group (p value not reported)**	***Functional, exercise duration, activity, exercise and work*: greater improvement in treatment group (p<0.04**)	***Cognitive function*: greater improvement in treatment group (p=0.05)** *Depression*: no significant differences between groups			8 participants dropped out, 4 in each group, however no participants dropped out due to adverse effects	12

Vaccine	Staphylococcus toxoid	Andersson (1998)[49] n=28			*Depression and pain*: no significant differences between groups *Psychological assessment*: some improvement in treatment group but no significant differences between groups		***Clinical global impression*: greater improvement in treatment group ($p<0.05$)**	4 participants were excluded, 3 on placebo: 1 because of malignancy, 2 because of severe depression, and 1 on vaccine treatment because of a psychotic reaction	9 (NB controlled trial)
		Zachrisson (2002)[50] n=98		*Global impression, symptoms, pain:* **statistically significant difference in favour of treatment group for CGI ($p<0.001$) and 'feeling good' item on fibromyalgia impact qre.**				10 dropouts during study. 13 patients in the treatment group and 7 in the placebo group experienced side effects.	14

Main results of pharmacological treatment trials (Table 3)

Very few of the RCTs evaluating pharmacological interventions showed a beneficial effect. No benefit was found in patients with CFS from treatment with anticholinergic agents,[51-53] antidepressants (either in treating symptoms of depression or any of the other outcome measures reported)[33, 54, 55] or growth hormone.[56] However some studies reported a positive effect on individual outcomes.

Oral NADH led to a greater improvement in symptoms (the only outcome investigated) in the intervention group compared to the control group in one small RCT,[57] but no significant difference in symptoms in another low quality RCT.[58] A trial of melatonin versus phototherapy found significant improvements in sleep, vitality and mental health, but worsening of bodily pain in the melatonin group.[59]

The effects of steroid treatment were investigated in seven RCTs of participants with CFS. Three of these RCTs evaluated hydrocortisone.[60-62] One found an improvement, of borderline statistical significance, in general health but not in activity, depression, mood or symptom measures.[60] The second smaller RCT found improvements in clinical global impression, fatigue, symptoms and disability, although the improvement in disability was not significant.[61] The third found improvement in fatigue and hormone levels.[62] Two RCTs assessed fludrocortisone, and did not find any association between treatment and the outcomes investigated.[63,64] One RCT of fludrocortisone and hydrocortisone combined found no significant benefit of treatment[65] and a seventh RCT of topical nasal corticosteroids also found no effect of treatment.[66]

One RCT and one controlled trial investigated the effect of monoamine oxidase inhibitors in participants with CFS.[67, 68] The RCT evaluated moclobemide, and found no benefit of treatment.[67] The small controlled trial of selegiline was associated with greater improvement in tension, anxiety and vigour in the intervention group compared to the control group, but not with functional capacity, fatigue, illness severity or symptom measures.[68]

A trial of dexamphetamine found significant improvements in fatigue in the treated group.[69] Reduced food consumption was a side effect in this group.

One very small RCT (n=10) evaluated the effects of the antihypertensive drug clonidine and found no significant effect on cognitive function.[70]

Adverse events serious enough to cause people to withdraw from the study occurred with galanthamine hydrobromide,[51, 52] phenelzine[54], fludrocortisone[64] and fluoxetine.[55]

Table 3 Results of pharmacological treatment trials

Results in boldindicate statistically significant differences between treatment groups (p<0.05)

Intervention		Author (Year), number of participants	Results						
			Resource Use	Physical	Psychological	Physiological	Quality of life and general health	Drop-outs/ Adverse effects	Validity score
Pharmacological									
Anticholinergic	Galanthamine hydrobromide	Snorrason (1996)[51] n=49		*Sleep disturbance, fatigue, myalgia:* no significant differences between groups	*Cognitive function:* no significant differences between groups		*Work capacity/satisfaction:* no significant differences between groups	5 participants, 3 on treatment, 2 on placebo dropped out. 1 participant dropped out due to dizziness, 1 due to headaches. In 30% of participants dosage was reduced due to adverse effects, mainly nausea.	9
	Galantamine hydrobromide	Blacker (2004)[52] n=434		*Global impression, fatigue, symptoms:* no significant differences between groups	*Cognitive function:* no significant difference between groups			130 patients withdrew. 389 patients reported adverse events, of which 88 withdrew	15
	Sulbutiamine	Tiev (1999)[53] n=326		*Fatigue, activity:* no significant differences between groups			*Clinical global impression and illness severity:* no significant differences between groups	16 participants dropped out, 9 on active treatment and 7 on placebo. 1 in each group dropped out because of non-serious side effects	10
Antidepressant	Phenelzine	Natelson (1996)[54] n=24		*Functional and fatigue*: no significant differences between groups	*Mood and depression*: no significant differences between groups		*Illness severity and symptom score*: no significant differences between groups	6 participants, all from active treatment group dropped out, 3 because of side-effects	8
	Fluoxetine	Vercoulen (1996)[55] n=107		*Fatigue*: no significant differences between groups	*Depression*: no significant differences between groups		*Recovery*: no significant differences between groups	15% of treatment group and 4% placebo group dropped out because of side effects including skin reactions, haematoma, nausea, headache. Tremor and perspiration were also reported more frequently in the fluoxetine group.	12

	GET & Fluoxetine	Wearden (1998)[33] n=136		*Fatigue and functional work capacity:* fluoxetine had no effect	*Depression:* no significant differences between treatment groups		*General health:* no significant changes between groups	22 drop outs at 3 months, 40 at 6 months. More drop-outs in exercise than control (25/68 v 15/69), no difference in drop-outs between fluoxetine and placebo. 11 dropped out due to side effects, 16 due to lack of efficacy	17
Hormone	Growth hormone	Moorkens (1998)[56] n=20		*Physical examination*: no significant differences between groups				3 participants withdrew, however no participants dropped out due to adverse effects	5
	Melatonin vs phototherapy	Williams (2002)[59] n=30		*Symptoms, fatigue:* **improved sleep (p=0.03), vitality (p=0.016) and mental health (p=0.046) with melatonin, worsening of bodily pain (p=0.044)**	*Anxiety, depression:* no significant effects of treatment			12 of initial 42 patients withdrew, 10 due to time and social demands of the study	5
Monoamine oxidase	Moclobemide	Hickie (2000)[67] n=90		*Disability:* no significant differences between groups	*Mood:* no significant differences between groups	*Immunologic measures:* no significant differences between groups	*Global improvement:* no significant difference between groups	6 in placebo group and 7 in moclobemide group withdrew, all withdrew due to adverse effects	19
	Selegiline	Natelson (1998)[68] n=25		*Functional measure and fatigue*: no significant differences between groups	***Mood*: tension anxiety & vigour showed greater improvement on treatment (p<0.01)** *Depression*: no significant differences between groups		*Illness severity and symptom measures*: no significant differences between groups	6 participants did not complete the trial, however, no participants dropped out due to adverse effects	11 (NB controlled trial)

Intervention		Author (Year), number of participants	Results						
			Resource Use	**Physical**	**Psychological**	**Physiological**	**Quality of life and general health**	**Drop-outs/Adverse effects**	**Validity score**
NADH	Oral NADH	Forsyth (1999)[57] n=26					***Symptom measure:* greater improvement in treatment group (p<0.05)**	11 participants were withdrawn from the study, however, no participants dropped out due to adverse effects	12
		Santaella (2004)[58] N=20		*Symptoms:* no significant difference between groups				11 dropped out of 31 initially randomised. No adverse events were reported in treatment group	3
Dexamphetamine	dexamphetamine	Olson (2003)[69] n=20		*Fatigue, sleep:* **significant difference in favour of treatment group for fatigue (p<0.02)**			*SF36 scores:* no significant difference between groups	Reduced food consumption reported by 5 patients in treatment group, one in placebo group.	8
Antihypertensive	Clonidine	Morris (2002)[70] n=10			*Cognitive function:* no significant effects			One patient withdrew after GP prescribed fluoxetine.	12
Steroids	Hydrocortisone	McKenzie (1998)[60] n=70	*Activity*: no significant differences between groups	*Depression and Mood*: no significant differences between groups			*General health*: Greater improvement in treatment group, borderline significant differences between the groups (p=0.06) *Symptoms measures:* no significant differences between groups	7 participants withdrew, however, no participants dropped out due to adverse effects	14
	Hydrocortisone	Cleare (1999)[61] n=32	***Fatigue:* greater improvement with treatment (p=0.009)** *Disability:* greater improvement on treatment, no significant improvement overall				***Clinical global impression:* greater number of participants improved on treatment** *Symptom measure:* significant improvement within treatment group (p=0.04) not seen in placebo group (p=0.21), do not report on significance of difference in improvement between groups	3 participants dropped out before treatment started	18
		Cleare (2002)[62] n=120?	*Fatigue:* **'significantly' greater improvement in treatment group (p value not reported)**		*Hormone levels:* greater increase in cortisol response to HCRH in treatment group (significance not reported)				2

	Fludrocortisone	Peterson (1998)[63] n=25		*Functional measure and Exercise and work (treadmill)*: no significant differences between groups	*Mood and cognitive function*: no significant differences between groups		*Symptom measure:* no significant differences between groups	4 participants dropped out of study, 3 on treatment 1 on placebo, due to worsening of symptoms and surgery (1 participant)	16
	Fludrocortisone	Rowe (2001)[64] n=100		*Fatigue, activity*: no significant differences between groups	*Depression, mood:* no significant differences between groups	*Tilt test*: no significant differences between groups	*Global improvement, wellness and general health:* no significant differences between groups	21 participants dropped out, 8 on placebo, 13 on fludrocortisone, most due to adverse effects (in both groups)	18
	Hydrocortisone and fludrocortisone	Blockmans (2003)[65] n=80		*Fatigue:* no significant differences between groups	*Anxiety and depression:* no significant differences between groups	*Blood pressure:* no significant differences between groups	*SF-36, wellbeing:* no significant differences between groups	9 in treatment group and 11 in placebo group dropped out. Only one dropped out due to adverse events	14
	Topical nasal corticosteroids	Kakumanu (2001)[66]		*Fatigue, daytime sleepiness, muscle pain:* no significant improvement with treatment			*Daily activity:* no significant improvement with treatment		3

Main results of alternative medicine treatment trials (Table 4)

Two RCTs assessed the effectiveness of homeopathy.[71, 72] One study reported 'greater improvement' with treatment, but no measurements were presented and so it is difficult to interpret the findings.[71] The authors of the study state that participants were suffering from ME; however, the Oxford criteria for CFS were used to make the diagnosis. This study also scored poorly on the validity assessment (6 out of 20). The other, high quality RCT reported significant improvements in one of five measures of fatigue and on some physical dimensions of the functional limitations profile in the treatment group.[72] No adverse effects were reported in either group.

Massage therapy improved measures of fatigue, pain and sleep, depression and cortisol levels in one small RCT in those diagnosed with chronic fatigue immune deficiency syndrome (CFIDS).[73] Osteopathy also reportedly improved measures of fatigue, back pain and sleep, anxiety and cognitive function and general health in a controlled trial of patients diagnosed with ME. However, the quality of this study was poor (score = 0 out of 20).[74]

Table 4 Results of alternative therapy (homeopathy) treatment trial

Results in bold indicate statistically significant differences between treatment groups (p<0.05)

Intervention	Author (Year), number of participants	Results						
		Resource Use	Physical	Psychological	Physiological	Quality of life and general health	Drop-outs/Adverse effects	Validity score
Alternative								
Homeopathy Any homeopathic remedy	Awdry (1996)[71] n=64					Greater improvement with treatment than in control group (no figures presented)	3 participants dropped out, 2 in homeopathy group, however, no participants dropped out due to adverse effects	6
	Weatherley-Jones (2004)[72] n=103		***Fatigue, functional limitations:*** **significant differences in favour of treatment group for fatigue (p=0.04) and some physical dimensions of the Functional Limitations Profile (p value not reported)**				11 withdrew from treatment arm (5 did not complete treatment) and 8 from placebo arm (6 did not complete treatment)	17
Massage therapy	Field (1997)[73] n=20		***Fatigue, Pain and sleep:*** **greater improvement in intervention group compared to control (p<0.05)**	***Depression:*** **greater improvement in treatment group compared to control(p<0.005)**	*Laboratory measures:* no difference in levels of norepinephrine or epinephrine, **significant decrease in cortisol levels in treatment group (p<0.01)**		Not stated	9
Osteopathy	Perrin (1998)[74] n=58		*Fatigue, back pain, sleep:* greater improvement in intervention group compared to control (p value not reported)	*Depression*: no difference between groups *Anxiety and cognitive function:* greater improvement in treatment group compared to control (p value not reported)		*General health and Nottingham health questionnaire*: greater improvement in treatment group compared to control (p value not reported)	2 drop outs in treatment group, 17 in control, reasons for drop-outs not stated	0 (NB controlled trial)

Main results of supplement treatment trials (Table 5)

Two studies investigated the effect of essential fatty acid supplements. One RCT in patients with CFS found some non-significant improvement as perceived by the participants, as well as non-significant improvements in depression, but not in general symptoms.[75] A slightly larger RCT investigated the effect of essential fatty acid supplements in those diagnosed with post viral fatigue syndrome (PVFS).[31] Improvement (as perceived by the participants) was reported in the intervention group, along with an improvement in symptoms and a greater shift towards normal levels of cell fatty acid concentration.

Magnesium supplements led to improvements in measures of energy and pain, emotional reactions, general health and laboratory measures but not in sleep, physical mobility or social isolation in one small RCT of patients with CFS.[76] One very small RCT assessed the effects of liver extract in patients with CFS but found no difference in outcomes between the intervention and control groups.[77]

General supplements had no effect in two RCTs and one controlled trial of patients with CFS.[78-80] These studies also scored poorly on the validity assessment (6-10 out of 20).

RCTs of pollen extract[81] and medicinal mushrooms[82] reported no significant effects of treatment. A RCT of acclydine and amino acids[83] reported significantly more improvement in IGF-1 levels in the intervention than control group, but no significant difference in global improvement or symptoms. A RCT of acetyl-L-carnitine and propionyl-L-carnitine found significant improvements in fatigue and cognitive function associated with treatment.[84]

Reasons for dropping out of the studies were not well described in the supplement trials, however in the magnesium trial, two participants left the intervention group after experiencing a generalised rash.[76]

Table 5 Results of supplement treatment trials

Results in bold indicate statistically significant differences between treatment groups (p<0.05)

Intervention	Author (Year), number of participants	Results						
		Resource Use	Physical	Psychological	Physiological	Quality of life and general health	Drop-outs/Adverse effects	Validity score
Essential fatty acids (36mg gamma-linoleic acid (GLA), 17mg eicosapentanoic acid (EPA), 11mg docosahexanoic acid (DHA), 255mg linoleic acid (LA), plus 10 IU vitamin E.)	Warren (1999)[75] n=50			*Depression*: trend for treatment group to show greater improvement (p=0.09)		*Symptom measure*: no significant differences between groups *Participant assessment of improvement:* trend for greater improvement in treatment group (p=0.09)	2 in treatment group dropped out before trial started, 5 in each group withdrew during trial, felt that they were not getting any better	16
	Behan (1990)[31] n=63				***Fatty acid concentration:* greater shift towards normal levels in treatment groups (most were statistically significant)**	***Symptom measure*: greater improvement in treatment group (p<0.001) for all 5 symptom groups assessed *Participants assessment of improvement:* greater improvement in treatment group (p<0.0001)**	No drop-outs	17
Magnesium	Cox (1991)[76] n=34		***Energy and pain:* significant improvement in treatment group compared to control (p=0.001)** *Sleep and physical mobility:* no significant differences between groups	***Emotional reactions:* significant improvement in treatment group compared to control (p=0.001)** *Social isolation:* no significant differences between groups	*Laboratory measures:* greater improvement in magnesium concentrations of whole blood and red blood cells in treatment group, no measure of significance presented. After treatment red cell magnesium was in the normal range in all treated participants but only in 1 placebo participant	***General health:* significant improvement in treatment group compared to control (p=0.001)**	2 treatment group participants dropped out, 1 because of generalised rash	15
Liver extract	Kaslow (1989)[77] n=15		*Activity and energy:* no significant differences between groups	*Mental health:* no significant differences between groups		*Symptom measure:* no significant differences between groups	1 participant dropped out as did not return completed questionnaire, although did complete treatment	10

Acetyl-L-carnitine and propionyl-L-carnitine	Vermeulen (2004)[84] n=90		*Global improvement, fatigue, pain:* **significant improvement in general fatigue in PLC (p=0.004) and combined group (p=0.000); significant improvement in mental fatigue in ALC group (p=0.015)**	*Attention, concentration:* **'significant' improvements in all groups**			8 patients withdrew due to side effects and 8 withdrew due to lack of efficacy.	10
Acclydine and amino acids	De Becker (2001)[83] n=90		*Global improvement, symptoms:* improvements seen in intervention group above control group but groups were not compared statistically		*IGF-1 levels:* **significantly more improvement in intervention than placebo group (p<0.0002)**			3 (NB controlled trial)
Pollen extract	Ockerman (2000)[81] n=22		*Fatigue, sleep, symptoms:* comparisons were not made between groups	*Depression:* comparisons were not made between groups	*Erythrocyte fragility:* comparisons were not made between groups		1 withdrawal due to moving away. 'Slight intestinal convenience' was the only side effect for a few days in 1 or 2 patients	9
RM-10: medicinal mushrooms	Rothschild (2002)[82] n=70		*Symptoms:* improved more in the treatment group (measure of significance not presented)				2 dropped out of treatment group, not reported for placebo group.	3
General supplements	Martin (1994)[78] n=42		*Physical:* no significant differences between groups			*General health:* no significant differences between groups	12 participants withdrew before 3 months, further 11 before 6 months, adverse effects not discussed	10 (NB controlled trial)
	Stewart (1987)[80] n=12		*Fatigue:* suggestion of greater improvement in treatment group *Bowel movements and digestion:* increased and improved in treatment groups				2 participants dropped out, adverse effects not discussed	6
	Brouwers (2002)[79] n=53		*Fatigue, symptoms, improvement, functional impairment, activity:* no significant differences between groups				3 dropped out from the supplement group due to nausea, and one in each group for other reasons	10

Main results of other treatment trials (Table 6)

One controlled trial of combination treatment (including CBT) in patients with CFS was also included.[85] A greater number of participants returned to work in the intervention group (the only outcome measured); however, 49 of the 71 original participants were not followed up. This study also scored very poorly on the validity assessment, receiving a score of three out of a possible 20 and so these results should be interpreted with caution.

A controlled trial of 'broad-based management' (mainly information and advice) in people diagnosed with post-infectious fatigue syndrome found significant improvements in the intervention group in measurements of fatigue, somatic symptoms and self-efficacy.[86] Again, a low score on validity assessment (two points out of 20) indicates that these results should be treated with caution.

A very small controlled trial of a buddy/mentor programme found significant improvements in the treatment group compared to control for fatigue severity but not for any of the other six outcomes investigated.[87]

A trial of 'group therapy', which was not well described, found no significant effects of treatment.[88]

An unpublished trial of a low sugar, low yeast diet, compared to healthy eating, also found no significant effect of treatment.[89]

A RCT of multiple symptom-based treatments (including supplements) found significant improvements in favour of the treatment group in symptoms scores, overall response and fibromyalgia-specific symptoms.[90] This trial scored 19 points out of a possible 20 in the validity assessment.

Table 6: Other treatment trials

Results in bold indicate statistically significant differences between treatment groups (p<0.05)

Intervention	Author (Year), number of participants	Results						
		Resource Use	Physical	Psychological	Physiological	Quality of life and general health	Drop-outs/Adverse effects	Validity score
Combination multitreatment	Marlin (1998)[85] n=71					*Employment status*: Greater number of participants returned to work in treatment group (significance not reported)	49/71 were not followed up. The authors do not report on adverse effects	3 (NB controlled trial)
Multitreatment (including supplements)	Teitelbaum (2001)[90]		***Symptoms, response, fibromyalgia impact qre:* significant differences in favour of treatment group (p=0.0002)**				One patient in each group dropped out because of side effects and one in each group for reasons not reported. 24 reported adverse events in treatment group, 22 in placebo group	19
Broad-based management	Goudsmit (1996)[86] n=52			*Uncertainty, self-efficacy:* Improvement in self-efficacy in intervention group compared to control group (p=0.13) *Anxiety and depression:* No significant differences between groups.		***Symptoms:* Significant improvement in intervention groups compared to control group in fatigue (p=0.03) and somatic symptoms (p=0.04).** No significant differences between groups for cognitive difficulty. *Functional impairment:* No significant differences between groups. *Coping:* No significant differences between groups.	Eight excluded from analysis: 3 in intervention group and 5 controls. Two wishes to discontinue treatment: not stated from which group. 9% of intervention group and 18% of controls 'felt worse' at the end of the study.	2 (NB controlled trial)
Buddy/mentor programme	Schlaes (1996)[87] n=12		***Fatigue severity*: greater improvement in treatment group compared to control (p<0.03)**	*Positive thinking, depression, psychological distress, perceived stress, coping strategies, perceived social support:* no significant differences between groups			2 dropped out, one in each group, could not complete post-test measures due to severity of illness.	4 (NB controlled trial)
Group therapy	Soderberg (2001)[88] n=14		***Fatigue:*** results not reported			***Quality of life:*** comparisons were not made between groups	One withdrawal in control group	1
Low sugar low yeast diet	Hobday (2005, unpublished)[89] n=57		***Fatigue:*** no significant differences between groups	*Anxiety, depression:* no significant differences between groups		***General health:*** no significant differences between groups	8 in the LSLY arm and 9 in the control arm were lost to follow-up	11

Severely affected

One RCT assessed participants who had been ill for three years or more, separately from participants who had been ill for less than three years. The study reported no differences in response to fludrocortisone between the two groups.[64] A controlled trial of broad-based management also found no differences in response between those who had been ill for shorter and longer periods of time.[86] In the same study, participants were also grouped according to degree of initial functional impairment, emotional distress, and fatigue. No differences in response were seen in those with a greater degree of initial functional impairment and emotional distress, however those who reported more initial fatigue showed greater improvements in self-efficacy scores ($p=0.04$).[86]

One study of rehabilitation treatment for inpatients found some benefits of treatment.[30] Patients with high fatigue and disability scores were included in an RCT of a general supplement, but no significant treatment effects were seen.[79] The inclusion criteria for the trial of pollen extract state that only relatively serious cases were included.[81]

Very limited numbers of studies considered subgroups of patients. For example, no studies were found that compared the effects of treatment in bed and wheelchair bound patients with those who were less restricted by their illness, or that assessed whether treatment had different effects in those where the diagnosis had been made using criteria for CFS compared with those where the diagnosis had been made using criteria for ME. It was unclear in many trials how severely affected the participants were.

Evidence relating to children

One RCT of immunoglobulin G included only children.[91] A significant improvement in functional score (based on attempts and attendance at school or work and physical or social activities) was reported in the intervention group compared to the control group. Significantly more children in the intervention group had an improvement in score of 25% or more. A second RCT of immunoglobulin included both adults and children according to standard definitions, although no participants under the age of 16 were included.[41] No significant improvements were seen in symptom scores and in functional capacity in the intervention group compared to the control group. The findings from both of these studies have also been presented in the main immunological section. The use of blood products such as immunoglobulin is associated with known risks and so the use of this treatment should be carefully considered.

One controlled trial of rehabilitation/CBT in children reported significant improvements in the treatment group for measures of global wellness.[92] One RCT of CBT in children reported significant improvements in symptoms and attendance at school.[93] In both, the intervention was compared to routine care.

No evaluations of other interventions investigated in children were identified.

Table 7 Treatment trials in children

Results in bold indicate statistically significant differences between treatment groups (p<0.05)

Intervention	Author (Year), number of participants	Results						
		Resource Use	Physical	Psychological	Physiological	Quality of life and general health	Drop-outs/Adverse effects	Validity score
CBT	Stulemeijer (2004)[93] n=69		***Physical functioning, fatigue, symptoms:*** **significant difference in favour of CBT group (p<0.003)**			***School attendance:*** **significant difference in favour of treatment group (p=0.04)**	6 patients dropped out during treatment. 7 were missing from CBT group and 2 from control group at final assessment	16
Modified CBT	Viner (2004)[92]		*CFS severity:* better result in intervention group, significance not reported			*Global wellness, school attendance:* **significantly better in treatment group (p<0.05)**	No withdrawals	2 (NB controlled trial)
Immuno-globulin	Rowe (1997)[91] n=71		***Functional*: greater improvement in number improved and change in functional score in treatment group (p<0.04)**				No participants dropped out due to adverse effects, one participant in the placebo group moved away and so was withdrawn from the study	16

Validity of included studies

Most RCTs scored well on the objectivity and validity of outcomes, blinding of investigators and participants, baseline comparability of groups, completeness of follow-up and appropriate statistical analysis (Appendix 3). RCTs generally scored poorly on the concealment of treatment allocation and many failed to use an intention to treat analysis. Controlled trials scored less well on the objectivity and validity of outcomes and on all other validity criteria. Two of the eight controlled trials in which groups were not comparable at baseline did adjust for baseline differences or confounding factors. Only one of the controlled trials used a sample size calculation.

No one intervention type scored more highly on the validity criteria than any other.

Summary of results

The results of each trial, ranked according to validity score, are presented in Table 8. Where studies presented their findings as within group differences rather than as differences between the intervention and control group, these results are presented but should be treated with caution. The findings from each study should be considered alongside the methodological quality.

Of the 70 included trials 36 (51%) showed some beneficial effect of the intervention and 20 of these (29%) showed an overall beneficial effect, one study reported a negative effect of the intervention. Overall, of those studies that found some beneficial effect of the intervention, three studies (two of immunological interventions and one of supplements) found a benefit for physiological outcome measurements only. Some studies investigated a large number of outcomes - the range across studies was from 1 to 15 - making it possible that any statistically significant differences could have arisen by chance. The results of those studies evaluating multiple outcomes should therefore be treated with caution.

Behavioural

In the behavioural category, cognitive behavioural therapy showed positive results. Four[22 259493] of the five RCTs evaluating CBT found a positive overall effect of the intervention and these studies also scored highly on validity assessment. One RCT which also included immunologic therapy[24] and one RCT[38] and two controlled trials of modified CBT,[27, 92] did not find overall beneficial effects of CBT. These studies also scored lower on the validity assessment, especially one of the controlled trials which scored 1 out of a possible 20. Two studies (one RCT, one controlled trial) of rehabilitation, including CBT, showed a positive overall effect[28, 30] but scored less than 50% on validity assessment. An overall beneficial effect was also found in two controlled trials of two different multi-treatment approaches, one of which included CBT[85] and one of which was based on providing information and advice.[86] However, the methodological quality of both these studies was very poor. A controlled trial of a buddy/mentor programme found a beneficial effect for one of the seven outcomes investigated; this study scored poorly on the validity assessment and only included 12 participants.[87]

Graded exercise therapy (GET) also showed promising results: four of five RCTs found an overall beneficial effect of the intervention compared to the control groups. Two of these RCTs scored highly in the validity assessment, (scoring 17 out of a possible 20).[32, 34]

Immunological

In the immunological category two small RCTs evaluated interferon; one of these found no beneficial effect[42] and the other showed some positive effects although this was in relation to physiological outcomes only.[43] The methodological quality of both these studies was fairly poor; scoring 6 and 11 respectively, out of a possible 20 on the validity assessment. Four RCTs assessed the effects of immunoglobulin in patients with CFS; of these one showed an overall beneficial effect,[91] one showed some positive effects[39], and two found no effect.[40, 41] All four of these RCTs scored reasonably well on the validity assessment, achieving scores of between 13 and 16 out of 20. Immunoglobulin is a blood product and so there is a risk of the possible transfer of, for example, infectious diseases.

One immunological RCT of ampligen found an overall beneficial effect,[44] and a positive effect was found in one small controlled trial of staphylococcus toxoid[49] and one larger RCT.[50] A small RCT of the antihistamine oral terfenadine reported no beneficial effects.[48] These four studies scored between 9 and 14 on the validity assessment.

A small RCT of acyclovir reported a greater improvement in anxiety, depression and confusion in the control group compared to the treatment group, however, no differences in treatment effect were found for the other six outcomes investigated.[45] This study scored 15 out of 20 on the validity assessment. Small RCTs of gancyclovir[46] and inosine pranobex[47] showed no effect of treatment and a positive effect on laboratory outcomes, respectively.

Pharmacological

In the pharmacological category two RCTs of fludrocortisone reported no effect of treatment. These studies were of reasonable quality.[63, 64] Some beneficial effects of hydrocortisone were found in two RCTs.[61, 62] One of these studies scored highly on the validity assessment with a score of 18 out of 20, the other was of poor quality with a validity score of 2. Trials of anti-depressants[53-55, 67] reported no effects of treatment either on symptoms of depression or on any of the other outcome measures reported.

One poor quality RCT showed an overall beneficial effect of oral NADH[57] and another of lower quality showed no effect.[58] A poor quality RCT of melatonin[59] reported an overall positive effect of treatment. One controlled trial of selegiline reported some positive effects of treatment but found no overall effect.[68]

Alternative / complementary

Homeopathic therapies were evaluated in two RCTs, one of poor quality[71] and one of good quality.[72] Some positive effects of homeopathy were seen in the better quality trial. One controlled trial of osteopathy found some non-significant improvements in the intervention group, but the values were estimated from graphs and so the results may not be entirely accurate.[74] This study scored very poorly on the validity assessment, scoring 0. A poor quality study of massage therapy found an overall positive effect.[73]

Supplements

In the supplements category one good quality RCT of essential fatty acids reported no beneficial effects of the intervention[75] and one found an overall beneficial effect.[31] Magnesium supplements were found to have an overall beneficial effect in the one good quality RCT where these were evaluated, but this result has never been replicated.[76] Three fairly poor quality trials evaluated general supplements, but none found a positive effect.[78-80] Poor quality RCTs of liver extract,[77] pollen extract[81] and medicinal mushrooms[82] also reported no beneficial effects.

A poor quality RCT of acetyl-L-carnitine[84] reported overall beneficial effects, and a poor quality trial of acclydine and amino acids reported beneficial effects in physiological measures.[83]

Other

Two controlled trials[85, 86] and one high quality RCT[90] of combined treatments showed mixed results, only the RCT reporting overall beneficial effects of treatment. A small controlled trial of a buddy/ mentor programme showed some positive effects.[87]

It must be noted for most of the interventions the results are based on one or two studies, which may limit the generalisability of the findings. Another factor which may limit the applicability of the findings is the inclusion criteria specified in some trials. For example, in some studies participants were only eligible if they could physically get to the clinic, which implies a certain level of fitness. Those people who were unable to walk or to get out of bed were automatically excluded and so it is not possible to assess whether the interventions investigated would be effective, ineffective or even hazardous for a more severely disabled group of people. However, in many of the trials very limited information was given about participants who were ineligible or indeed about the baseline functioning on many of those who were included. Therefore, it is difficult to extrapolate how the findings might transfer to other people with CFS and/or ME.

Table 8: Summary of study results

Treatment	Number of patients	Outcomes investigated	Any effect	Overall effect	Validity score (Maximum 20)
BEHAVIOURAL					
CBT[22]	60	**PH**; PS; **QOL**	+	+	18
GET & Fluoxetine[33]	136	**PH;** PS; QOL	+	<>	17
GET[32]	66	**PH**; PS; **LAB; QOL**	+	+	17
GET[34, 37]	148	**PH;** PS**; QOL**	+	+	17
CBT[26]	270	**PH; PS; QOL**	+	+	16
CBT[25]	60	**PH**; PS; **QOL**	+	+	15
CBT[93]	69	**PH; QOL**	+	+	16
CBT + DLE[24]	90	PH; PS; LAB; **QOL**	+	<>	13
GET[35]	49	**PH**	+	+	9
GET[36]	61	**PS; PH:** LAB	+	+	9
Rehab[28]	47	**PH; QOL**	+	+	9
CBT/ rehab[30]	130	**PH; PS; QOL**	+	+	8
CBT/ rehab[29]	97	PH; PS; **QOL**	+	<>	7
CBT[38]	65	PH; PS;QOL	<>	<>	3
CBT[92]	56	PH; **QOL**	+	<>	2
CBT[27]	44	PH; PS; QOL	<>	<>	1
IMMUNOLOGICAL					
Immunoglobulin [91]	71	**PH**	+	+	16
Immunoglobulin [40]	30	PH; LAB; QOL	<>	<>	15
Acyclovir[45]	27	PH; **PS**; LAB; QOL	–	<>	15
Staphylococcus toxoid[50]	98	**PH**	+	+	14
Immunoglobulin[39]	49	PS; **QOL**	+	<>	13
Immunoglobulin[41]	99	PH; PS; LAB; QOL	<>	<>	13
Ampligen[44]	92	**RU; PH; PS**	+	+	12
Terfenadine[48]	30	PH; QOL	<>	<>	12
Alpha interferon[43]	30	**LAB**; QOL	+	<>	11
Gancyclovir[46]	11	PH	<>	<>	?
Staphylococcus toxoid[49]	28	PS; **QOL**	+	<>	9
Inosine pranobex[47]	16	PH; **LAB;** QOL	+	<>	6
Interferon[42]	20	PH	<>	<>	6
PHARMACOLOGICAL					
Moclobemide[67]	90	PH; PS; LAB; QOL	<>	<>	19
Hydrocortisone[61]	32	**PH;** QOL	+	<>	18
Fludrocortisone[64]	100	PH; PS; LAB; QOL	<>	<>	18
Fludrocortisone[63]	25	PH; PS; QOL	<>	<>	16
Galantamine hydrobromide[52]	434	PH; PS	<>	<>	15
Hydrocortisone and fludrocortisone[65]	80	PH; PS; LAB; QOL	<>	<>	14
Hydrocortisone[60]	70	PH; PS; QOL	<>	<>	14
Clonidine[70]	10	PS	<>	<>	12
Oral NADH[57]	26	**QOL**	+	+	12
Fluoxetine[55]	107	PH; PS; QOL	<>	<>	12
Selegiline[68]	25	PH; **PS**; QOL	+	<>	11
Phenelzine[54]	24	PH; PS; QOL	<>	<>	10
Sulbutiamine[53]	326	PH; QOL	<>	<>	10
Galanthamine hydrobromide[51]	49	PH; PS; QOL	<>	<>	9
Dexamphetamine[69]	20	**PH**; QOL	+	<>	8
Growth hormone[56]	20	PH	<>	<>	5
Melatonin[59]	30	**PH; PS**	+	+	5
Topical nasal corticosteroids[66]	28	PH	<>	<>	3
Oral NADH[58]	20	PH	<>	<>	3
Hydrocortisone[62]	120	**PH**; LAB	+	<>	2
COMPLEMENTARY/ ALTERNATIVE					
Homeopathy[72]	103	**PH**	+	<>	17
Massage therapy[73]	20	**PH; PS; LAB**	+	+	9
Any homeopathic remedy[71]	64	QOL	<>	<>	6
Osteopathy[74]	58	PH; PS; QOL	<>	<>	0
SUPPLEMENTS					
Essential fatty acids*[31]	63	**LAB; QOL**	+	+	17
Essential fatty acids*[75]	50	PS; QOL	<>	<>	16
Magnesium[76]	34	**PH; PS;** LAB**; QOL**	+	+	15
Liver extract[77]	15	PH; PS; QOL	<>	<>	10
Acetyl-L-carnitine and propionyl-L-carnitine[84]	90	**PH; PS**	+	+	10
General supplements[79]	53	PH	<>	<>	10

General supplements[78]	42	PH; QOL	<>	<>	10
Pollen extract[81]	22	PH; PS; QOL; LAB	<>	<>	9
General supplements[80]	12	PH	<>	<>	6
Acclydine and amino acids[83]	90	PH; **LAB**	+	<>	3
Medicinal mushrooms[82]	70	PH	<>	<>	3
OTHER					
Combination[90]	72	**PH**	+	+	19
Low sugar low yeast diet[89]	57	PH; PS	<>	<>	11
Buddy/ mentor[87]	12	**PH**; PS; QOL	+	<>	4
Combination[85]	71	QOL	<>	<>	3
Combination[86]	52	PS**; QOL**	+	<>	2
Group therapy[88]	14	PH; QOL	<>	<>	1

+ indicates a positive effect of treatment; – indicates a negative effect of treatment; <> indicates no effect of treatment

*Essential fatty acids (both studies) = 36mg gamma-linoleic acid (GLA), 17mg eicosapentanoic acid (EPA), 11mg docosahexanoic acid (DHA), 255mg linoleic acid (LA), plus 10 IU vitamin E.

† For studies in which the duration of intervention was different from the duration of follow-up, the duration of intervention in shown in brackets

Outcome codes: RU = resource use; PH = physical; PS = psychological; LAB = laboratory and physiological; QOL = quality of life and general health. Outcomes which showed a significant difference between intervention and control groups are highlighted in bold

Controlled studies are shaded in the table, all other studies are RCTs.

DISCUSSION

Methodological quality of included studies

There are now a considerable number of studies evaluating interventions for the treatment and management of CFS/ME and many of them have used robust research methods; the majority of the included studies were RCTs and many of these were of high methodological quality (Table 8). However, RCTs generally scored poorly for concealment of treatment allocation and many failed to use an intention-to-treat analysis. These issues should be addressed in designing future clinical trials of interventions for CFS/ME.

Outcomes

A fundamental problem in evaluating interventions for CFS/ME is that the wide variety of outcome measures used in the included studies makes it difficult to compare the effects of interventions across studies. Even when studies evaluated the same outcome, they used a variety of scales and measures to do so. This heterogeneity made it impossible to combine studies by meta-analysis. We have summarised our results (Table 8) in a way designed to convey as much information as possible in a relatively small space, but this presentation has limitations. Achievement of statistically significant differences between groups may be influenced by sample size and results may be statistically but not clinically significant. Our measure of 'overall effect' represents an attempt to deal with this issue by showing which studies reported a statistically significant treatment effect on two or more clinical outcomes.

Interventions

Although we have discussed all the studies evaluating a particular intervention together, the treatment offered to patients receiving a particular type of therapy in practice may vary considerably, particularly for behavioural interventions. For example, in the CBT study by Stulemeijer et al.[93], participants in the intervention group received ten individual therapy sessions over 5 months in a hospital child psychology department, whereas in the study by Whitehead et al.[95] the intervention was a form of 'brief CBT' delivered by general practitioners. Further standardisation of methods for delivering behavioural interventions in research and practice would be desirable.

Participants in included studies and diagnostic criteria

The studies included in our review also show a lack of uniformity in terms of case definitions for CFS/ME, study inclusion and exclusion criteria and the basic information provided about the participants. For example, baseline functional status and duration of illness are not always reported. This makes it difficult to assess the generalisability of the findings of many of these studies.

Withdrawals and drop-outs

Some studies of behavioural interventions have reported significant rates of withdrawal from treatment or loss to follow-up, as high as 20–40% in some studies[9596]. This update did not find any new evidence of adverse effects (sufficient to cause withdrawal from treatment) associated with GET or CBT. However, reasons for withdrawals were often poorly reported and should be investigated in more detail in future studies. The new studies included in the update confirmed previous reports of withdrawals because of adverse events associated with immunological/antiviral and pharmacological interventions.

Duration of follow-up

There remains a lack of long-term follow-up data for most interventions, although a 5-year follow-up of the RCT of CBT by Deale and colleagues showed maintained benefit of the intervention for several outcomes[23] and a 2-year follow-up of one RCT of GET was published in 2004.[34]

Children

The pre-specified subgroups investigated in this update were children and adolescents and those severely affected by CFS/ME. Guidelines for the management of CFS/ME were published by the Royal College of Paediatrics and Child Health in 2004.[97] The recommendations were largely developed by consensus because of a lack of specific evidence for this age group. GET and CBT were recommended for consideration based on extrapolation from studies in adults. The effectiveness of CBT for adolescents is supported by a recent high-quality RCT,[93] although this had only 69 participants.

Patients with severe CFS/ME

There remains a lack of studies evaluating the effectiveness of interventions for patients severely affected by CFS/ME. The protocols for many clinical studies require patients to attend a clinic for treatment and/or assessment. These conditions may exclude people severely affected with CFS/ME from taking part. The balance between effectiveness and adverse effects of interventions may be different in more severely affected compared with less severely affected patients and methods of delivery/doses may need to be different. Research to evaluate the effectiveness of interventions for severely affected patients should be considered a priority.

Combination therapy

No new studies of combination therapy were added to the updated review. Given that it is likely that many patients with CFS/ME have tried a number of different interventions, this remains a notable gap in the research literature.

CONCLUSIONS

- A total of 70 trials investigated the effectiveness of seven different categories of intervention: behavioural, immunological, antiviral, pharmacological, supplements, complementary/ alternative and other.

- Overall the interventions demonstrated mixed results in terms of effectiveness. All conclusions about effectiveness should be considered together with the methodological inadequacies in some of the studies.

- Interventions which have shown evidence of effectiveness include CBT and GET.

- There is insufficient evidence about how sub-groups of patients may respond differently to treatments and further studies investigating additional subgroups are needed.

- In some of the included studies bed or wheelchair restricted patients and children have been excluded, which raises questions about the applicability of findings to all people with CFS/ME.

- CBT and immunoglobulin G are the only interventions which have been investigated in young people.

- There is insufficient evidence for additive or combined effects of interventions where more than one therapy is used.

- Future research could usefully compare CBT and GET and there is a need to evaluate the effectiveness of pacing, ideally in comparison to CBT and GET.

- Future research needs to combine scientific rigour with patient acceptability.

- The large number of outcome measures used makes standardisation of outcomes a priority for future research.

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APPENDIX 1: LITERATURE SEARCH STRATEGIES

The following databases were searched, no limits were imposed. The results were then imported to individual Endnote libraries for appraising.

Database	Date searched	Number of hits
AMED	24/08/05	1281
Cochrane Library CENTRAL	09/05/05	4666
Embase	25/04/05	2513
HEED	01/06/05	0
Inside Conferences	11/05/05	203
Medline	25/04/05	6318
Medline (economic searches)	01/06/05	61
NHSEED	01/06/05	0
PASCAL	11/05/05	1065
PsycINFO	26/04/05	1195
SSCI	26/04/05	1279

AMED (1985 – April 2005), Ovid
Searched 26/04/05

1 Fatigue Syndrome, Chronic/
2 chronic fatigue syndrome.ti,ab.
3 myalgic encephalomyelitis.ti,ab.
4 akureyri disease$.ti,ab.
5 chronic epstein barr virus.ti,ab.
6 cfids.ti,ab.
7 (chronic fatigue and immune dysfunction syndrome$).ti,ab.
8 chronic mononucleosis.ti,ab.
9 effort syndrome$.ti,ab.
10 iceland$ disease$.ti,ab.
11 low natural killer cell syndrome$.ti,ab.
12 neuromyasthenia.ti,ab.
13 post viral fatigue syndrome$.ti,ab.
14 postviral fatigue syndrome$.ti,ab.
15 post viral syndrome$.ti,ab.
16 postviral syndrome$.ti,ab.
17 post infectious fatigue.ti,ab.
18 postinfectious fatigue.ti,ab.
19 raggedy ann$ syndrome$.ti,ab.
20 royal free disease$.ti,ab.
21 royal free epidemic$.ti,ab.
22 royal free hospital disease$.ti,ab.
23 tapanui disease$.ti,ab.
24 yuppie flu.ti,ab.
25 yuppy flu.ti,ab.
26 chronic infectious mononucleosis like syndrome$.ti,ab.
27 ME.ti.
28 CFS.ti,ab.
29 myalgic encephalopathy.ti,ab.
30 or/1-29

1281 records were retrieved.

Cochrane Library, CENTRAL, (2005 Issue2) http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME
Searched 09/05/05
1 MeSH descriptor Fatigue Syndrome, Chronic explode all trees in MeSH products
#2 "myalgic encephalomyelitis" in Record Title or "myalgic encephalomyelitis" in Abstract
#3 chronic fatigue syndrome in Record Title or chronic fatigue syndrome in Abstract
#4 biography in Publication Type
#5 duplicate-publication in Publication Type
#6 historical-article in Publication Type
#7 interview in Publication Type
#8 retraction-of-publication in Publication Type
#9 cases in Publication Type
#10 (#1 OR #2 OR #3)
#11 (#4 OR #5 OR #6 OR #7 OR #8 OR #9)
#12 (#10 AND NOT #11)
#13 "akureyri disease*" in Record Title or "akureyri disease*" in Abstract
#14 "chronic epstein barr virus" in Record Title or "chronic epstein barr virus" in Abstract
#15 "cfids" in Record Title or "cfids" in Abstract
#16 (chronic fatigue and immune dysfunction syndrome*) in Record Title or (chronic fatigue and immune dysfunction syndrome*) in Abstract
#17 (chronic mononucleosis) in Record Title or (chronic mononucleosis) in Abstract
#18 "effort syndrome*" in Record Title or "effort syndrome*" in Abstract
#19 (iceland* next disease*) in Record Title or (iceland* next disease*) in Abstract
#20 (low next natural next killer next cell next syndrome*) in Record Title or (low next natural next killer next cell next syndrome*) in Abstract
#21 neuromyasthenia in Record Title or neuromyasthenia in Abstract
#22 (post next viral next fatigue next syndrome) in Record Title or (post next viral next fatigue next syndrome) in Abstract
#23 (postviral next fatigue next syndrome*) in Record Title or (postviral next fatigue next syndrome*) in Abstract
#24 (post next viral next syndrome*) in Record Title or (post next viral next syndrome*) in Abstract
#25 (postviral next syndrome*) in Record Title or (postviral next syndrome*) in Abstract
#26 (post next infectious next fatigue) in Record Title or (post next infectious next fatigue) in Abstract,
#27 (postinfectious next fatigue) in Record Title or (postinfectious next fatigue) in Abstract
#28 (raggedy next ann* next syndrome*) in Record Title or (raggedy next ann* next syndrome*) in Abstract
#29 (royal next free next disease*) in Record Title or (royal next free next disease*) in Abstract
#30 (royal next free next epidemic*) in Record Title or (royal next free next epidemic*) in Abstract
#31 (royal next free next hospital next disease*) in Record Title or (royal next free next hospital next disease*) in Abstract
#32 (tapanui next disease*) in Record Title or (tapanui next disease*) in Abstract
#33 "yuppie flu" in Record Title or "yuppie flu" in Abstract
#34 "yuppy flu" in Record Title or "yuppy flu" in Abstract
#35 (chronic next infectious next mononucleosis next like next syndrome*) in Record Title or (chronic next infectious next mononucleosis next like next syndrome*) in Abstract
#36 (ME) in Record Title
#37 (CFS) in Record Title or (CFS) in Abstract
#38 (myalgic next encephalopathy) in Record Title or (myalgic next encephalopathy) in Abstract
#39 (#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)
#40 (#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38)
#41 (#39 OR #40)
#42 (#41 AND NOT #11)
#43 (#42 OR #12)
4,666 records were retrieved

Embase (1980 – 2005 Week 17), Ovid
Searched 25/04/05

1 Fatigue Syndrome, Chronic/
2 chronic fatigue syndrome.ti,ab.
3 myalgic encephalomyelitis.ti,ab.
4 akureyri disease$.ti,ab.
5 chronic epstein barr virus.ti,ab.
6 cfids.ti,ab.
7 (chronic fatigue and immune dysfunction syndrome$).ti,ab.
8 chronic mononucleosis.ti,ab.
9 effort syndrome$.ti,ab.
10 iceland$ disease$.ti,ab.
11 low natural killer cell syndrome$.ti,ab.
12 neuromyasthenia.ti,ab.
13 post viral fatigue syndrome$.ti,ab.
14 postviral fatigue syndrome$.ti,ab.
15 post viral syndrome$.ti,ab.
16 postviral syndrome$.ti,ab.
17 post infectious fatigue.ti,ab.
18 postinfectious fatigue.ti,ab.
19 raggedy ann$ syndrome$.ti,ab.
20 royal free disease$.ti,ab.
21 royal free epidemic$.ti,ab.
22 royal free hospital disease$.ti,ab.
23 tapanui disease$.ti,ab.
24 yuppie flu.ti,ab.
25 yuppy flu.ti,ab.
26 chronic infectious mononucleosis like syndrome$.ti,ab.
27 ME.ti.
28 CFS.ti,ab.
29 myalgic encephalopathy.ti,ab.
30 or/1-29

5213 records were retrieved

HEED (June 2005)
Searched 01/06/05

TI=chronic fatigue syndrome
AB=chronic fatigue syndrome
TI=myalgic encephalomyelitis
AB=myalgic encephalomyelitis
TI=akureyri disease*
AB=akureyri disease*
TI=chronic epstein barr virus
AB=chronic epstein barr virus
TI=CFIDS
AB=CFIDS
CS=1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or10
TI=(chronic fatigue and immune dysfunction syndrome*)
AB=(chronic fatigue and immune dysfunction syndrome*)
TI=chronic mononucleosis
AB=chronic mononucleosis
TI=effort syndrome*
AB=effort syndrome*
TI=iceland* disease*
AB=iceland* disease*
TI=low natural killer cell syndrome*
AB=low natural killer cell syndrome*
CS=12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
CS=11 or 22
TI=neuromyasthenia

AB=neuromyasthenia
TI=post viral fatigue syndrome*
AB=post viral fatigue syndrome*
TI=postviral fatigue syndrome*
AB=postviral fatigue syndrome*
TI=post viral syndrome*
AB=post viral syndrome*
TI=postviral syndrome*
AB=postviral syndrome*
TI=post infectious fatigue
AB=post infectious fatigue
TI=postinfectious fatigue
AB=postinfectious fatigue
TI=raggedy ann* syndrome*
AB=raggedy ann* syndrome*
TI=royal free disease*
AB=royal free disease*
CS=24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
CS=46 or 23
TI=royal free epidemic*
AB=royal free epidemic*
TI=royal free hospital disease*
AB=royal free hospital disease*
TI=tapanui disease*
AB=tapanui disease*
TI=yuppie flu
AB=yuppie flu
TI=yuppy flu
AB=yuppy flu
TI=chronic infectious mononucleosis like syndrome*
AB=chronic infectious mononucleosis like syndrome*
TI=CFS
TI=myalgic encephalopathy
AB=myalgic encephalopathy
CS=48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58
CS=59 or 47
0 records were retrieved

Inside Conferences, Dialog
Searched 11/05/05
1 (CHRONIC(W)FATIGUE(W)SYNDROME)/TI,AB
2 (MYALGIC(W)ENCEPHALOMYELITIS)/TI,AB
3 (AKUREYRI(W)DISEASE?)/TI,AB
4 (CHRONIC(W)EPSTEIN(W)BARR(W)VIRUS)/TI,AB
5 CFIDS/TI,AB
6 (CHRONIC(W)FATIGUE(3W)IMMUNE(W)DYSFUNCTION(W)SYNDROME?)/TI,AB
7 (CHRONIC(W)MONONUCLEOSIS)/TI,AB
8 (EFFORT(W)SYNDROME?)/TI,AB
9 (ICELAND?(W)DISEASE?)/TI,AB
10 (LOW(W)NATURAL(W)KILLER(W)CELL(W)SYNDROME?)/TI,AB
11 NEUROMYASTHENIA/TI,AB
12 (POST(W)VIRAL(W)FATIGUE(W)SYNDROME?)/TI,AB
13 (POSTVIRAL(W)FATIGUE(W)SYNDROME?)/TI,AB
14 (POST(W)VIRAL(W)SYNDROME?)/TI,AB
15 (POSTVIRAL(W)SYNDROME?)/TI,AB
16 (POST(W)INFECTIOUS(W)FATIGUE)/TI,AB
17 (POSTINFECTIOUS(W)FATIGUE)/TI,AB
18 (RAGGEDY(W)ANN? (W)SYNDROME?)/TI,AB
19 (ROYAL(W)FREE(W)DISEASE?)/TI,AB

20 (ROYAL(W)FREE(W)EPIDEMIC?)/TI,AB
21 (ROYAL(W)FREE(W)HOSPITAL(W)DISEASE?)/TI,AB
22 (TAPANUI(W)DISEASE?)/TI,AB
23 (YUPPIE(W)FLU)/TI,AB
24 YUPPY(W)FLU)/TI,AB
25 (CHRONIC(W)INFECTIOUS(W)MONONUCLEOSIS(W)LIKE(W)SYNDROME?)/TI,AB
26 (MYALGIC(W)ENCEPHALOPATHY)/TI,AB
27 S1:S26
28 RD S27
203 records were retrieved

Medline (1966 – April Week 2 2005), Ovid
Searched 25/04/05

1 Fatigue Syndrome, Chronic/
2 chronic fatigue syndrome.ti,ab.
3 myalgic encephalomyelitis.ti,ab.
4 or/1-3
5 biography.pt.
6 duplicate-publication.pt.
7 historical-article.pt.
8 interview.pt.
9 retraction-of-publication.pt.
10 cases.pt.
11 or/5-10
12 4 not 11
13 akureyri disease$.ti,ab.
14 chronic epstein barr virus.ti,ab.
15 cfids.ti,ab.
16 (chronic fatigue and immune dysfunction syndrome$).ti,ab.
17 chronic mononucleosis.ti,ab.
18 effort syndrome$.ti,ab.
19 iceland$ disease$.ti,ab.
20 low natural killer cell syndrome$.ti,ab.
21 neuromyasthenia.ti,ab.
22 post viral fatigue syndrome$.ti,ab.
23 postviral fatigue syndrome$.ti,ab.
24 post viral syndrome$.ti,ab.
25 postviral syndrome$.ti,ab.
26 post infectious fatigue.ti,ab.
27 postinfectious fatigue.ti,ab.
28 raggedy ann$ syndrome$.ti,ab.
29 royal free disease$.ti,ab.
30 royal free epidemic$.ti,ab.
31 royal free hospital disease$.ti,ab.
32 tapanui disease$.ti,ab.
33 yuppie flu.ti,ab.
34 yuppy flu.ti,ab.
35 chronic infectious mononucleosis like syndrome$.ti,ab.
36 ME.ti.
37 CFS.ti,ab.
38 myalgic encephalopathy.ti,ab.
39 or/13-38
40 4 or 39
41 40 not 11
6318 records were retrieved.

Medline (1966 – Week 3 May 2005), Ovid
Searched 01/06/05
Economic searches

1 Fatigue Syndrome, Chronic/
2 chronic fatigue syndrome.ti,ab.
3 myalgic encephalomyelitis.ti,ab.
4 or/1-3
5 biography.pt.
6 duplicate-publication.pt.
7 historical-article.pt.
8 interview.pt.
9 retraction-of-publication.pt.
10 cases.pt.
11 or/5-10
12 4 not 11
13 akureyri disease$.ti,ab.
14 chronic epstein barr virus.ti,ab.
15 cfids.ti,ab.
16 (chronic fatigue and immune dysfunction syndrome$).ti,ab.
17 chronic mononucleosis.ti,ab.
18 effort syndrome$.ti,ab.
19 iceland$ disease$.ti,ab.
20 low natural killer cell syndrome$.ti,ab.
21 neuromyasthenia.ti,ab.
22 post viral fatigue syndrome$.ti,ab.
23 postviral fatigue syndrome$.ti,ab.
24 post viral syndrome$.ti,ab.
25 postviral syndrome$.ti,ab.
26 post infectious fatigue.ti,ab.
27 postinfectious fatigue.ti,ab.
28 raggedy ann$ syndrome$.ti,ab.
29 royal free disease$.ti,ab.
30 royal free epidemic$.ti,ab.
31 royal free hospital disease$.ti,ab.
32 tapanui disease$.ti,ab.
33 yuppie flu.ti,ab.
34 yuppy flu.ti,ab.
35 chronic infectious mononucleosis like syndrome$.ti,ab.
36 CFS.ti,ab.
37 myalgic encephalopathy.ti,ab.
38 economics/
39 exp "COSTS AND COST ANALYSIS"/
40 economics,dental/
41 "VALUE OF LIFE"/
42 exp ECONOMICS, HOSPITAL/
43 economics, medical/
44 economics, nursing/
45 economics, pharmaceutical/
46 or/38-45
47 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).tw.
48 (expenditure$ not energy).tw.
49 (value adj1 money).tw.
50 budget$.tw.
51 or/47-50
52 46 or 51
53 letter.pt.
54 editorial.pt.
55 historical article.pt.
56 or/53-55

57 52 not 56
58 animal/
59 Humans/
60 58 not (58 and 59)
61 57 not 60
62 (metabolic adj cost).ti,ab,sh.
63 ((energy or oxygen) adj cost).ti,ab,sh.
64 61 not (62 or 63)
65 or/12-37
66 64 and 65
61 records were retrieved.

NHSEED (1995 -2005), Cairs B
Searched 01/06/05
s chronic w fatigue w syndrome
s myalgic w encephalomyelitis
s akureyri w disease*
s chronic w epstein w barr w virus
s CFIDS
s (chronic w fatigue) and (immune w dysfunction w syndrome*)
s chronic w mononucleosis
s effort w syndrome*
s iceland* w disease*
s low w natural w killer w cell w syndrome*
s neuromyasthenia
s post w viral w fatigue w syndrome*
s postviral w fatigue w syndrome*
s post w viral w syndrome*
s postviral w syndrome*
s post w infectious w fatigue
s postinfectious w fatigue
s raggedy w ann* w syndrome*
s royal w free w disease*
s royal w free w epidemic*
s royal w free w hospital w disease*
s tapanui w disease*
s yuppie w flu
s yuppy w flu
s chronic w infectious w mononucleosis w like w syndrome*
s CFS
s myalgic w encephalopathy
s 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 29 or 21 or 22 or 23 or 24 or 25 or 26 or 27
0 records were retrieved.

PASCAL, Dialog
Searched 11/05/05
1 (CHRONIC(W)FATIGUE(W)SYNDROME)/TI,AB
2 (MYALGIC(W)ENCEPHALOMYELITIS)/TI,AB
3 (AKUREYRI(W)DISEASE?)/TI,AB
4 (CHRONIC(W)EPSTEIN(W)BARR(W)VIRUS)/TI,AB
5 CFIDS/TI,AB
6 (CHRONIC(W)FATIGUE(3W)IMMUNE(W)DYSFUNCTION(W)SYNDROME?)/TI,AB
7 (CHRONIC(W)MONONUCLEOSIS)/TI,AB
8 (EFFORT(W)SYNDROME?)/TI,AB
9 (ICELAND?(W)DISEASE?)/TI,AB
10 (LOW(W)NATURAL(W)KILLER(W)CELL(W)SYNDROME?)/TI,AB
11 NEUROMYASTHENIA/TI,AB
12 (POST(W)VIRAL(W)FATIGUE(W)SYNDROME?)/TI,AB
13 (POSTVIRAL(W)FATIGUE(W)SYNDROME?)/TI,AB

14 (POST(W)VIRAL(W)SYNDROME?)/TI,AB
15 (POSTVIRAL(W)SYNDROME?)/TI,AB
16 (POST(W)INFECTIOUS(W)FATIGUE)/TI,AB
17 (POSTINFECTIOUS(W)FATIGUE)/TI,AB
18 (RAGGEDY(W)ANN? (W)SYNDROME?)/TI,AB
19 (ROYAL(W)FREE(W)DISEASE?)/TI,AB
20 (ROYAL(W)FREE(W)EPIDEMIC?)/TI,AB
21 (ROYAL(W)FREE(W)HOSPITAL(W)DISEASE?)/TI,AB
22 (TAPANUI(W)DISEASE?)/TI,AB
23 (YUPPIE(W)FLU)/TI,AB
24 YUPPY(W)FLU)/TI,AB
25 (CHRONIC(W)INFECTIOUS(W)MONONUCLEOSIS(W)LIKE(W)SYNDROME?)/TI,AB
26 (MYALGIC(W)ENCEPHALOPATHY)/TI,AB
27 S1:S26
28 RD S27
1065 records were retrieved.

PsycINFO (1872 – 2005/04 Week 2), WebSPIRS
Searched 26/04/05
#33 #30 or #31 or #32
#32 #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29
#31 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
#30 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#29 ((myalgic encephalopathy)in AB) or ((myalgic encephalopathy)in TI)
#28 ((CFS)in AB) or ((CFS)in TI)
#27 ((chronic infectious mononucleosis like syndrome*)in AB) or ((chronic infectious mononucleosis like syndrome*)in TI)
#26 ((yuppy flu)in AB) or ((yuppy flu)in TI)
#25 ((yuppie flu)in AB) or ((yuppie flu)in TI)
#24 ((tapanui disease*)in AB) or ((tapanui disease*)in TI)
#23 ((royal free hospital disease*)in AB) or ((royal free hospital disease*)in TI)
#22 ((royal free epidemic*)in AB) or ((royal free epidemic*)in TI)
#21 ((royal free disease*) in AB) or ((royal free disease*)in TI)
#20 ((raggedy ann* syndrome*) in AB) or ((raggedy ann* syndrome*) in TI)
#19 ((postinfectious fatigue)in AB) or ((postinfectious fatigue)in TI)
#18 ((post infectious fatigue)in AB) or ((post infectious fatigue)in TI)
#17 ((post viral syndrome*)in AB) or ((post viral syndrome*)in TI)
#16 ((postviral syndrome*)in AB) or ((postviral syndrome*)in TI)
#15 ((postviral fatigue syndrome*)in AB) or ((postviral fatigue syndrome*)in TI)
#14 ((post viral fatigue syndrome*)in AB) or ((post viral fatigue syndrome*)in TI)
#13 ((neuromyasthenia)in AB) or ((neuromyasthenia)in TI)
#12 ((low natural killer cell syndrome*)in AB) or ((low natural killer cell syndrome*)in TI)
#11 ((iceland* disease*) in AB) or ((iceland* disease*) in TI)
#10 ((effort syndrome*) in AB) or ((effort syndrome*) in TI)
#9 ((chronic mononucleosis) in AB) or ((chronic mononucleosis) in TI)
#8 ((chronic fatigue and immune dysfunction syndrome*) in AB) or ((chronic fatigue and immune dysfunction syndrome*) in TI)
#7 ((cfids)in AB) or ((cfids)in TI)
#6 ((chronic epstein barr virus) in AB) or ((chronic epstein barr virus)in TI)
#5 ((akureyri disease*) in AB) or ((akureyri disease*) in TI)
#4 ((myalgic encephalomyelitis) in AB) or ((myalgic encephalomyelitis) in TI)
#3 ((myalgic encephalomyelitis) in AB) or ((myalgic encephalomyelitis) in TI)
#2 CHRONIC-FATIGUE-SYNDROME
#1 ((chronic fatigue syndrome) in AB)or((chronic fatigue syndrome) in TI)
1195 records retrieved.

Science Citation Index (1945 – 2005), ISI Web of Knowledge
Searched 26/06/05

TI=chronic fatigue syndrome or TS= chronic fatigue syndrome
TI= myalgic encephalomyelitis or TS= myalgic encephalomyelitis
(TI=akureyri disease* or TS=akureyri disease*)
(TI=chronic epstein barr virus or TS=chronic epstein barr virus)
(TI=cfids or TS=cfids)
(TI=(chronic fatigue and immune dysfunction syndrome*) or TS=(chronic fatigue and immune dysfunction syndrome*))
(TI=chronic mononucleosis or TS=chronic mononucleosis)
(TI=effort syndrome* or TS=effort syndrome*)
(TI=iceland* disease* or TS=iceland* disease*)
(TI=low natural killer cell syndrome* or TS=low natural killer cell syndrome*)
(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)
(TI=neuromyasthenia or TS=neuromyasthenia)
(TI=post viral fatigue syndrome* or TS=post viral fatigue syndrome*)
(TI=postviral fatigue syndrome* or TS= postviral fatigue syndrome*)
(TI= post viral syndrome* or TS=post viral syndrome*)
(TI=postviral syndrome* or TS=postviral syndrome*)
(TI=post infectious fatigue or TS=post infectious fatigue)
(#23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33)
(TI=postinfectious fatigue or TS= postinfectious fatigue)
(TI=raggedy ann* syndrome* or TS= raggedy ann* syndrome*)
(TI=royal free disease* or TS=royal free disease*)
(TI=royal free epidemic* or TS=royal free epidemic*)
(#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21)
(TI=royal free hospital disease* or TS=royal free hospital disease*)
(TI=tapanui disease* or TS=tapanui disease*)
(TI= yuppie flu or TS= yuppie flu)
(TI=yuppy flu or TS=yuppy flu)
(TI=(chronic infectious mononucleosis like syndrome*) or TS=(chronic infectious mononucleosis like syndrome*))
(TI=CFS or TS=CFS)
(TI=myalgic encephalopathy or TS=myalgic encephalopathy)
(#23 or #24 or #25 or #26 or #27 or #28 or #29 or #30)
(#11 or #22 or #31)

1279 records retrieved. This search was run without using ME as a search term as this skewed the results by including titles with “me” in not just ME. In most cases a paper about ME would include one of the other terms for ME as well so it is not anticipated that any major papers were missed.

Social Science Citation Index (1945-2005), ISI Web of Knowledge
Searched 03/05/05

#31 (#11 or #22 or #30)
#30 (#23 or #24 or #25 or #26 or #27 or #28 or #29)
#29 (TI=myalgic encephalopathy or TS=myalgic encephalopathy)
#28 (TI=CFS or TS=CFS)
#27 (TI=(chronic infectious mononucleosis like syndrome*) or TS=(chronic infectious mononucleosis like syndrome*))
#26 (TI=yuppy flu or TS=yuppy flu)
#25 (TI=yuppie flu or TS=yuppie flu)
#24 (TI=tapanui disease* or TS=tapanui disease*)
#23 (TI=royal free hospital disease* or TS=royal free hospital disease*)
#22 (#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21)
#21 (TI=royal free epidemic* or TS=royal free epidemic*)
#20 (TI=royal free disease* or TS=royal free disease*)
#19 (TI=raggedy ann* syndrome* or TS=raggedy ann* syndrome*)
#18 (TI=postinfectious fatigue or TS=postinfectious fatigue)
#17 (TI=postviral syndrome* or TS=postviral syndrome*)
#16 (TI=post infectious fatigue or TS=post infectious fatigue)
#15 (TI=post viral syndrome* or TS=post viral syndrome*)

#14 (TI=postviral fatigue syndrome* or TS=postviral fatigue syndrome*)
#13 (TI=post viral fatigue syndrome* or TS=post viral fatigue syndrome*)
#12 (TI=neuromyasthenia or TS=neuromyasthenia)
#11 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)
#10 (TI=low natural killer cell syndrome* or TS=low natural killer cell syndrome*)
#9 (TI=iceland* disease* or TS=iceland* disease*)
#8 (TI=effort syndrome* or TS=effort syndrome*)
#7 (TI=chronic mononucleosis or TS=chronic mononucleosis)
#6 (TI=(chronic fatigue and immune dysfunction syndrome*) or TS=(chronic fatigue and
#5 (TI=cfids or TS=cfids)
#4 (TI=chronic epstein barr virus or TS=chronic epstein barr virus)
#3 (TI=akureyri disease* or TS=akureyri disease*)
#2 TI=myalgic encephalomyelitis or TS=myalgic encephalomyelitis
#1 TI=chronic fatigue syndrome or TS=chronic fatigue syndrome
691 records retrieved. This search was run without using ME as a search term as this skewed the results by including titles with “me” in not just ME. In most cases a paper about ME would include one of the other terms for ME as well so it is not anticipated that any major papers were missed.

APPENDIX 2: DATA EXTRACTION TABLES FOR QUESTION 3

1. Behavioural interventions (CBT/ GET/ pacing)

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Cox (2002)[29] **Study design** Controlled trial **Level of evidence** 2-	**Number:** 97 **Adults or children?:** Adults **Inclusion criteria:** Confirmed diagnosis of CFS with no other secondary diagnosis; aged 15-60 years; current or pending inpatient for management approach **Exclusion criteria:** Other specific diagnoses such as Parkinson's disease, MS, post-traumatic stress disorder, post-polio syndrome and/or personality disorder; aged 15-60 years; previous admission for management approach; previous management by CFS team as an outpatient; non-completion of inpatient treatment programme (staying less than 14 days) **Diagnosis/ case definition:** CDC (1994) **Age:** mean 33 yrs treatment group, 37 yrs control group **% Female:** 79% treatment group, 83% control group **Duration of illness:** median 56 months treatment group, 60.5 months control group **Baseline functioning:** 92% not working or studying in treatment group, 97% in control group **Further details:** 5% past history of anxiety, 13% in treatment group and 16% in control group had past history of depression Recruited from NHS trust neurosciences centre Diagnosis discussed with the medical team	Occupational Therapy Lifestyle management Programme uses principles of CBT and graded activity within a biopsychosocial framework. Series of 10 educational topics for daily management of CFS. waiting list control group **Number of participants in each group** 61 in treatment group, 36 in control group	Withdrawals: Questionnaire completion rate 6 months after discharge was 46/60 in the treatment group and 19/35 in the control group. Adverse events:

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: SF-36 physical functioning **Results in intervention group** 6 months(n=44): 20 improved, 14 stayed the same, 10 got worse **Results in control group** 6 months(n=19): 7 improved, 3 stayed the same, 9 got worse **Comments** no significant difference between groups	**Outcome measured** Health and Fatigue Qre - total fatigue **Results in intervention group** 6 months (n=43): 25 improved, 6 stayed the same, 13 got worse **Results in control group** 6 months (n=19): 10 improved, 3 stayed the same, 6 got worse **Comments** no significant difference between groups	**Outcome measured** Fatigue Perceived Fatigue Rating Scale **Results in intervention group** 6 months (n=43): 26 improved, 17 got worse **Results in control group** 6 months (n=19): 11 improved, 8 got worse **Comments** no significant difference between groups	**Outcome measured** Emotional distress Perceived Fatigue Rating Scale **Results in intervention group** 6 months (n=43): 25 improved, 2 stayed the same, 16 got worse **Results in control group** 6 months (n=19): 11 improved, 8 got worse **Comments** no significant difference between groups

Outcome 5	Outcome 6	Outcome 7	Outcome 8
Outcome measured Maintaining activity Illness management questionnaire **Results in intervention group** 6 months (n=43): 27 improved, 1 stayed the same, 15 got worse **Results in control group** 6 months (n=19): 9 improved, 3 stayed the same, 7 got worse **Comments** significant difference in favour of treatment group (p=0.03)	**Outcome measured** Accommodating to illness Illness management questionnaire **Results in intervention group** 6 months (n=43): 31 improved, 12 got worse **Results in control group** 6 months (n=19): 7 improved, 1 stayed the same, 11 got worse **Comments** significant difference in favour of treatment group (p=0.02)	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments: At discharge (end of treatment) there were significant differences between the gorups in: pain after exercise and total pain on the HFQ, fatigue and emotional distress on the PFRS, and maintaining activity, accommodating to illness and information seeking on the IMQ. At 3 months post-discharge there were significant differences between groups for length of current tiredness and pain after exercise on the HFQ, and maintaining activity, accommodating to illness and information seeking on the IMQ. At 6 months post-discharge there were significant differences between groups in health transition on the SF36, length of current tiredness on the HFQ and maintaining activity and accommodating to illness on the IMQ.			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Cox (2002)[30] **Study design** Controlled trial **Level of evidence** 2-	**Number:** 130 **Adults or children?:** Adults **Inclusion criteria:** Confirmed diagnosis of CFS with no other secondary diagnoses, aged 15 - 60 years, current or pending inpatient for management approach, completion of treatment programme (for inpatient group) **Exclusion criteria:** Other specific diagnoses such as Parkinson's disease, MS, PTSD, post polio syndrome and/ or personality disorder. Previous admission for specified CFS management approach, previous outpatient management by CFS team, non-completion of inpatient treatment programme. **Diagnosis/ case definition:** CDC (1994) **Age:** treatment group mean 33 yrs, control group mean 37 yrs **% Female:** 79% treatment group, 83% control group **Duration of illness:** median 56 months treatment gorup, 60.5 months comparison group **Baseline functioning:** 92% not working or studying in the treatment group, 97% in the control group **Further details:** None Recruited through a neuroscience Centre and a national ME charity. Experimental group were inpatients, control group were from the inpatient waiting list. 80% in the treatment group and 78% in the control group reported 'infection/ virus' at onset. 84% in each group currently on medication including tricyclic antidepressant, 5HT uptake inhibitor, hypnotic, analgesics.	Combined CBT and graded activity intervention not described **Number of participants in each group** 65 inpatient group, 37 control group	Withdrawals: 5 withdrew from experimental group, 18 from the control group Adverse events:

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Functional status SF36: physical functioning; role functioning - physical; bodily pain; general health; vitality; social functioning; role functioning - emotional; mental health; reported health transition **Baseline values intervention group** 27 (22.03); 11.4 (24.6); 35.07 (22.72); 31.23 (19.21); 19.04 (18.19); 25.04 (19.34); 53.21 (46.23); 58.18 (18.25); 3.2 (1.05) **Baseline values control group** 27.86 (19.6); 5.71 (19.26); 33.86 (21.78); 24.97 (15.29); 15.57 (15.52); 29.27 (24.43); 66.67 (43.54); 60.91 (23.57); 3.4 (1.1) **Results in intervention group** 30.46 (21.48); 13.07 (22.55); 40.4 (26.34); 31.3 (16.8); 25.23 (19.88); 33.52 (26.11); 70.44 (38.86); 61.73 (20.78); 2.7 (1) **Results in control group** 30 (22.36); 5.26 (13.38); 44.95 (25.73); 34.63 (21.25); 25.79 (23.35); 38.82 (27.92); 70.18 (39.9); 68.63 (21.72); 2.9 (1.15) **Comments** no significant differences between groups on on any subscale at 6 months	**Outcome measured** Scale of Perceived Ability and Recovery current level of ability; future level to achieve; influenced by you; influenced by others **Baseline values intervention group** 32.2 (14.9); 88.6 (15.4); 77.4 (20.8); 70.9 (21.6) **Baseline values control group** 37.4 (13.6); 84.9 (14.6); 84 (21.4); 75.1 (21.2) **Results in intervention group** 38.3 (20.2); 82.9 (16.9); 71.7 (19.1); 61.2 (21) **Results in control group** 41.1 (18.2); 82.6 (16.6); 72.6 (15.2); 63.2 (21.1) **Comments** no significant differences between groups	**Outcome measured** Disability visual analogue scale (max 40) **Baseline values intervention group** 29.9 (6.8) **Baseline values control group** 29.9 (7) **Results in intervention group** 28 (7.9) **Results in control group** 27.3 (23.3) **Comments** no significant difference between groups	**Outcome measured** Mood Hospital anxiety and depression scale **Baseline values intervention group** Anxiety: 8.5 (4.7), depression: 7.9 (3.8) **Baseline values control group** Anxiety: 8.9 (5.6), depression: 7.9 (4.2) **Results in intervention group** Anxiety: on discharge 7.8 (4.2), 3 months post discharge 7.3 (4.4), 6 months post discharge 7 (4.7); Depression: on discharge 6.5 (3.8), 3 months post discharge 6.7 (4.6), 6 months post discharge 7.3 (4.5) **Results in control group** Anxiety: on discharge 8.5 (5.4), 3 months post discharge 8 (5.5), 6 months post discharge 6.8 (5.4); depression: on discharge 7.4 (4.4), 3 months post discharge 7 (3.6), 6 months post discharge 5.7 (3.6) **Comments** no significant differences between groups

Outcome 5	Outcome 6	Outcome 7	Outcome 8
Outcome measured Fatigue Chalder fatigue questionnaire (total fatigue) **Baseline values intervention group** 23.7 (7.4) **Baseline values control group** 23.8 (6.1) **Results in intervention group** on discharge 20.8 (7.7), 3 months post discharge 18.3 (7.9), 6 months post discharge 19.6 (7.8) **Results in control group** on discharge: 21.8 (7), 3 months post discharge 20 (7.8), 6 months post discharge 21 96) **Comments** no significant differences between groups	**Outcome measured** Pain max score 6 **Baseline values intervention group** 4.2 (1.7) **Baseline values control group** 4 (1.5) **Results in intervention group** on discharge 3.3 (1.7), 3 months post discharge 3.4 (1.7), 6 months post discharge 3.7 (1.7) **Results in control group** on discharge 4 (1.7), 3 months post discharge 3.7 (1.9), 6 months post discharge 3.7 (1.3) **Comments** significant difference between groups on discharge (p<0.05)	**Outcome measured** Profile of Fatigue Related Symptoms Fatigue; emotional distress; cognitive difficulties; somatic symptoms **Baseline values intervention group** 4.2 (1.3); 2.3 (1.3); 3.4 (1.4); 2.8 (1.4) **Baseline values control group** 4.3 (1.3); 2.4 (1.8); 3.2 (1.6); 2.9 (1.4) **Results in intervention group** on discharge: 3.7 (1.5); 2.1 (1.4); 3.1 (1.4); 2.4 (1.4), 3 months post discharge: 3.7 (1.6); 2.1 (1.5); 3 (1.4); 2.3 (1.5), 6 months post discharge: 4 (1.5); 2 (1.3); 3 (1.6); 2.3 (1.4) **Results in control group** on discharge: 4.4 (1.3); 2.5 (1.7); 3.2 (1.4); 2.7 (1.5), 3 months post discharge: 4.1 (1.3); 2.3 (1.7); 3 (1.4); 2.6 (1.4), 6 months post discharge: 3.7 (1.5); 2 (1.5); 2.9 (1.1); 2.3 91.3) **Comments** significant difference between groups in fatigue scores at discharge (p<0.02), improvement in fatigue on discharge (p<0.003) and improvement in emotional distress on discharge (p<0.03)	**Outcome measured** Illness Management Questionnaire maintaining activity; accommodating the illness; focusing on symptoms; information seeking **Baseline values intervention group** 3.2 (1); 3.9 (1); 3.4 (1); 3.9 (1) **Baseline values control group** 3.5 (1); 3.8 (1.); 3.4 (1); 3.8 (1) **Results in intervention group** on discharge: 2.9 (1); 4.3 (1); 3.2 (1); 4 (1), 3 months post discharge: 3 (1); 4.3 (1); 3.1 (1); 3.7 (1), 6 months post discharge: 2.9 (1); 4.3 (1); 3.1 (1); 3.5 (1) **Results in control group** on discharge: 3.5 91); 3.7 (1); 3.2 (1); 3.3 (1), 3 months post discharge: 3.5 91); 3.8 (1); 3.4 (1); 3.3 (1), 6 months post discharge: 3.4 (1); 3.8 (1); 3.2 (1); 3.1 (1) **Comments** significant difference between groups on discharge for maintaining activity, accommodating to illness and information seeking; and at 3 and 6 months post discharge for maintaining activity and accommodating to illness

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Deale (1997)[22] **Study design** RCT **Level of evidence** 1++	**Number:** 60 **Adults or children?:** Not stated **Inclusion criteria:** Consecutive referrals. Patients taking antidepressant medication or anxiolytics were eligible if dose was stable for 3 months before entry and during the trial. Excluded if had somatisation disorder, severe depression, ongoing physical investigations, concurrent new treatment and inability to attnd all treatment sessions **Exclusion criteria:** **Diagnosis/ case definition:** Oxford **Age:** Mean 31 (sd=9) in CBT group, mean 38 (sd=11) in relaxation group	CBT Patients recevied either 13 sessions over 4-6 months of CBT (graded activity and cognitive restructuring) or relaxation Patients were seen individually **Number of participants in each group** 30 in each group	Withdrawals: 7 patients dropped out of treatment and completed no more clinical measures: 3 from CBT, 1 found it ineffective, 1felt too ill to attend as an outpatient (received inpatient CBT and improved), 1 improved and wanted no further treatment. 4 patients withdrew from relaxation, 1 felt to ill to continue, 1 gave no

	% Female: 70% female in CBT group, 67% in relaxation group **Duration of illness:** Mean 3.4 (sd=2.1) years in CBT group, mean 4.6 (sd=3.3) years in realxation group **Baseline functioning:** Both groups had near maximum scores on measures of functional impairment and fatigue, scores on general health questionnaire were moderate, but depression was not marked. **Further details:** 5 patients had additional diagnoses of dysrhthmia, 9 had major depression, 3 had anxiety disorders, and 6 had both depression and anxiety disorders Patients recruited from specialist CFS clinic, No significant differences between group for marital status, social class, proportion unemployed, proportion with psychiatric diagnosis, use of antidepressants or patient attribution of symptoms to physical illness. 12 patients used antidepressants and 2 used anxiolytics Also met CDC 94 criteria		reason & 2 found relaxation exercises overly tiring. Adverse events:

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Improvement in physical functioning Proportion improved at 6 month follow-up. Increase of 50 or more from pre-treatment to 6 months follow-up or end score of 83+ on physical functioning scale of Gerneral Healh survey **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 70% excluding drop-outs, 63% including drop-outs **Results in control group** 19% excluding drop-outs, 17% including drop-outs **Comments** Drop-outs classified as not improved. Difference between groups = 51% (95% CI: 28-74), excluding drop-outs, 46% (95% CI: 24-68) including drop outs, p<0.001 for both comparisons	**Outcome measured** Functioning Physical functioning scale of Medical Outcomes Study Short-Form General Health Survey **Baseline values intervention group** 25.5 (18.9) **Baseline values control group** 27.8 (27.1) **Results in intervention group** 71.6 (28.0) **Results in control group** 38.4 (26.9) **Comments** p for the difference between groups >0.50	**Outcome measured** Work Work and Social adjustment scale **Baseline values intervention group** 6.0 (1.2) **Baseline values control group** 6.1 (1.3) **Results in intervention group** 3.3 (2.2) **Results in control group** 5.4 (1.8) **Comments** p for the difference between groups <0.001	**Outcome measured** Goals Long-term goals rating (mean of two) **Baseline values intervention group** 7.0 (0.7) **Baseline values control group** 6.8 (1.0) **Results in intervention group** 2.9 (1.9) **Results in control group** 5.9 (1.8) **Comments** p for the difference between groups <0.001

Outcome 5	Outcome 6	Outcome 7	Outcome 8
Outcome measured Fatigue Fatigue problem rating **Baseline values intervention group** 7.0 (0.9) **Baseline values control group** 6.3 (1.2) **Results in intervention group** 3.4 (2.2) **Results in control group** 5.5 (1.9) **Comments** p for the difference between groups <0.001	**Outcome measured** Fatigue Fatigue questionnaire **Baseline values intervention group** 10.2 (1.3) **Baseline values control group** 9.5 (2.6) **Results in intervention group** 4.1 (4.0) **Results in control group** 7.2 (4.0) **Comments** p for the difference between groups <0.01	**Outcome measured** Depression BDI score **Baseline values intervention group** 14.5 (7.2) **Baseline values control group** 14.2 (6.1) **Results in intervention group** 10.1 (6.9) **Results in control group** 12.3 (8.5) **Comments** p for the difference between groups >0.30	**Outcome measured** General health General health questionnaire **Baseline values intervention group** 6.2 (3.6) **Baseline values control group** 6.0 (4.2) **Results in intervention group** 3.4 (3.7) **Results in control group** 4.3 (3.9) **Comments** p for the difference between groups >0.70
Additional comments: Results presented are at 6 month follow-up, results presented as mean (sd) unless otherwise stated			
Outcome 9	**Outcome 10**	**Outcome 11**	**Outcome 12**
Outcome measured: Employment Proportion employed **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 56% **Results in control group** 39% **Comments** p=0.05	**Outcome measured** Work Mean hours worked per week **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 19.92 (sd=15.82) **Results in control group** 9.89(sd=15.82) **Comments** p<0.05	**Outcome measured** Global improvement **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Logistic regression analysis of predictors of global improvement showed that age showed a significant relationship with global improvement, age and illness duration showed significant association with MOS physical functioning score and illness duration showed significant association with fatigue questionnaire. Pre-treatment fatigue score or psychiatric disorder showed no association with any measure of global improvement.	**Outcome measured:** Global improvement Self rating **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 70% better or much better **Results in control group** 31% better or much better **Comments** p for the difference between groups <0.01

Outcome 13	Outcome 14	Outcome 15	Outcome 16
Outcome measured Satisfaction Patient satisfaction with treatment outcome **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 78% satisfied or very satisfied **Results in control group** 50% satisfied or very satisfied **Comments** p for the difference between groups <0.05	**Outcome measured** Usefulness Patient assessment of usefulness of treatment **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 96% useful or very useful **Results in control group** 85% useful or very useful **Comments** p for the difference between groups >0.10	**Outcome measured** Functioning Blinded assessor rating of physical functioning at 3 month follow-up **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 80% better or much better **Results in control group** 26% better or much better **Comments** p for the difference between groups <0.001	**Outcome measured** Fatigue Blinded assessor rating of fatigue at 3 month follow-up **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 72% better or much better **Results in control group** 17% better or much better **Comments** p for the difference between groups <0.001

Results at 5 year follow up (Withdrawals: 25 CBT patients and 28 relaxation patients followed up at 5 years)

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Global improvement Proportion much or very much better **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 64% **Results in control group** 36% **Comments** p<0.05	**Outcome measured** Functioning MOS physical functioning scale, proportion with score>83 **Baseline values intervention group** 0 **Baseline values control group** 0 **Results in intervention group** 48% **Results in control group** 32% **Comments** p=0.272	**Outcome measured** Fatigue Fatigue questionnaire, proportion with score <4 **Baseline values intervention group** 0% **Baseline values control group** 7% **Results in intervention group** 32% **Results in control group** 25% **Comments** p=0.571	**Outcome measured** General health GHQ score < 4 **Baseline values intervention group** 30% **Baseline values control group** 33% **Results in intervention group** 48% **Results in control group** 54% **Comments** p=0.579

Outcome 5	Outcome 6	Outcome 7	Outcome 8
Outcome measured Symptoms Course of symptoms over time **Baseline values intervention group** **Baseline values control group** **Results in intervention group** absent: 68%, fluctuated markedly 28%, worsened or consistently severe 4% **Results in control group** Steadily improved or absent: 43%, fluctuated markedly 36%, worsened or consistently severe 21% **Comments** p=0.05	**Outcome measured** Relapses **Baseline values intervention group** **Baseline values control group** **Results in intervention group** None:36%, 1/2:12%, 3/4 20%, 5+: 32% **Results in control group** None:7%, 1/2:11%, 3/4 21%, 5+: 61% **Comments** p=0.05	**Outcome measured** CFS Proportion that no longer meet UK criteria **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 52% **Results in control group** 39% **Comments** p=0.415	**Outcome measured** Status Completely recovered **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 24% **Results in control group** 5% **Comments** p=0.05

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Friedberg (1994)[27] **Study design** Controlled trial **Level of evidence** 2-	**Number:** 44 **Adults or children?:** Not stated **Inclusion criteria:** Not stated **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1988) **Age:** mean 35.7 in treatment group, 39.7 in control **% Female:** 95.5% women in treatment group, 67.2 in control (p<0.02) **Duration of illness:** 32.5 months in treatment group, 74 in control **Baseline functioning:** Both groups had significantly elevated fatigue severity scores compared to depression control group (p<0.002) **Further details:** 17/22 participants had a current psychiatric condition, major depression in 10 cases, 11/22 in control group had diagnosed psychiatric illness, major depression in 6 cases. Patients recruited from neurology clinic and through local CFS support group. No significant differences between two groups with respect to demographic variables or severity of illness. Patients offered CBT those that refused assigned to no-treatment group Not stated	CBT Patients either treated with CFS or untreated CBT modelled for chronic pain, used group therapy format, structured on following interventions: shared coping, relxation training and guided imagery, cognitive therapy techniques, and behavioural presecription **Number of participants in each group** 22 in treatment, 22 in control	Withdrawals: 2 patients who did not want CBT refused to participate in control group. Adverse events: Not stated

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Depression Depression symptom score. CES-D scale, 20 item self-report scale scored from 0-60 **Baseline values intervention group** **Baseline values control group** **Results in intervention group** lower than pre-treatment score, p=0.058 **Results in control group** No significant difference **Comments**	**Outcome measured** Stress symptom score Brief symptom inventory, 53 item self-report scale **Baseline values intervention group** **Baseline values control group** **Results in intervention group** No significant difference **Results in control group** No significant difference **Comments**	**Outcome measured** Fatigue fatigue severity score, 9 items on 7 point Likert scale **Baseline values intervention group** **Baseline values control group** **Results in intervention group** No significant difference **Results in control group** No significant difference **Comments**	**Outcome measured** Cognition Fatigue related cognition scale, 14 item self-report scale developed by one of trial authors **Baseline values intervention group** **Baseline values control group** **Results in intervention group** Significant reduction, p<0.023 **Results in control group** No significant difference **Comments**
Additional comments: Those with higher CES-D scores at baseline improved more than those with low CES-D scores (median split), high scores improved in depression (p<0.001), stress (p<0.01), fatigue severity (p<0.05), and fatigue related thinking (p<0.04)			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Fulcher (1997)[32] **Study design** RCT **Level of evidence** 1++	**Number:** 66 **Adults or children?:** Adults **Inclusion criteria:** Patients excluded who had a current psychiatric disorder or symptomatic insomnia as assessed by DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders, third edition, revised) **Exclusion criteria:** **Diagnosis/ case definition:** Oxford **Age:** mean = 37.2 (sd=10.7) **% Female:** 74% women **Duration of illness:** Median duration = 2.7 years (range 0.6 - 19 years) **Baseline functioning:** **Further details:** Not stated Mean BMI= 23.8 (sd=4.6). Twenty patients were taking full dose anti=-depressants, 10 were taking low dose tricyclic antidepressants as hypnotics, 44 patients blamed viruses for their illnesses Physical screening investigations were carried out or, when appropriate, full recent records were obtained from referring doctors to ensure other disorders had been discounted.	GET Patients randomly assigned to either graded aerobic exercise or flexibility treatment weekly for 12 weeks Patients attended for supervised treatment and given next week's exercise prescription, home exercise was prescribed on at least 5 days a week with initial sessions lasting between 5 & 15 mins with intensity of 40% of peak oxygen consumption (roughly 50% max heart rate), daily exercise prescription increased by 1 or 2 minutes up to a maximum of 30 minutes, intensity increased to 60% peak oxygen consumption, patients given heart rate monitors to ensure did not exceed level prescribed. Main exercise was walking but also encouraged to take other forms of exercise, advised not exceed prescribed exercise during a good phase, if patients complained of increased fatigue were advised to continue with same level of exercise for extra week and increase when fatigue had lessened. Control subjects were taught stretching routine and relaxation techniques building up to longer sessions like exercise group, specifically told to avoid doing any extra physical activities **Number of participants in each group** 33 in each group	Withdrawals: 7 patients dropped out: 4 in exercise group and 3 in control, 1 from each group dropped out as said treatment made them worse Adverse events:

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: General health CGI-I scale. Self rated global impression change scores after treatment range from 1 (very much better), 2 (Much better), 3 (A little better), 4 (no change), 5 (a little worse), 6 (much worse) to 7 (very much worse) **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 1: 9 (31%); 2:7 (24%); 3:11 (38%); 41: (3%); 5: 1 (3%); 6:0; 7:0 **Results in control group** 1: 2 (7%); 2:6 (20%); 3:18 (60%); 4: 3 (10%); 5: 0; 6:1(3%); 7:0 **Comments** Analysis by intention to treat showed that 17/33 patients improved with exercise and 9/33 improved with flexibility treatment (chi2=4.06, p=0.04)	**Outcome measured** Physical Physiological variables **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Exercise group showed significant increase in: peak oxygen consumption and maximum ventilation but not in any other physiological measures compared to control.	**Outcome measured** Symptom measure Various symptomatic and functional measures **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Chalder fatigue score, total fatigue score, physical fatigue score, SF36 total score, SF36 physical function score and SF-36 general health score were significantly better in the exercise than in the flexibility groups. No difference in mental fatigue score, depression score, anxiety score or sleep total score	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Moss-Morris (2005)[35] **Study design** RCT **Level of evidence** 1+	**Number:** 49 **Adults or children?:** Adults **Inclusion criteria:** Aged between 18 and 65, meeting CFS criteria. **Exclusion criteria:** Patients who were unable to undergo exercise testing for medical reasons or who were already taking part in a regular and consistent exercise programme. **Diagnosis/ case definition:** CDC 1994 **Age:** mean 36.7 years GET group, 45.5 yrs control group **% Female:** 60% GET group, 79% control group **Duration of illness:** median 2.67 years GET group, 5.00 years control group **Baseline functioning:** 22% unemployed and unable to work due to disability **Further details:** Recruited from specialist CFS private general practice in New Zealand. Around 25% of participants suffered from anxiety/ depression.	12 week graded exercise programme versus standard care. Programme consisted of CBT rationale, developing individual plan for exercise programme, target heart rate set at 40% VO2max, attained on treadmill test, to be maintained for 1-15 minutes 4-5 times per week. Researchers and participants met weekly to reassess goals. Standard care included advice on managing diet, stress and CFS symptoms. **Number of participants in each group:** 25 in GET group and 24 in control group	Withdrawals: 3/25 dropped out of treatment and 3/24 did not return follow-up questionnaires at 12 weeks Adverse events: Not stated

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Clinical Global Impression **Results in intervention group** 12/22 were much or very much better **Results in control group** 5/21 were much or very much better **Comments** Statistically significant difference (p=0.04)	**Outcome measured:** Physical fatigue (14 item fatigue scale) **Baseline values intervention group** 14.55 (5.40) **Baseline values control group** 14.61 (4.86) **Results in intervention group** 7.91 (7.06) **Results in control group** 14.27 (5.75) **Comments** p=0.02	**Outcome measured:** Mental fatigue (14 item fatigue scale) **Baseline values intervention group** 9.90 (3.74) **Baseline values control group** 10.74 (3.90) **Results in intervention group** 6.00 (4.06) **Results in control group** 10.14 (4.27) **Comments** p=0.03	**Outcome measured:** total fatigue score (14 item fatigue scale) **Baseline values intervention group** 24.45 (8.79) **Baseline values control group** 25.35 (8.05) **Results in intervention group** 13.91 (10.88) **Results in control group** 24.41 (9.69) **Comments** p=0.02
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome measured **Baseline values intervention group** **Baseline values control group** G **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments:			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Powell (2001)[37] **Study design** RCT **Level of evidence** 1++	**Number:** 148 **Adults or children?:** Both **Inclusion criteria:** **Exclusion criteria:** **Diagnosis/ case definition:** Oxford **Age:** mean 34 in group 1 & 2, 32 in group 3 & 4 **% Female:** % female: 24 group 1, 28 group 2, 33 group 3, 31 group 4 **Duration of illness:** Mean (months): 48.6 group 1, 51.2 group 2, 51.5 group 3, 55.0 group 4 **Baseline functioning:** **Further details:** Not stated Not stated	Graded exercise and discussion of symptoms **Number of participants in each group** 34 in control, 37 in group 2, 39 in group 3, 38 in group 4	Withdrawals: 21 dropped out, 19 in intervention groups, dropped out during treatment: 8 for medical reasons, 7 for psychiatric reasons, 4 gave no reason, 1 emigrated, 1 was dissatisfied with treatment Adverse events: Not stated

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Physical functioning SF 36 (range 10-30, 30 is best functioning). **Baseline values intervention group** Group 2: 16.00 (14.99, 17.01) Group 3: 15.77 (14.57, 16.97), Group 4: 15.95 (14.84, 17.05) **Baseline values control group** Group 1: 16.32 (15.15, 17.50) **Results in intervention group** Group 2: 25.08 (23.34, 26.81), Group 3: 24.26 (22.54, 25.98), Group 4: 24.89 (23.35, 26.43) **Results in control group** Group 1: 16.94 (15.44, 18.44) **Comments** p<0.001 for each intervention group compared to control, no difference between interventions	**Outcome measured** Fatigue Measured on scale from 0-11, 11 is most severe **Baseline values intervention group** Group 2: 10.35 (9.98, 10.72), Group 3: 9.92 (9.22, 10.63), Group 4: 10.24 (9.85, 10.62) **Baseline values control group** Group 1: 10.61 (10.36, 10.88) **Results in intervention group** Group 2: 3.24 (1.78, 4.71), Group 3: 3.47 (2.05, 4.87), Group 4: 3.11 (1.84, 4.37) **Results in control group** Group 1: 10.06 (9.31, 10.81) **Comments** p<0.001 for each intervention group compared to control, no difference between interventions	**Outcome measured** Depression Measured on HAD scale: range 0-21, >10 = clinical depression **Baseline values intervention group** Group 2: 9.27 (8.03, 10.51), Group 3: 9.03 (7.81, 10.24), 9.03 (7.84, 10.21) **Baseline values control group** Group 1: 10.35 (8.93, 11.78) **Results in intervention group** Group 2: 4.24 (3.00, 5.49), Group 3: 4.62 (3.22, 6.01), Group 4: 4.21 (2.92, 5.50) **Results in control group** Group 1: 10.06 (8.39-11.72) **Comments** No measure of significance presented	**Outcome measured** Anxiety Measured on HAD scale as outcome 3 **Baseline values intervention group** Group 2: 10.62 (9.13, 12.12), Group 3: 10.03 (8.40, 11.65), Group 4: 10.21 (8.75, 11.67) **Baseline values control group** Group 1: 11.18 (9.55, 12.80) **Results in intervention group** Group 2: 7.14 (5.79, 8.48), Group 3: 6.51 (5.13, 7.90), Group 4: 7.71 (6.14, 9.29) **Results in control group** Group 1: 10.06 (8.40-11.72) **Comments** No measure of significance presented
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome measured Sleep Sleep problems measured on scale of Jenkins et al, range 0-20, 20 indicated maximum problems **Baseline values intervention group** Group 2: 12.43 (10.82, 14.05), Group 3: 13.54 (12.10, 14.97), Group 4: 13.03 (11.39, 14.66) **Baseline values control group** Group 1:12.79 (11.13, 14.45) **Results in intervention group** Group 2: 6.70 (4.98, 8.43), Group 3: 8.56 (6.80, 10.33), Group 4: 7.13 (5.55, 8.71) **Results in control group** Group 1: 11.53 (9.67-13.39) **Comments** No measure of significance presented	**Outcome measured** Improvement Clinically significant improvement as assessed by authors **Baseline values intervention group** **Baseline values control group** **Results in intervention group** Group 2: 26/37, Group 3: 27/39, Group 4: 26/38 **Results in control group** Group 1: 2/34 **Comments** p<0.001 using a chi-squared test	**Outcome measured** Improvement Patients report of being very much or much better **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 84% **Results in control group** 12% **Comments** No measure of significance presented	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments: Results given are at 12 month follow-up. Also presented results after 3 and 6 months. Results presented as mean (95% CI). Patients rated physiological explanations offered for their symptoms as very important.			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Powell (2004)[34] **Study design** RCT **Level of evidence** 1++	**Number:** 148 **Adults or children?:** Both **Inclusion criteria:** Patients aged 15-55, scored <25 on physical functioning subscale of SF36. Excluded if undergoing further physical investigations or other treatments including antidepressant therapy, had psychotic illness, somatisation disorder, eating disorder or history of substance abuse, if confined to wheelchair or bed **Exclusion criteria:** **Diagnosis/ case definition:** Oxford **Age:** mean 34 in group 1 & 2, 32 in group 3 & 4 **% Female:** % female: 24 group 1, 28 group 2, 33 group 3, 31 group 4 **Duration of illness:** Mean (months): 48.6 group 1, 51.2 group 2, 51.5 group 3, 55.0 group 4 **Baseline functioning:** Between 11 and 15% were working, 15-17% were receiving disability benefits, 3-10% were taking antidepressants, 17-20% believed in physical cause of illness **Further details:** not stated Recruited from consecutive referrals to CFS and infectious diseases clinic. Randomisation was stratified by scores on HAD depression scale Same study as Powell 2001[37], followed up at 2 years. 32 patients from the control group were offered the intervention after 1 year and assessed 1 year later	Graded exercise and discussion of symptoms Group 1: standardised medical care, given pack without medical explanation but which engouraged regular activity and positive thinking. Group 2 (minimum education): patients received 2 individual treatment sessions over 2 weeks, causal explanations given for symptoms, graded exercise programme designed for each patient, given comprehensive educational pack, followed up with phone calls at 3 and 6 months. Group 3 (telephone intervention): same as group 2 but also received 7 planned telephone contacts lasting 30 mins each, rationale for treatment reiterated and problems with exercise discussed, Group 4 (maximum educational intervention): same as group 2 but also received 7 one hour face-to-face treatment sessions, similar to phone calls. **Number of participants in each group** 34 in control, 37 in group 2, 39 in group 3, 38 in group 4	Withdrawals: Adverse events:

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Physical functioning SF 36 (range 10-30, 30 is best functioning). **Baseline values intervention group** Group 2: 16.00 (14.99, 17.01) Group 3: 15.77 (14.57, 16.97), Group 4: 15.95 (14.84, 17.05) **Baseline values control group** Group 1: 16.32 (15.15, 17.50) **Results in intervention group** Group 2 24.11 (5.94) Group 3: 23.64 (6.39) Group 4: 25.45 (4.72) **Results in control group** Group 1: not reported **Comments** no significant difference between groups	**Outcome measured** Fatigue score Measured on scale from 0-11, 11 is most severe **Baseline values intervention group** Group 2: 10.35 (9.98, 10.72), Group 3: 9.92 (9.22, 10.63), Group 4: 10.24 (9.85, 10.62) **Baseline values control group** Group 1: 10.61 (10.36, 10.88) **Results in intervention group** Group 2: 4.46 (4.78) Group 3: 3.59 (4.69) Group 4: 2.84 (3.67) **Results in control group** Group 1, not reported **Comments** no significant difference between groups	**Outcome measured** Depression score Measured on HAD scale: range 0-21, >10 = clinical depression **Baseline values intervention group** Group 2: 9.27 (8.03, 10.51), Group 3: 9.03 (7.81, 10.24), 9.03 (7.84, 10.21) **Baseline values control group** Group 1: 10.35 (8.93, 11.78) **Results in intervention group** Group 2: 5.11 (5.12) Group 3: 4.77 (4.67) Group 4: 4.08 (4.33) **Results in control group** Group 1: not reported **Comments** no measure of significance presented	**Outcome measured** Anxiety Measured on HAD scale as outcome 3 **Baseline values intervention group** Group 2: 10.62 (9.13, 12.12), Group 3: 10.03 (8.40, 11.65), Group 4: 10.21 (8.75, 11.67) **Baseline values control group** Group 1: 11.18 (9.55, 12.80) **Results in intervention group** Group 2: 7.65 (4.78) Group 3: 7.03 (5.07); Group 4: 7.13 (4.47 **Results in control group** Group 1: not reported **Comments** no measure of significance presented
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome measured Sleep Sleep problems measured on scale of Jenkins et al, range 0-20, 20 indicated maximum problems **Baseline values intervention group** Group 2: 12.43 (10.82, 14.05), Group 3: 13.53 (12.10, 14.97), Group 4: 13.03 (11.39, 14.66) **Baseline values control group** Group 1:12.79 (11.13, 14.45) **Results in intervention group** Group 2: 7.62 (5.30) Group 3: 8.15 (5.59) Group 4: 7.92 (5.50) **Results in control group** Group 1: not reported **Comments** no measure of significance presented	**Outcome measured** Clinical Global Impression Scale **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 70/90 (78%) reported being much better or very much better at 2 years **Results in control group** **Comments**	**Outcome measured** Clinically significant outcome improvement assessed by authors (relates to SF36 physical functioning scores) **Baseline values intervention group** **Baseline values control group** **Results in intervention group** Group 2: 20 Group 3: 23 Group 4: 26 **Results in control group** **Comments**	**Outcome measured** No longer fulfilled trial criteria **Baseline values intervention group** **Baseline values control group** **Results in intervention group** Group 2: 17 Group 3: 22 group 4: 24 **Results in control group** **Comments**
Additional comments: At the end of the trial 14/30 patients who crossed over at one year from the control group achieved a clinically significant outcome. 7/30 no longer met trial criteria and 17/25 who completed the educational intervention reported being much better or very much better.			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Prins (2001)[26] **Study design** RCT **Level of evidence** 1++	**Number:** 270 **Adults or children?:** Adults **Inclusion criteria:** Aged 18-60, no previous or current engagement in CFS research, not pregnant or engaged in pregnancy stimulating techniques and living within one and a half gours travelling time of the 3 centres. Patients in CFS group could not undergo further medical examinations of other treatments for CFS during study period **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1994) **Age:** Mean (sd): CBT 36.2 (9.4), Support: 37.1 (10.6), control: 36.7 (10.3) **% Female:** 19-24% female **Duration of illness:** Mean (sd) years: CBT: 4.9 (4.8), support: 6.6 (6.4), control: 5.3 (5.4) **Baseline functioning:** Not stated **Further details:** Not stated Recruited from outpatient clinics at departments of internal medicine Participants did not have to meet the CDC criteria of 4/8 additional symptoms. Score of 40+ on subscale fatigue severity of Checklist of individual strength and score of 800+ of Sickness Impact Profile	CBT CBT group: 16 sessions of 1 hour over 8 months, basic elements cognitive restructuring, building up activity, returning to work and relapse prevention Guided support groups: 11 group meetings of one and a half-hours during 8 months, treatment orientation non-directive and client-centered. Natural course (control): no interventions offered and no further requirements, patients could attend other examinations or treatments **Number of participants in each group** 92 in CBT group , 90 in support group, 88 in no treatment	Withdrawals: 6 patients excluded (not included in overall number): 5 developed other diseases during trial, one was pregnant at pre-test. 2 patients did not meet criteria for CFS due to pre-morbid anorexia nervosa. 37 in CBT group, 29 in support group and 18 in control group dropped out. 10 patients in CBT did not start treatment, 8 in support group did not start. 23 CBT group, 17 support group and 9 control group stopped treatment. During follow-up 4 in CBT, 4 in support and 9 in control group dropped out (dropped out of treatment or did not attend assessments) Adverse events: Not stated, but very large number of drop-outs

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Fatigue CIS fatigue score. Results presented as change from baseline to follow-up and mean (SE). Results presented on ITT basis **Baseline values intervention group** **Baseline values control group** **Results in intervention group** CBT: -11.8 (1.4) **Results in control group** Support: -6.5 (1.2), Control: -6.6 (1.0) **Comments**	**Outcome measured** Psychological well-being Measured on SCL90. Results presented as mean(sd). Results presented on ITT basis **Baseline values intervention group** CBT: 170 (38.5) **Baseline values control group** Support: 169 (41.5), Control: 166 (36.0) **Results in intervention group** CBT: 138 (35.1) **Results in control group** Support: 153 (33.9), Control: 147 (32.8) **Comments** F=4.96, p=0.001 for differences between groups (group x time)	**Outcome measured** Quality of life Measured on EuroQol scale. Results presented on ITT basis **Baseline values intervention group** CBT: 46 (17) **Baseline values control group** Support 43 (16), Control: 40(14) **Results in intervention group** CBT: 57 (22) **Results in control group** Support: 44 (19), Control: 49 (19) **Comments** F=3.92, p=0.004 for differences between groups (group x time)	**Outcome measured** Work Number of hours at work during 12 days. Results presented on ITT basis **Baseline values intervention group** CBT: 16.3 (21.1) **Baseline values control group** Support: 12.8 (19.1), Control: 13.5 (18.6) **Results in intervention group** CBT: 23.1 (28.1) **Results in control group** Support: 11.0 (15.4), Control: 16.8 (21.8) **Comments** F=2.60, p=0.036 for differences between groups (group x time)
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome measured Fatigue Proportion of participants with a clinically significant improvement in fatigue on CIS fatigue score **Baseline values intervention group** **Baseline values control group** **Results in intervention group** CBT: 20/58=35% **Results in control group** Support: 8/62=13%, Control: 13/76=17% **Comments** p=0.009 comparing CBT to support and 0.026 comparing CBT to control	**Outcome measured** Functional Proportion of participants with a clinically significant improvement in Karnofsky score **Baseline values intervention group** **Baseline values control group** **Results in intervention group** CBT: 28/57=49% **Results in control group** Support: 12/62=19%. Control: 17/75=23% **Comments** p=0.001 comparing CBT to support and 0.001 comparing CBT to control	**Outcome measured** Improvement Proportion of participants with self-rated improvement **Baseline values intervention group** **Baseline values control group** **Results in intervention group** CBT: 29/58=50% **Results in control group** Support: 9/62=15%, Control: 24/76=32% **Comments** p<0.001 comparing CBT to support and 0.034comparing CBT to control	**Outcome measured** Functional Impairment Measured using Sickness Impact Profile. Results presented as change from baseline to follow-up and mean (SE). Results presented on ITT basis **Baseline values intervention group** **Baseline values control group** **Results in intervention group** CBT: -590 (80) **Results in control group** Support: -320 (80), Control: -390 (80) **Comments**
Additional comments: All results presented are at follow-up after 14 months. Results also presented at post-test (8 months) , similar to follow-up so not presented here. In CBT group predictors for post-test fatigue severity were pre-test score, type of activity pattern and focusing on bodily symptoms (R2=20)			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Sharpe (1996)[25] **Study design** RCT **Level of evidence** 1+	**Number:** 60 **Adults or children?:** Adults **Inclusion criteria:** Consecutive patients aged 18-60, with major complaint of fatigue. Patients excluded if currently receiving psychotherapy or antidepressant drugs (unless taking same dose for at least 3 months without improvement), were unwilling to accept randomisation or unavailable for follow-up, met criteria for severe depression or had histroy of bipolar affective disorder, schizophrenia, or substance misuse or were at significant risk of suicide or in need of urgenet psychiatric treatment **Exclusion criteria:** **Diagnosis/ case definition:** Oxford **Age:** 18-60 **% Female:** M:F: 12:18 in CBT group, 7:23 in standard care group **Duration of illness:** In months: Median 17 in CBT group, 20 in control, mean 33.6 in CBT, 29.7 in control, range 6-91 months **Baseline functioning:** Groups did not differ on functional impairment, or psychiatric diagnoses. Patients in CBT group spent more days in bed (3.3 vs 1.6), and fewer were actively employed. **Further details:** Not stated Treatment groups did not differ substantially with respect to age, sex, educational level, marital status. 20% reported infection onset in CBT group, 22% in control Also fulfilled CDC 94 criteria	CBT Medical care alone compared with medical care plus CBT Patients with medical care alone told to increase their level of activity as much as they felt able, and reassured that hthere was no organic cause. CBT group given 16 1 hour individual sessions over 4 monthsFinal assessment was at 12 months. **Number of participants in each group** 30 in each group	Withdrawals: Complete data not available for one patiend, did not attend 12 month follow-uo. Phone call to patient indicated no substantial change since previous evlauation, so these data used for both. 7 patients (3 in CBT group) refused to do walking test on one or more occasions so previous test results used. Adverse events: 2 participants in CBT group attributed deterioration in symptoms to treatment

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Functioning Proportion of patients with normal functioning at 12 months follow-up (achieved Karnofsky score of 80 or more) **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 73% **Results in control group** 27% **Comments** Difference in proportion = 47 (95% CI: 24-69) %, p<0.001, difference increased over time	**Outcome measured** Functioning Proportion of patients with at least 10 point improvement on Karnofsky scale at 12 months follow-up **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 73% **Results in control group** 23% **Comments** Difference in proportion = 50 (95% CI: 28-72) %, p<0.001, difference increased over time	**Outcome measured** Work status Improvement in work status **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 63% **Results in control group** 20% **Comments**	**Outcome measured** Global improvement Proportion of patients reporting much improved or very much improved, or worse or very much worse, measured on CGI scale (7 point patient rated scale) **Baseline values intervention group** **Baseline values control group** **Results in intervention group** Imprved: 60%, Deteriorated: 13% **Results in control group** Improved: 23%, Deteriorated: 10% **Comments**
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome measured Illness beliefs Proportion of patients reporting reduction in strength of illness beliefs, measured on Likert type scales **Baseline values intervention group** **Baseline values control group** **Results in intervention group** Illness mainly physical:33%, cause is a virus, 48%, illness is ME 17%, avoidance of exercise 60% **Results in control group** Illness mainly physical:7%, cause is a virus, 20%, illness is ME 27%, avoidance of exercise 30% **Comments** All differences in proportions were significant (p<0.05), exetp for the belief that illness is ME	**Outcome measured:** Activitites Percentage interference with activities **Baseline values intervention group** 65 **Baseline values control group** 64 **Results in intervention group** 50 **Results in control group** 37 **Comments** Difference in change between the groups = 14(95% CI: 3 to 25), p<0.05	**Outcome measured** Rest Number of days in bed per week **Baseline values intervention group** 3.3 **Baseline values control group** 1.6 **Results in intervention group** 0.9 **Results in control group** 2.0 **Comments** Difference in change between the groups = 2.8(95% CI: 1.7 to 4.0), p<0.05	**Outcome measured** Exercise Distance walked in 6 minutes (m) **Baseline values intervention group** 437 **Baseline values control group** 435 **Results in intervention group** 481 **Results in control group** 424 **Comments** Difference in change between the groups = 55(95% CI: 17 to 94), p<0.05
Additional comments: All results presented are after 12 months follow-up			
Outcome 9	**Outcome 10**	**Outcome 11**	

Outcome measured Fatigue Fatigue severity, graded 0-10 **Baseline values intervention group** 7.8 **Baseline values control group** 7.9 **Results in intervention group** 4.3 **Results in control group** 6.3 **Comments** Difference in change between the groups = 1.9(95% CI: 0.5 to 3.3), p<0.05	**Outcome measured** Anxiety Measured on hospital anxiety and depression scale **Baseline values intervention group** 6.3 **Baseline values control group** 8.4 **Results in intervention group** 4.4 **Results in control group** 6.8 **Comments** Difference in change between the groups = 0.3(95% CI: -1.6 to 2.2), p>0.05	**Outcome measured** Depression Measured on hospital anxiety and depression scale **Baseline values intervention group** 6.7 **Baseline values control group** 6.8 **Results in intervention group** 3.6 **Results in control group** 5.8 **Comments** Difference in change between the groups = 2.0 (95% CI: 0.0 to 4.1), p<0.06	

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Stulemeijer (2004)[93] **Study design** RCT **Level of evidence** 1-	**Number:** 69 **Adults or children?:** Children **Inclusion criteria:** All consecutive patients with major complaint of fatigue aged 10 to 17.2 years, meeting CDC 1994 criteria, referred to outpatient clinic between 1999 and 2002 **Exclusion criteria:** Patients with psychiatric comorbidity. **Diagnosis/ case definition:** CDC (1994) **Age:** mean 15.6 yrs CBT, 15.7 yrs control **% Female:** 89% CBT, 91% controls **Duration of illness:** median 16 months CBT, 18 months controls **Baseline functioning:** Fatigue severity (checklist individual strength) CBT 52.5 (3.8), control 51.6 (4.3). Physical functioning (SF36) CBT 42.1 (16.5), control 45.3 (17.0). Full school attendance CBT 4/35, control 6/34 **Further details:** not stated 10 in CBT group and 7 in control group had a passive activity pattern (spend most time lying down and go out infrequently) Detailed history and physical and laboratory examinations were undertaken. Severe fatigue and severe functional impairment were defined as a score of 40 or more on the fatigue severity subscale of the checklist individual strength and a weighted score of 65 or less on the SF36 physical functioning subscale.	CBT Ten individual sessions over 5 months. For relatively active patients, treatment began with recognition and acceptance of limitations and reduction of activity. Activity levels were then increased. For inactive patients, a programme of activity building was started as soon as possible. Parents were involved in both CBT groups and return to full time education was a goal. Control group = waiting list for CBT **Number of participants in each group** 36 CBT, 35 waiting list	Withdrawals: 6 patients dropped out during treatment. 7 were missing from CBT group and 2 from control group at final assessment Adverse events: none reported

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Fatigue severity checklist individual strength **Baseline values intervention group** 52.5 (3.8) **Baseline values control group** 51.6 (4.3) **Results in intervention group** 30.2 (16.8). Treatment effect = 14.5 (95% CI: 7.4, 21.6), p=0.001 **Results in control group** 44.0 (13.4) **Comments**	**Outcome measured** Physical functioning SF-36 **Baseline values intervention group** 42.1 (16.5) **Baseline values control group** 45.3 (17.0) **Results in intervention group** 69.4 (28.0). Treatment effect 17.3 (95% CI: 6.2, 28.4), p=0.003 **Results in control group** 55.3 (21.1) **Comments**	**Outcome measured** School attendance hours attended/ hours that should have been attended **Baseline values intervention group** 46.2 (38.9) **Baseline values control group** 56.4 (38.6) **Results in intervention group** 74.7 (37.8). Treatment effect 18.2 (95% CI: 0.8, 35.5), p=0.040 **Results in control group** 66.7 (36.0) **Comments**	**Outcome measured** Additional symptoms unrefreshing sleep; muscle pain; impaired concentration; tiredness after exercise; headache; impaired memory; multijoint pain; sore throat; sensitive lymph nodes. Rated on a 4 point Likert scale. **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** At 5 months in CBT group, significantly greater decrease in prevalence of: feeling ill after exercise, impaired concentration, unrefreshing sleep, muscle pain, headache.

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Taylor (2004)[28] **Study design** RCT **Level of evidence** 1+	**Number:** 47 **Adults or children?:** Adults **Inclusion criteria:** see diagnosis details **Exclusion criteria:** exclusionary medical conditions (e.g. hyperthyroidism) **Diagnosis/ case definition:** CDC (1994) **Age:** mean 49.0 yrs immediate, 44.9 yrs delayed programme **% Female:** 91% immediate, 100% delayed group **Duration of illness:** not stated **Baseline functioning:** not stated **Further details:** none stated Recruited from local CFS self-help groups, Chicago area physicians specialising in CFS treatment, advertisements on CFS newsletters, Chicago-area newspapers, CFS web sites and listservs and local TV Screening process to confirm self-diagnosis: CFS screening questionnaire (Jason et al 1997[98]), semistructured psychiatric interview (SCID for DSM-IV), collection of medical records documenting CFS diagnosis	Rehabilitation programme Integrative consumer driven rehabilitation programme consisting of: 8 sessions of illness-management group (bi-weekly over 4 months), followed by 7 months of peer counselling, focusing on goal attainment control group received 'delayed' programme (assume usual care while waiting?) **Number of participants in each group** 23 immediate programme, 24 delayed programme	Withdrawals: none Adverse events: none reported

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Symptom severity CFS symptom rating form (Jason et al 1997[98]): 0 no problem, 100 severe problem **Baseline values intervention group** 15.1 (3.0) **Baseline values control group** 14,2 (2.8) **Results in intervention group** after group phase 14.4 (3.5); after one on one phase 13.9 (3.5) **Results in control group** after group phase: 14.3 (2.7); after one on one phase 14.8 (2.8) **Comments** significant interaction p<0.05	**Outcome measured** Overall quality of life Quality of Life Index, final scores 0-30, higher scores indicate higher life quality **Baseline values intervention group** 13.1 (4.3) **Baseline values control group** 14.0 (3.9) **Results in intervention group** after group phase 13.2 (3.8); after one on one phase 15.7 (3.7) **Results in control group** after group phase: 14.6 (4.8); after one on one phase 14.6 (4.1) **Comments** significant interaction p<0.05	**Outcome measured** QoL health and functioning **Baseline values intervention group** 12.9 (1.6) **Baseline values control group** 13.1 (1.7) **Results in intervention group** after group phase 12.8 (1.8); after one on one phase 14.1 (1.7) **Results in control group** after group phase 13.6 (2.1); after one on one phase 13.6 (1.8) **Comments**	**Outcome measured** QoL social and economic **Baseline values intervention group** 15.0 (1.2) **Baseline values control group** 15.4 (0.7) **Results in intervention group** after group phase 15.2 (0.8); after one on one phase 15.6 (0.8) **Results in control group** after group phase 15.5 (1.0); after one on one phase 15.5 (0.9) **Comments**
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome measured QoL psychological and spiritual **Baseline values intervention group** 15.0 (1.2) **Baseline values control group** 15.0 (1.1) **Results in intervention group** after group phase 15.0 (1.1); after one on one phase 15.5 (1.1) **Results in control group** after group phase 15.2 (1.3); after one on one phase 15.1 (1.2) **Comments**	**Outcome measured** QoL family **Baseline values intervention group** 15.4 (0.9) **Baseline values control group** 15.7 (1.0) **Results in intervention group** after group phase 15.4 (1.0); after one on one phase 15.6 (0.8) **Results in control group** after group phase 15.5 (1.0); after one on one phase 15.5 (0.9) **Comments** significant interaction p<0.05	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments: Linear growth models were estimated comparing programme and control conditions for each outcome using random effects regression analyses			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Viner (2004)[92] **Study design** Controlled trial **Level of evidence** 2+	**Number:** 56 **Adults or children?:** Children **Inclusion criteria:** children (aged 9-17) who met CDC diagnostic criteria **Exclusion criteria:** Those with treatable medical causes of fatigue, those on drugs known ot cause fatigue, those in whom somatoform disorder or school refusal was considered to be the diagnosis **Diagnosis/ case definition:** CDC (1994) **Age:** mean 13.9 yrs rehab, 14.4 yrs supportive care group **% Female:** 58% rehab, 59% supportive care **Duration of illness:** mean 25.7 months rehab, 28.1 months supportive care **Baseline functioning:** Of 78 children in the initial assessment, 62% had severe CFS, 29% moderate and 9% minimal CFS/ME **Further details:** a depressed mood was noted in 33 of the 78 children initially assessed Young people with CFS/ME seen by joint GOSH and UCL Hospitals Adolescent Medicine service between June 1998 and December 2002. modified for use with children and adolescents by using a three month duration of fatigue. Severity defined as follows: minimal: wellness score and school attendance both >= 75%, moderate: either or both scores >=50% but <75%, severe: either or both scores <50%.	Rehabilitative treatment Outpatient rehabilitative treatment (supportive care plus graded activities/ exercise programme and family sessions) compared with supportive care alone. Followed up for 3-24 months. **Number of participants in each group** 26 rehabilitation group, 22 supportive care alone	Withdrawals: data was available on outcome of treatment in 56 (remainder too early in follow-up). 22 had supportive care and 26 entered rehabilitation programme. The remaining 8 were prescribed SSRI either with supportive care or the programme, and they are not included in the analysis. Adverse events: none reported.

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Global wellness score Self-rated - asked to provide an average score for the previous month on a scale between 100 (best) and 0 (worst) **Baseline values intervention group** 50 **Baseline values control group** 50 **Results in intervention group** 85 (p<0.01) **Results in control group** 67 **Comments** Mean change in wellness score: 31% controls, 71% treatment group (p<0.05)	**Outcome measured** School attendance Average school attendance in the previous three months. **Baseline values intervention group** 20 **Baseline values control group** 40 **Results in intervention group** 90 (p<0.05) **Results in control group** 40 **Comments** change in school score 25% control, 182% rehabilitation group (p<0.01). Those in the programme had higher school attendance from nine months after beginning treatment, with this difference reaching significance after 12 months (p=0.02).	**Outcome measured** CFS severity **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 43% resolved (35% of severe cases resolved) **Results in control group** 4.5% resolved (64% of severe cases remained severe) **Comments** Resolution defined as wellness score >=90% and school attendance of >=95%	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments: No major individual factors were associated with response to treatment, however improvement in wellness score in the whole group was correlated with older age at onset (p<0.05) and shorter duration of illness (p<0.001) irrespective of treatment.			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Wallman (2004)[36] **Study design** RCT **Level of evidence** 1-	**Number:** 61 **Adults or children?:** Adults **Inclusion criteria:** Aged between 16 and 74 years, diagnosed with CFS (CDC 1994 criteria). **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1994) **Age:** 16-74 years (mean not reported) **% Female:** 84% graded exercise, 69% controls **Duration of illness:** not stated **Baseline functioning:** **Further details:** six diagnosed with major depressive disorder in the previous 12 months. Not stated which intervention group they were in. Recruited from notices placed in medical surgeries and advertisements in local newspapers Written confirmation of CFS diagnosis provided by doctor	Graded exercise with pacing Initial exercise 5-15 mins based on mean HR during submaximal exercise tests. Walking, cycling or swimming. Instructed to exercise every 2nd day unless they had a relapse (exercise reduced instead). Duration 12 weeks. comparator: relaxation/ flexibility therapy every second day over 12 weeks **Number of participants in each group** 32 graded exercise, 29 controls	Withdrawals: One excluded after randomisation because BMI too high to participate in exercise test. None reported during the study Adverse events: none reported

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Resting heart rate and blood pressure **Baseline values intervention group** 75 (71-78) bpm, 79 (76-82)/ 117 (112-121) mmHg **Baseline values control group** 74 (70-78) bpm, 80 (76-84)/119 (114-124) mmHg **Results in intervention group** 72 (69-75) bpm, 74 (71-76)/ 112 (108-116) mmHg **Results in control group** 74 (70-78) bpm, 76 (74-79)/ 120 (115-125) mmHg **Comments** comparisons seem to have been made within groups rather than between groups	**Outcome measured** Exercise test values Oxygen uptake (mL/kg/min), Respiratory exchange ratio, net blood lactate production (mmol/L) **Baseline values intervention group** 15.6 (13.3 - 17.7), 0.97 (0.93 - 1.01), 1.7 (1.4 - 1.9) **Baseline values control group** 15.8 (13.7 - 17.9), 0.98 (0.94 - 1.02), 1.6 (1.4 - 1.9) **Results in intervention group** 17.1 (14.9 - 19.2), 1.03 (0.99 - 1.06), 1.8 (1.5 - 2.1) **Results in control group** 14.4 (12.4 - 16.4), 1.00 (0.96 - 1.04), 1.4 (1.1 - 1.7) **Comments** comparisons seem to have been made within groups rather than between groups	**Outcome measured** Achievement of target heart rate during the exercise test **Baseline values intervention group** 70% **Baseline values control group** 64% **Results in intervention group** 74% **Results in control group** 53% **Comments**	**Outcome measured** Psychological results HADS depression, HADS anxiety, mental fatigue, physical fatigue **Baseline values intervention group** 6.5 (5.3 - 7.6), 7.3 (5.8 - 8.7), 6.3 (5.6 - 7.0), 11.6 (10.1-13.0) **Baseline values control group** 7.1 (5.9 - 8.2), 8.7 (7.5 - 9.9), 5.6 (5.0 - 6.1), 11.4 (10.4 - 12.3) **Results in intervention group** 4.8 (3.6 - 5.9), 5.7 (4.4 - 6.9), 4.5 (3.9 - 5.2), 8.1 (6.9 - 9.4) **Results in control group** 6.5 (5.5 - 7.6), 7.8 (6.5 - 9.2), 4.8 (4.2 - 5.5), 9.6 (8.3 - 10.9) **Comments** scores significantly lower in the exercise group (p=0.027)
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome measured Cognitive results Stroop test 82 questions; Stroop test 95 questions **Baseline values intervention group** 73.7 (68.0 - 79.3), 80.1 (73.1 - 87.0) **Baseline values control group** 70.0 (61.3 - 78.9), 75.8 (64.6 - 87.0) **Results in intervention group** 79.4 (78.0 - 80.8), 87.5 (81.4 - 93.6) **Results in control group** 71.1 (63.3 - 78.9), 73.1 (60.3- 85.9) **Comments** significantly in favour of the exercise group on the more difficult level of the test (p=0.029)	**Outcome measured** Clinical global impression self-rated **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 5 very much better, 14 much better, 10 a little better, 3 no change **Results in control group** 2 very much better, 10 much better, 10 a little better, 6 no change, 1 a little worse **Comments** no significant difference between the two groups	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Wearden (1998)[33] **Study design** RCT **Level of evidence** 1++	**Number:** 136 **Adults or children?:** Adults **Inclusion criteria:** Aged 18+. Pre-menopausal women required to take precautions against pregnancy. Excluded: those with schizophrenia, bipolar disorder, eating disorder, alcohol or illicit drug misuse, current suicidal ideation, history of ischaemic heart disease, inability to read and write English. Those on antidepressants underwent a 2 weeks washout. **Exclusion criteria:** **Diagnosis/ case definition:** Oxford **Age:** mean 38.7 (10.8) **% Female:** 97 F 39 M **Duration of illness:** median (!QR): 28.0 (39.5) months **Baseline functioning:** 62 fulfilled DSM-III-R criteria for a current psychiatric diagnosis, 14 had major depression, 32 had either dysthymia or non-specific depressive disorder, 14 had various anxiety disorders and 2 had somatisation disorder. **Further details:** none stated 114 had changed their occupation. 35 were members of a self-help group.	GET & fluoxetine 1. Fixed daily dose 20mg fluoxetine plus graded exercise. 2. Graded exercise and placebo drug. 3. Exercise control (activity diaries) and fluoxetine. 4. Exercise control and placebo drug. placebo controlled AND controlled for the amount of therapist contact. Treatment by physiotherapist on 8 occasions over 6 months. Graded exercise: subjects instructed to carry out preferred aerobic activity (walking/ jogging, swimming or cycling) for 20mins at least 3x per week. Activity intensity initially set at a level which utilised oxygen at 75% of subject's tested functional maximum. Exercise intensity was increased when there was a consistent recorded reduction of 10 beats per minute in post-exercise heart rate for one week and two points on the perceived exertion scale. Exercise control groups: subjects not offered specific advice on how much exercise to take but told to do what they could when they felt capable and rest when they felt they needed to. All trial participants kept activity diaries which were reviewed every 4 weeks. **Number of participants in each group** GET+F 33; GET+P 34; ExP+F 35; ExP+P 34	Withdrawals: 22 dropped out by 3 months and 40 by 6 months. More dropouts in exercise vs non-exercise groups (25/68 vs 15/69, $p<0.05$). No sig difference in dropout rates fluoxetine vs placebo (24/68 vs 16/69). 11 dropped out due to side effects (9 F, 2 P), 16 due to lack of efficacy (which groups not stated) and 13 for other reasons or no reason. Dropouts significantly more likely to be members of self help orgs (15/39 vs 20/95, $p=0.04$), have changed/ given up job (38/40 vs 76/96, $p=0.02$) and have worse baseline scores on MOS health perception scale. Adverse events: not stated: 11 dropped out due to them though.

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Fatigue Chalder's 14 item fatigue scale, self-rated questionnaire. Primary outcome = change in score and % of subjects scoring below case level on the fatigue scale. **Baseline values intervention group** Ex+P 33.7(33.0 to 36.9); Ex+F 35.9 (34.4 to 37.5); ExP+F 34.4(32.0 to 36.7) **Baseline values control group** ExP+P 34.0(32.3 to 35.7) **Results in intervention group** ex+P -5.7(-9.5 to -1.9); Ex+F -6.0(-9.7 to -2.3); ExP +F -3.0(-5.9 to -0.2) **Results in control group** ExP+P -2.7(-5.4 to 0.01) **Comments** there were trends for exercise to improve fatigue scale scores at wk12 (mean change 2.1(-0.6 to 4.8, p=0.13) and at wk26 (mean change 2.9(-0.2 to 6.1, p=0.07). Fluoxetine had no effect on fatigue scale at week 12 or wk26. At the beginning of the study no subjects in any group were in the non-case range for fatigue. At 26 weeks results were as follows: Ex+F 6, Ex+P 6, ExP+F 2, ExP+P 2. Interim (12wks) scores and non-case numbers are given in the paper but I haven't extracted them - do you think I should?	**Outcome measured** General health MOS short form scales: physical function, role or occupation function, social function, social function, pain, health perceptions, mental health. Secondary outcome measure = change in score. **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** No significant changes on any MOS scale. Values not reported.	**Outcome measured** Depression Hospital anxiety and depression scales (HAD). Secondary outcome = change in score. **Baseline values intervention group** Ex+F 9.4(3.6), Ex+P 8.5(2.9). ExP+F 9.1(4.2) **Baseline values control group** ExP+P 8.1(3.3) **Results in intervention group** Mean change: Ex+F -2.0(-3.3 to -0.7); Ex+P -1.2(-2.5 to 0.2); ExP+F -1.7(-3.0 to -0.5) **Results in control group** Mean change ExP+P -1.3(-2.3 to -0.3) **Comments** no significant effects of exercise or fluoxetine on HAD scores at 26 weeks. IN complete analysis F reduced score at 12 weeks but in ITT analysis there were no differences. No effects of exercise on HAD case level of depression but fluoxetine treated group reduced from 13 to 5 with one new case arising. Placebo group cases reduced from 5 to 0 but 5 new cases arose.	**Outcome measured** Physical functional work capacity. Calculated as mL of oxygen consumed in the final minute of exercise per kg body weight. **Baseline values intervention group** Ex+F 23.1(9.3); Ex+P 19.9(6.5); ExP+F 22.7(8.7) **Baseline values control group** ExP+P 26.0(9.9) **Results in intervention group** mean change: Ex+F 2.0 (0.4 to 3.5); Ex+P 2.8(0.8 to 4.8); ExP+F 1.0(-0.9 to 3.0) **Results in control group** mean change ExP+P -0.1 (-1.7 to 1.6) **Comments** there was a significant effect of exercise on functional work capacity at week 26 (and at week12) n=132 mean change = 1.9(0.15 to 3.69) p=0.03. Fluoxetine had no significant effect on fwc at either time point.
Additional comments: 21 dropouts were reassessed at the end of the trial There was no worsening of scores on the fatigue scale, functional work capacity, HAD depression scale and MOS health perception scale.			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Whitehead (2002)[38] **Study design** RCT **Level of evidence** 1-	**Number:** 65 **Adults or children?:** Adults **Inclusion criteria:** All GP practices in 2 health authorities in NW England were eligible to take part. **Exclusion criteria:** not stated **Diagnosis/ case definition:** CDC (1994) **Age:** mean 36 yrs CBT, 41 yrs control **% Female:** 54% CBT, 64% control **Duration of illness:** mean 21 months CBT, 33 months control **Baseline functioning:** **Further details:** not stated Randomised by GP practice (35% of practices agreed to participate, 50% recruited participants), but analysis by participant only.	CBT GP-delivered "brief CBT" consisting of patient information booklet (explanatory models of CFS), recoridng levels of activity and encouraging gradual increase at appropriate level and rate. Discussion of beliefs and behaviours around CFS. Control group: usual care (including referral to secondary care) **Number of participants in each group** 26 CBT, 39 control group	Withdrawals: 2 patients moved away and 6 were found not to meet diagnostic criteria. At 6 months, follow up data was available for 18 people in the intervention group and 28 people in the control group. At 12 months data was available for 9 people in the intervention and 21 people in the control group. Adverse events:

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Fatigue 11 item self-completion scale: score of >=3 indicates severe or disabling fatigue. Likert scoring, max fatigue = 33. **Baseline values intervention group** 25.58 **Baseline values control group** 24.26 **Results in intervention group** 6 months 21.89, 12 months 19.11 **Results in control group** 6 months 20.04, 12 months 19.57 **Comments** no significant difference between intervention and control groups	**Outcome measured** Disability London Handicap Scale (LHS) 0 (worst) to 100 (best) **Baseline values intervention group** 58.25 **Baseline values control group** 62.77 **Results in intervention group** 6 months 65.03, 12 months 59.2 **Results in control group** 6 months 63.52, 12 months 65.62 **Comments** no significant difference between intervention and control groups	**Outcome measured** Anxiety and Depression Hospital Anxiety and Depression Scale (HAD) **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** no significant differences between intervention and control groups	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments: 31 GPs who used the management package were asked about patients' use of it. 21 GPs replied, of these, all but one person started to use the diaries. 5 patients used diaries for one month or less. Eight used diaries for 6 months or more and 4 for 12 months or more.			

2. Immunological/ antiviral interventions

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Andersson (1998)[49] **Study design** Controlled trial **Level of evidence** 2-	**Number:** 28 **Adults or children?:** Adults **Inclusion criteria:** Patients had been granted a sickness pension or had been on the sick list, full-time or part-time, for at least six months **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1994) **Age:** 33-64 (mean 47, sd=7.3) **% Female:** All women **Duration of illness:** 5-37 years, mean = 12.9years **Baseline functioning:** No significant differences between 2 groups prior to treatment in any of the laboratory tests or psychometric variables **Further details:** None stated All had history of repeated infections and ongoing mild infections. All were had been certified sick for at least 6 months Subjects had to meet criteria for CFS outlined by CDC and criteria for Fibromyalgia outlined by the American College of Rheumatology.	Staphylococcus toxoid vaccine Given at increasing dose of 0.01, 0.05, 0.1, 0.2, 0.5 and 1.0 ml of fully potent vaccine or placebo (sterile water injection). Each dose given twice with one injection per week Injection given subcutaneously in gluteal region by a nurse. Study duration = 12 weeks **Number of participants in each group** 14	Withdrawals: Four patients were excluded during the study, 1 because of malignancy, 2 because of severe depression and 1 because of psychotic illness, 3 were on placebo and the one with a psychotic reaction was on vaccine treatment Adverse events: Not stated

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Depression Zumg-s self rating depression scale used - 20 items measuring both somatic and affective components of depression assessed on 4 point scale (1=normal, 4=maximum severity), expressed in percentages **Baseline values intervention group** 39.5 (range 38-48) **Baseline values control group** 47 (range 45-50) **Results in intervention group** 38 (range 37-41), decrease was not significant **Results in control group** 39 (36-44), p-value for change from baseline <0.05 **Comments** No significant intergroup differences	**Outcome measured** Psychological assessment Comprehensive psychopathological rating scale (CPRS), 15 reported and observed items on 7 scale steps from 0 (normal) to 6 (maximum severity) **Baseline values intervention group** CPRS fatigue score: 5 (range 4-5) CPRS pain score: 5 (range 4-5) **Baseline values control group** CPRS fatigue score: 5 (range 4-5). CPRS pain score 4(range 4-5) **Results in intervention group** CPRS fatigue score: 3 (range 2-4), p<0.01 for change CPRS pain score: 4 (range 4-4), p<0.01 **Results in control group** CPRS fatigue score: 4 (range 4-5), p>0.05. CPRS pain score 5(range 4-5), p>0.05 **Comments** Other CPRS items that improved significantly (at 5% level) in vaccine treated groups were being worried, concentration difficulties, memory difficulties, sleep difficulties & vegetative symptoms, no significant intergroup differences with regard to these items	**Outcome measured** Clinical global impression Clinical global improvement rated as whether or not due to treatment **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 7/13 on vaccine assessed as minimally improved, 3 as much improved and 3 as unchanged. Improvement statistically significant compared to placebo group (p<0.05) **Results in control group** 3/11 minimally improved, remaining 8 unchanged **Comments**	**Outcome measured** Pain Momentarily perceived pain measured using visual analogue scale, varying from no pain to worst pain imaginable. (median values presented) **Baseline values intervention group** 6.5 (95% CI: 3.5-6.5) **Baseline values control group** 6.5 (95% CI: 5.0-6.5) **Results in intervention group** 4.1 (95% CI: 2.8-5.0) **Results in control group** 4.2 (95% CI: 3.2-5.6) **Comments** Significant decreases reported in both groups, no differences in change between the groups

Outcome 5	Outcome 6	Outcome 7	Outcome 8
Outcome measured Pain Average pain in last week measured using visual analogue scale, varying from no pain to worst pain imaginable (median values presented). **Baseline values intervention group** 6.0 (95% CI: 4.9-7.2) **Baseline values control group** 6.5 (95% CI: 5.2-6.5) **Results in intervention group** 4.2 (95% CI:3.0-6.0), p-value for change from baseline >0.05 **Results in control group** 5.2 (95% CI:3.2-6.2), p-value for change from baseline <0.05 **Comments** Authors do not report whether the difference from baseline to final differed between the 2 groups	**Outcome measured** Pain Pressure pain threshold determined with hand-held electronic pressure algometer **Baseline values intervention group** 20 kPa(95% CI:1-56) **Baseline values control group** 32 kPa(95% CI:5-152) **Results in intervention group** 47 kPa (95% CI:14-124) p-value for change >0.05 **Results in control group** 76 kPa(95% CI:11-129) p-value for change >0.05 **Comments** Authors do not report whether the difference from baseline to final differed between the 2 groups	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Brook (1993)[42] **Study design** RCT **Level of evidence** 1-	**Number:** 20 **Adults or children?:** Adults **Inclusion criteria:** Peformance status of ECOG (Eastern Cooperative Oncology Group) I or II. **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1988) **Age:** Not stated **% Female:** 14 women, 6 men **Duration of illness:** 1-11 years **Baseline functioning:** ECOG score of all patients combined: 0:0; I: 8; II: 12 **Further details:** Not stated Not stated No further details	Interferon Patients randomised to interferon alpha 2b group or control group Cross-over study - control group treated after 3 motnhs. Three meagaunits of interferon - alpha 2b was administered subcutaneously thrice weekly for 12 weeks after which the patients were observed for a further 12 months **Number of participants in each group** 11 patients received immediate therapy, 9 in control group	Withdrawals: 1 patient in control group decided not to be treated. 1 patient in treatment group withdrew after 2 weeks due to adverse effects (increased fatigue). Adverse events: Therapy was reasonably well-tolerated and side effects, which were most prominent durings weeks 2-4 of treatment were no worse than those seen during therapy for other treatments. None of the side effects persisted after end of therapy except mild alopecia which resolved in 3 months and mild boils which presisted for up to a year in 2 women.

Results

Outcome 1
Outcome measured: Activity Graded according to ECOG scale: 0: able to carry out normal activity without restrictions; I: restricted in physically struous activity but ambulatory and able to do light work; II: ambulatory and capable of self care but unable to work; III: capable of only limited self care and confined to bed or chair for >50% of waking hours; IV: totally disabled and confined to bed or chair **Baseline values intervention group** Not stated **Baseline values control group** Not stated **Results in intervention group** 3/20 patients completely recovered (scored=0, baseline scores were I in 2 patients and II in 1 patient) . 2 /20 patients improved (both were II at start of trial) **Results in control group** 0/20 reovered significantly **Comments** 4 patients that improved on treatment all reported acute virus-type illness at start of their disease. Improvements remained in all patients at 8 or 12 months follow-up.

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Diaz-Mitoma (2003)[47] **Study design** RCT **Level of evidence** 1-	**Number:** 16 **Adults or children?:** Adults **Inclusion criteria:** CFS diagnosis (inclusion criteria not explicitly stated) **Exclusion criteria:** malignancy, pregnancy, major organ or system pathology **Diagnosis/ case definition:** CDC 94 & 88 **Age:** mean 45 years 8 months **% Female:** 81% **Duration of illness:** at least 6 months **Baseline functioning:** not stated. **Further details:** two patients also had a diagnosis of depression. Eight women also had significant signs of fibromyalgia. Caucasian, referred from Nightingale Research Foundation in Ottawa. 14 patients had diagnosis of CFS as defined in 1988 and 1994 CDC case definition. Diagnostic workup excluded malignancy and major organ or system pathology.	inosine pranobex (Isoprinosine) 500mg tablet of inosine pranobex versus methylcellulose placebo tablet Duration 3 months (single-blind) **Number of participants in each group** 10 in inosine arm, 6 in placebo arm	Withdrawals: one in each group Adverse events: Transient elevation of serum uric acid (presumed in treatment group)

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Improvement self-rated symptom severity **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 6 **Results in control group** 0 (not measured in placebo group) **Comments** all subsequent outcomes divided into 'improved' and 'not improved' for medication group vs 'placebo'	**Outcome measured** Cognitive deficit scores Cognitive deficit subset scores of the symptom checklist questionnaire (SCL-90-R), median **Baseline values intervention group** Improved 1.88, not improved 1.31 **Baseline values control group** 2.5 **Results in intervention group** Improved 1.88 (change -0.375), not improved 1.38 (change 0.063) **Results in control group** 2.25 (change -0.375) **Comments** None of the differences between groups was statistically significant	**Outcome measured** Global severity index; activities of daily living questionnaire **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** no statistically significant difference between the three groups	**Outcome measured** Karnofsky Performance Scale Median Karnofsky Performance Scores **Baseline values intervention group** improved 62.5, not improved 65.0 **Baseline values control group** 60.0 **Results in intervention group** improved: 0.6% change vs 0 median, 0 decreased, 2 increased. Not improved: 0% change vs 0 median, 1 decreased, 1 increased. **Results in control group** 3% change vs 0 median; 0 increased, 0 decreased **Comments**
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome measured Fibromyalgia tender points (median) **Baseline values intervention group** improved 12.5, not improved 10 **Baseline values control group** 16 **Results in intervention group** improved 10 (% change -3.3%), not improved 8.5 (% change 0.5%) **Results in control group** 17 (0% change) **Comments**	**Outcome measured** Immune function NK cell activity, CD4+ cell activity **Baseline values intervention group** **Baseline values control group** **Results in intervention group** Significant increase in NK lytic activity in improved vs not improved patients ($p<0.03$). Significantly greater numbers of CD4+ T helper cells in improved group at week 12 ($p<0.03$) **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Lerner (2001)[46] **Study design** RCT **Level of evidence** 2-	**Number:** 11 **Adults or children?:** Not stated **Inclusion criteria:** not stated **Exclusion criteria:** **Diagnosis/ case definition:** Not stated **Age:** mean 42.7 years **% Female:** 10/11 F **Duration of illness:** 35.1 months (mean) **Baseline functioning:** 1/11 had positive HCMV IgM titre. 4/11 had conifection with EBV. Energy index (EI) score mean 3.5 (max 10). Mean symptom score (0-1) was 0.81. **Further details:** none stated Cardiac tissues and blood samples tested negative for EBV. 2 tested positive for HCMV. Cardiomyopathic degenerative findings were noted in CFS patients. One had myocarditis. none stated	Gancyclovir Intravenous, 5mg/kg given q12h for 30 days, followed by oral ganciclovir 1g given q8h 6 months after discontinuation of iv ganciclovir, if no improvement observed and eleveated EBV antibodies, oral valacyclovir 1g given q6h added to oral ganciclovir treatment. Duration 18 months each arm. **Number of participants in each group** 11 (crossover trial)	Withdrawals: see adverse events Adverse events: When 2 patients with CFS who were undergoing right ventricular endomyocardial biopsies experienced serious pericardial bleeding, the study was ended prematurely.

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: HCMV and EBV antibody titres **Baseline values intervention group** 1/11 had positive HCMV IgM titre. 4/11 had coinfection with EBV. **Baseline values control group** **Results in intervention group** HCMV titre was absent after 30 days treatment. After administration of valacyclovir, EBV-EA titres decreased or became negative in 3 of the 4. **Results in control group** **Comments** Unchanging high positive titres of HCMV IgG antibody were noted throughout the 18 month trial.	**Outcome measured** Energy Index (EI) point scores score 0 = bedridden, 5=CFS, score 10= healthy. **Baseline values intervention group** mean 3.5 (n=7) **Baseline values control group** mean 4.4 (n=4) **Results in intervention group** 6 months (7 pts) mean 4.4. 12 months (7 pts) mean 5.8. 18 months (7 pts) mean 6.1 **Results in control group** 6 months (4 pts) mean 3.9 (6 months gancyclovir mean=4.4, then 6 months valacyclovir mean=6.1) **Comments**	**Outcome measured** Symptom scores e.g. chest pain, wooziness (lightheadedness and cognitive disturbance), palpitations at rest, muscle aches. Symptom score of 1 = presence of all 4 symptoms, 0= absence of all 4 symptoms. **Baseline values intervention group** mean 0.81 (11 pts) **Baseline values control group** mean 0.81 (11 pts) **Results in intervention group** 6 months (7 pts) 0.38. 12 months (7 pts) mean cumulative score = 0.28. 18 months (7 pts) 0.19 **Results in control group** 6 months (4 pts) mean 0.5. **Comments** problems as above.	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Lloyd (1993)[24] **Study design** RCT **Level of evidence** 1+	**Number:** 90 **Adults or children?:** Adults **Inclusion criteria:** Patients capable of bringing themselves to the clinic at biweekly intervals for 4 month period. Had not received previous immunologic therapy **Exclusion criteria:** **Diagnosis/ case definition:** Austrialia **Age:** 39.6 (sd=12.3, 17-65 years) **% Female:** 68 F, 22 M **Duration of illness:** mean 5.5 years, range 1-28 years **Baseline functioning:** Mean Karnofsky score at baseline was 71.4 (sd=8.1), pre-treatment activity spent median of 3.0 hours in non-sedentary activities per 24 hour period **Further details:** Around 75% had major depression Not stated Alternative medical explanations for symptoms excluded by history, physical examinations, and investigations including blood cell count, and renal and liver function tests, where clinically indicated additional tests were performed	Immunologic Dialyzable leukocyte extract in a dose of 5 * 1000000000 (including >50% mononuclear cells) designated for each treatment dose, donor leukocytes obtained from healthy family members for 50 patients and from unrelated donors for other 40. Received 8 biweekly intramuscular injections of disgnated leukocyte extract or placebo (lyophilized normal saline). CBT treatment as outpatients, 6 biweekly sessions lasting 30-60mins, aimed at re-establishing previous physical and social activity or Clinic control. Patients randomised to either CBT + DLE, DLE + clinic, CBT + placebo or placebo + clinic **Number of participants in each group** CBT+DLE: 20; DLE+ clinic: 26; Placebo + CBT: 21; Placebo + clinic: 23	Withdrawals: 2 patients withdrew during the trial, 1 in DLE + clinic group and 1 in placebo + clinic group, both were excluded from the analysis Adverse events: minor discomfort at injection site common with both treatments, reported in 76% (34/45)of treatment group and 44% (19/43) of placebo ($P<0.05$ from chi2 analysis), one treatment recipient developed pruritic skin eruption that did not necessitate discontinuation of therapy

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: General health Global well-being measured using 10 item visual analogue scales from which a cumulative score was calculated **Baseline values intervention group** Placebo + CBT: 406; DLE + clinic: 435; DLE + CBT: 458 **Baseline values control group** Placebo + clinic: 445 **Results in intervention group** Placebo + CBT: 469; DLE + clinic: 498; DLE + CBT: 596 **Results in control group** Placebo + clinic: 477 **Comments** Significantly greater improvement in DLE + CBT group compared to other groups (F=1.49, p<0.05)	**Outcome measured** Physical Physical capacity assessed by standardised diary of daily activities, measured as number of non-sedentary hours **Baseline values intervention group** Placebo + CBT: 5.5; DLE + clinic: 4.7; DLE + CBT: 4.3 **Baseline values control group** Placebo + clinic: 5.4 **Results in intervention group** Placebo + CBT: 5.2 DLE + clinic: 4.9; DLE + CBT: 4.9 **Results in control group** Placebo + clinic: 5.2 **Comments** No significant difference between groups (F=1.18, p>0.05)	**Outcome measured** Functional measure Patients rated by one investigator on Karnofsky performance scale **Baseline values intervention group** Placebo + CBT: 71.2; DLE + clinic: 72.2; DLE + CBT: 71.5 **Baseline values control group** Placebo + clinic: 70.5 **Results in intervention group** Placebo + CBT: 72.1; DLE + clinic: 74.8; DLE + CBT: 80.0 **Results in control group** Placebo + clinic: 73.4 **Comments** No significant difference between groups (F=1.11, p>0.05)	**Outcome measured** Fatigue Profile of mood states questionnaire used to quantitatively assess fatigue **Baseline values intervention group** Placebo + CBT: 22.8; DLE + clinic: 22.0, DLE + CBT:21.1 **Baseline values control group** Placebo + clinic: 20.8, **Results in intervention group** Placebo + CBT: 16.8; DLE + clinic: 16.9; DLE + CBT: 17.8 **Results in control group** Placebo + clinic: 17.3, **Comments** No significant difference between groups (F=1.15, p>0.05)
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome measured Confusion Profile of mood states questionnaire used to quantitatively assess confusion **Baseline values intervention group** Placebo + CBT: 14.8; DLE + clinic: 12.3; DLE + CBT: 14.8 **Baseline values control group** Placebo + clinic: 13.7, **Results in intervention group** Placebo + CBT: 12.8; DLE + clinic: 10.8; DLE + CBT: 14.4 **Results in control group** Placebo + clinic: 11.6, **Comments** No significant difference between groups (F=0.39, p>0.05)	**Outcome measured** Depression Profile of mood states questionnaire used to quantitatively assess depression **Baseline values intervention group** Placebo + CBT: 18.2; DLE + clinic: 15.1; DLE + CBT: 14.3 **Baseline values control group** Placebo + clinic: 17.1 **Results in intervention group** Placebo + CBT: 15.9; DLE + clinic: 10.1; DLE + CBT: 12.9 **Results in control group** Placebo + clinic: 14.6 **Comments** No significant difference between groups (F=0.70, p>0.05)	**Outcome measured** Immune outcomes CD4, CD8 cell counts and DTH skin response **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** No significant difference between treatment groups (p>0.05)	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments: Follow up at 7 months			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Lloyd (1990)[39] **Study design** RCT **Level of evidence** 1+	**Number:** 49 **Adults or children?:** Both **Inclusion criteria:** No previous immunologic therapy **Exclusion criteria:** **Diagnosis/ case definition:** Similar to CDC (1988) **Age:** 16 to 63 (mean=36) **% Female:** 25 males, 24 females **Duration of illness:** 12 to 180 months (median 47) **Baseline functioning:** 32 patients were unable to participate in work, none of patients was able to undertake sport or vigorous leisure activity and social activities of 45 patients were reported to be at least moderately reduced. Reduction in absolute count of T-cell subsets at the lower limit of normal ranges for testing laboratory found in 43% of patients, in CD4 subset in 9 patients, and in CD8 subset in 18 patients. Reduced DTH responses demonstrated in 33 patients, 40/49 patients had abnormal cell-mediated immunity evidenced by reduced DTH response and/or T-cell lymphopenia. 7/33 patients met criteria for current major depressive episode, 19 had mild depression **Further details:** None stated Acute viral like illness precipitated onset in 37 patients, 40 had abnormal cell-mediated immunity History of at least 6 months duration of marked exercise aggravated muscle fatigue, with abnormally prolonged recovery time, associated with typical constitutional and neuropsychiatric symptoms. CFS was producing frequent medical consultation and a substantial reduction in the ability to participate in usual daily activities when compared with subject's premorbid status. Other chronic infectious or immunodeficiency related disorders excluded	Immunoglobulin Patients either received intravenous immunoglobulin (2g(IgG)/kg) or placebo of 10% w/v maltose 3 infusions lasting 24 hours administered at monthly intervals, results show response to therapy 3 months after final infusion **Number of participants in each group** 23 in treatment arm, 26 in placebo	Withdrawals: 2 immunoglobulin recipients withdrew from study: one because of mild, but transient, abnormal liver function tests, other withdrew voluntarily after phlebitis had occurred with the first infusion Adverse events: Phlebitis and constitution symptoms including headaches, worsened fatigue and concentration impairment occurred more commonly in the immunoglobulin recipients than in the patients who received placebo. Phlebitis occurred in 35/65 immunoglobulin infusions & with 1 placebo infection, constitutional symptoms occurred in 53/65 immunoglobulin infusions and 19/78 placebo infusions.

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Symptom measure Symptoms and disability as assessed by the physician **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** 10/23 of immunoglobulin and 3/26 of the placebo recipients had marked reduction in symptoms and improvement in functional capacity (chi2=4.85, p=0.03)	**Outcome measured** Employment status Measure of functional capacity **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** 6/13 who responded (all immunoglobulin recipients) resumed pre-morbid employment status in full-time occupation or housework, 5 patients (3 immunoglobulin and 2 placebo) recommenced employment or other activities in a part-time capacity. 11/13 responders (9 immunoglobulin, 2 placebo) resumed involvement in leisure or sporting activities, all responders increased level of participation in social activities, in 8 patients (7 immunoglobulin) this increase allowed regular social events, in 8/10 immunoglobulin responders improvement in symptoms and function was noted within 3 weeks of first infusion and tended to increase incrementally after subsequent infusions. Remaining subjects had little to no change in ability to participate in work, leisure and social activities.	**Outcome measured** Quality of life Measured by QAL score on visual analogue scale, modified to include 10 aspects of physical and neuropsychiatric symptomology typical of CFS **Baseline values intervention group** 36 (sd=14) **Baseline values control group** 41(sd=16) **Results in intervention group** 36(sd=21) **Results in control group** 38(sd=14) **Comments** No significant differences when overall scores compared. However, significantly greater improvement in QAL score of responders in comparison to non-responders (as assessed by physician): improved by mean of 41% (sd=79%) in responders compared to mean of -12% (sd=33%) in non-responders, p<0.01	**Outcome measured** Depression 33 patients interviewed by psychiatrist completed self-report measures of depression (Zung scale) **Baseline values intervention group** 42(sd=8) **Baseline values control group** 38(sd=11) **Results in intervention group** 41(sd=11) **Results in control group** 40(sd=12) **Comments** No significant differences when overall scores compared.

Outcome 5	Outcome 6	Outcome 7	Outcome 8
Outcome measured Depression Psychiatrist rated patients on Hamilton Depression scale **Baseline values intervention group** 10.7(2.8) **Baseline values control group** 10.5(3.4) **Results in intervention group** 9(5) **Results in control group** 10(3) **Comments** No significant differences when overall scores compared. However, significantly greater improvement in Hamilton score of responders in comparison to non-responders (as assessed by physician): improved by mean of 42% (sd=57%) in responders compared to mean of -12% (sd=40%) in non-responders, p<0.01	**Outcome measured** Immune outcomes CD4 lymphocyte, PHA response and DTH response **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** 10 immunoglobulin recipients and 3 placebo recipients rated by physician as having responded had significant improvement in cell-mediated immunity, represented resolution of abnormal values in 7/8 patients who had reduced DTH response at entry and in 2/5 who had reduced CD4 counts at entry, 2/3 placebo responders had improvement in cell-mediated immunity, remaining patient did not undergo immunologic testing at follow-up	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments: In 23 immunoglobulin recipients % change in QAL score was positively correlated with improvement in Hamilton depression score (r=0.6, p<0.01) and improvement in cell-mediated immunity measured by CD4 count (r=0.4, p<0.05) and DTH (r=0.3, p=0.08)			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Peterson (1990)[40] **Study design** RCT **Level of evidence** 1+	**Number:** 30 **Adults or children?:** Not stated **Inclusion criteria:** No other explanation for chronic fatigue **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1988) **Age:** mean 40.8(11.2) **% Female:** 8M 22F **Duration of illness:** mean 3.8(2.2) **Baseline functioning:** mean number of CFS symptoms 8.8(1.3). 43.3% vocationally disabled. Low levels of total IgG and IgG1 in 40% of pts **Further details:** None stated 96.7% had viral-like onset of illness. All recruited from CFS research program at medical centre in Minnesota. Medical psychometric and psychiatric evaluations did not establish another explanation for chronic fatigue	Immunoglobulin G 1. IV IgG (1g/kg) every 30 days for 6 months. 2. Placebo= IV 1% albumin solution every 30 days for 6 months All treatments given at one centre. Pts permitted to take vitamins, NSAIDs, decongestants, antihistamines, oral contraceptives and other medicines prescribed by GPs during study. **Number of participants in each group** 15	Withdrawals: 2 due to adverse events (1 from each group). Adverse events: Symptoms occurring within 48h of treatment: headache 14/15 IgG group vs 9/15 placebo group. Major adverse experiences: 2 mentioned above who were removed from study plus 2 referred to specialists, one hospitalised and one returned to clinic repeatedly. Not stated which groups they were in. Also 18pts had GI complaints, 10 had fever and 6 had myalgias or arthralgias but we don't know which groups they were in.

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Symptom measure Self-assessment form - Symptom Checklist 90 **Baseline values intervention group** fatigue 14/14; prolonged postex fatigue 12/14; muscle weakness 12/14; myalgias 10/14; sleep disturbance 10/14; headaches 9/14; arthralgias 8/14 **Baseline values control group** fatigue 14/14; prolonged postex fatigue 14/14; muscle weakness 11/14; myalgias 10/14; sleep disturbance 10/14; headaches 7/14; arthralgias 11/14 **Results in intervention group** fatigue 14/14; prolonged postex fatigue 12/14; muscle weakness 8/14; myalgias 7/14; sleep disturbance 8/14; headaches 7/14; arthralgias 6/14 **Results in control group** fatigue 12/14; prolonged postex fatigue 11/14; muscle weakness 8/14; myalgias 8/14; sleep disturbance 5/14; headaches 6/14; arthralgias 9/14 **Comments** No statistically significant changes from baseline to end of study; no significant difference between the groups at the end of the study	**Outcome measured** Functional measure functional status and well being, self-assessment form - Medical outcome short study form (0=worst, 100=best), sd given in brackets **Baseline values intervention group** physical 63.1(25.9); social 6.1(6.4); health perceptions 8.5(18.4); mental health 63.7(17.1) **Baseline values control group** physical 66.1(21.0); social 5.7(3.0); health perceptions 12.0(14.8); mental health 59.7(13.4) **Results in intervention group** physical 56.0(23.2); social 5.2(5.5); health perceptions 20.5(25.0); mental health 58.3(17.4) **Results in control group** physical 51.8(22.2); social 9.4(7.9); health perceptions 16.3(13.1); mental health 62.9(13.3) **Comments**	**Outcome measured** Immune outcomes IgG1 and IgG3 levels **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** IgG1 levels of all pts receiving IgG fell within normal range following treatment 3 - effect not observed in placebo group. Overall increase in IgG3 levels associated with IV IgG therapy this subclass remained below the normal range in 6 pts at the end of the study	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Rowe (1997)[91] **Study design** RCT **Level of evidence** 1++	**Number:** 71 **Adults or children?:** Children (11-18) **Inclusion criteria:** Excluded if receiving steroid medication, NSAIDs, Immunomodulatory agents or were currently receiving or had received intravenous IgG. Aged 11-18. **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1994) **Age:** Mean 15.3 - 15.6 (2.0) **% Female:** 18 M, 53 F **Duration of illness:** mean placebo group 16.9(11.4) months, mean IgG 19.2(13.2) months **Baseline functioning:** Baseline mean percentage functional score placebo 25.9(20.5), IgG 23.9(19.7) **Further details:** None stated All referred to the Royal Children's' Hospital, Melbourne None given	Immunoglobulin G 1. Immunoglobulin G, 3 infusions of 1g/kg (max 1 L of 6g/100ml in 10% w/v maltose solution) given 1 month apart. 2. Placebo = 10% w/v maltose solution with 1% albumin equiv. All pts received additional information regarding services available such as Visiting Teacher Service, Distance Education (lessons by correspondence), availability of Social Security support and had access to a support group. **Number of participants in each group** IgG group 36, placebo group 35 (34 in analysis).	Withdrawals: One in the placebo group due to moving away. Adverse events: Reported side effects common with both solutions, particularly headache, fatigue and weakness, nausea, muscle aches and pains and difficulty concentrating. Full details given in paper.

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Functional measure Mean percentage functional score (compared with premorbid levels) based on proportion school/ work attempted, attendance at school/ work, proportion normal physical/ social activities attempted. **Baseline values intervention group** 23.9 (sd=19.7) **Baseline values control group** 25.9 (sd=20.5) **Results in intervention group** 49.9 at 3 months, 64.1 at 6 months (sd=28.2) **Results in control group** 44.6 at 3 months, 52.1 at 6 months (sd=31.4) **Comments** Comparison between the 2 groups was significant at 6 months (p<0.04). Nine in the IgG group returned to full function and 4 in the placebo group.	**Outcome measured** Functional measure Categorised as 'improved' or 'not improved', improvement being defined as 25% improvement in mean functional score at 6 months **Baseline values intervention group** 0 improved **Baseline values control group** 0 improved **Results in intervention group** 26 improved **Results in control group** 15 improved **Comments** p<0.02 for 6 month follow-up	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
See (1996)[43] **Study design** RCT **Level of evidence** 1+	**Number:** 30 **Adults or children?:** Adults **Inclusion criteria:** Excluded: pts who had received immunologic therapy during the previous year; also those with chronic infections I.e. HIV, TB, Borrelia, Coccidiodomycose immitis, Toxoplasma gondii), those with rheumatologic disorders, MS, thyroid disease, IgG deficiency and primary psychiatric illness. **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1988) **Age:** mean 37.2 (7.4) years, range 22-58 **% Female:** 6 M 24 F **Duration of illness:** 4.6 years (1-12) **Baseline functioning:** **Further details:** None stated referred from secondary care. Chronic infections and other chronic disease exclusion criteria screened for at trial entry.	Alpha interferon 1. Alfa 2a interferon (3 million units) s.c. 3 times per week. 2. Placebo (0.9% NaCl solution) s.c. 3 times p.w. For 12 weeks. Crossover trial. No washout. Each pt drank at least 16oz water with each dose and took 650mg acetominophen 2hrs following the dose to minimise side effects from interferon and ensure blinding **Number of participants in each group** 30 (crossover trial)	Withdrawals: 4 withdrew - all were receiving interferon at the time: 2 had neutropenia, one palpitations and one worsened fatigue. Adverse events: 4 pts had significant flu-like symptoms within 6 hrs of initial dose of interferon. 2 had new onset diarrhoea. 9 female pts complained of hair loss at some point during or after interferon therapy.

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Immune outcomes NK function, %NLP, CD4 count, CD8 count **Baseline values intervention group** NK 87.8(19.6)LU; %NLP 61.3(18.7)conA, 56.9(23.4)PHA, 80.3(20.9)PWM, 46.8(15.9)candida, 70.2(21.3)tetanus, 51.7(21.0)mumps **Baseline values control group** NK 89.1(18.9)LU; %NLP 62.3(23.1) conA, 59.6(21.3)PHA, 78.5(22.7)PWM, 49.4(15.6)candida, 71.5(19.8)tetanus, 54.8(22.6)mumps **Results in intervention group** NK increased significantly to 129.3(20.7) p<.05, f=3.51. Mean %NLP did not change. **Results in control group** No significant changes **Comments** CD4 and CD8 counts no significant changes except in one patient (CD4 rose from 422 to 673 after 12 weeks interferon).	**Outcome measured** Quality of life 0-60, 60 worst score **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Mean QOL score at baseline was 35.7(10.9) and did not change significantly after 12 weeks of placebo 31.4(9.2) or interferon 28.4(13.8) therapy.	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Steinberg (1996)[48] **Study design** RCT **Level of evidence** 1+	**Number:** 30 **Adults or children?:** Adults **Inclusion criteria:** No attempt was made to preselect patients with atopic disease. Subjects had to be aged 18 or more **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1988) **Age:** Mean 36.2 (11.4) years (range 19-74) **% Female:** 23 F 7 M **Duration of illness:** Not stated. **Baseline functioning:** **Further details:** None stated. Recruited from CFS research program, responded to a letter. 73% had an atopic history and 53% responded to skin tests. Thorough medical, psychometric and psychiatric examinations.	Oral terfenadine (antihistamine) 1. Terfenadine 60mg b.d. 2. Placebo b.d. Duration 2 months. Preceded by 2 week washout. Pts allowed to take oral contraceptives, antibiotics, vitamins, aspirin, NSAIDs, beta blockers and other prescribed medications. Not allowed antihistamines, decongestants, TCAs or ocular, nasal or bronchial anti-inflammatory agents. **Number of participants in each group** 15 (14 reported)	Withdrawals: 2 pts (one from each group) withdrew from the study due to 'no improvement' Adverse events: None stated

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Functional measure Self assessment using modified Medical Outcome study Short Form, reporting on physical and social functioning, health perceptions and mental health during the previous month (0 - 100 = worst to best) **Baseline values intervention group** physical function 60.32(14.27); social function 36.61(11.23); health perceptions 33.81(12.67); mental health 64.29(14.11) **Baseline values control group** Physical function 64.53(17.2); Social function 40.38(17.54); health perceptions 37.44(14.54); mental health 77.18(15.74) **Results in intervention group** Physical function 63.10(17.52); social function 34.52(11.49); health perceptions 30.95(13.49); mental health 63.89(21.36) **Results in control group** Physical function 69.66(18.09); social function 45.83(22.26); health perceptions 29.74(12.36); mental health 74.62(15.31) **Comments** mean (SD). All comparisons were-non-significant	**Outcome measured** Symptom measure Self assessment 4 point scale (none to severe) **Baseline values intervention group** Fatigue 10; postexertional fatigue 11; muscle weakness 7; myalgias 8; sleep disturbance 3; headaches 10; arthralgias 6 **Baseline values control group** Fatigue 12; postexertional fatigue 12; muscle weakness 6; myalgias 7; sleep disturbance 6; headaches 5; arthralgias 6 **Results in intervention group** Fatigue 12; postexertional fatigue 12; muscle weakness 8; myalgias 9; sleep disturbance 3; headaches 9; arthralgias 8 **Results in control group** Fatigue 10; postexertional fatigue 8; muscle weakness 7; myalgias 6; sleep disturbance 5; headaches 3; arthralgias 5 **Comments** Number reporting symptom. All comparisons were-non-significant	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Straus (1988)[45] **Study design** RCT **Level of evidence** 1+	**Number:** 27 **Adults or children?:** Adults **Inclusion criteria:** All had titres of antibodies to diffuse or restricted early antigens of EBV of >=1:40 or had to lack antibodies to EBNA (<1:2) **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1988) **Age:** mean 34.1 (sem 1.5) yrs **% Female:** M 8 F 19 **Duration of illness:** Mean 6.8 (se 1.4) yrs **Baseline functioning:** 12/27 vocationally disabled, 10/27 working part time. **Further details:** None stated Fatigue began insidiously in 4, during acute febrile illness in 10 and during mononucleosis-like illness in 7. Initial screening, followed by psychiatric assessment. Full physical examination conducted at NIH at beginning of each study phase by 1 physician blinded to treatment.	Acyclovir (antiviral) 1. Acyclovir 2. Placebo. Crossover trial. Drugs given 1 week iv (500mg per sq m body surface) to hospitalised pts, 30 days orally (acyclovir 800mg qid), with a 6 week washout period before alternate treatment was given. Pts permitted to take vitamins, nonsteroidal and nonnarcotic analgesics, decongestants, antihistamines, oral contraceptives and antibiotics during the study. **Number of participants in each group** 27 (crossover trial)	Withdrawals: 3 had reversible renal failure during acyclovir infusions and were withdrawn from the study. Adverse events: Nausea/ upset stomach: acyclovir 10 iv, 4 oral; placebo 5 iv, 0 oral. Vomiting: acyclovir 2 iv, 1 oral; placebo 1 iv, 0 oral. Diarrhoea: acyclovir 3 iv, 3 oral; placebo 0 iv, 1 oral. Dizziness/ disorientation: acyclovir 7 iv, 0 oral; placebo 3 iv, 0 oral. Headache: acyclovir 4 iv, 1 oral; placebo 1 iv, 0 oral. Jitteriness: acyclovir 1 iv, 0 oral; placebo 1 iv, 0 oral. Rash: acyclovir 0 iv, 2 oral; placebo 0 iv 0 oral. Other: acyclovir 14 iv, 9 oral; placebo 10 iv, 5 oral.

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Mood Self-assessment, Profile of Mood States Questionnaire **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Acyclovir vs placebo mean difference (SEM): Anxiety 2.92 (1.11) p=0.02; Depression 3.97(1.59) p=0.02; Anger 2.30(1.18) p=0.07; Vigour -2.05(1.26) p=0.12; Fatigue 1.26(1.10) p=0.27; Confusion 1.83(0.61) p<0.01. Score indicates improvement.	**Outcome measured** Personal wellbeing Wellness scores self assessment 0 for dying, 100 for being as well as they could imagine a person to be. **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** acyclovir vs placebo: mean difference -1.08 SEM 3.01 p>0.5	**Outcome measured** Temperature Oral temperature, self-measured **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Acyclovir vs placebo mean difference -0.02 SEM 0.03 p>0.5	**Outcome measured** Rest hours/ day **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Acyclovir vs placebo mean -0.05 SEM 0.38 p>0.5
Additional comments: 11 pts felt better during acyclovir treatment and 10 during placebo treatment. Neither acyclovir treatment nor clinical improvement correlated with alterations in laboratory findings, including titres of antibody to EBV or levels or circulating immune complexes or of leukocyte 2,5-oligoadenylate synthetase.			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Strayer (1994)[44] **Study design** RCT **Level of evidence** 1+	**Number:** 92 **Adults or children?:** Not stated **Inclusion criteria:** Severely debilitated subjects with KPS (Karnofsky performance score) from 20-60 were eligible, CFS diagnosed more than 12 months earlier and underwent diagnostic worlup to exclude other disorders whose symptomology might miic that of CFS, patients excluded if: pregnant/nursing **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1988) **Age:** Mean: 36 in treatment group, 35 in placebo **% Female:** 23M, 69F **Duration of illness:** Mean: 6.1 years in treatment group, 4.4 years in placebo group (p-value of difference =0.08) **Baseline functioning:** Incidence of all symptoms examined high in both groups (60-100% reported). 59% had non-exudative pharyngitis and 78% had evidence of cervical or axillary lymphadenopathy. **Further details:** None stated Groups well matched at baseline with regard to clinical status and levels of immunologic and virological markers, overall degree of physical debilitation, perceived cognitive impairment, m ge	RNA drug (Poly(I).Poly(C12U)) 24 week long, twice weekly intravenous infusion usually given over 35mins. Each patient assigned to treatment group received 4 doses of 200mg and then 400mg twice weekly, patients assigned to placebo group received equivalent volume of saline **Number of participants in each group** 45 received treatment, 47 placebo. Analysis on 41 in treatment group, 43 in placebo.	Withdrawals: 8 patients dropped out, 4 from each group, 3 of the placebo patients and one of the treatment patients dropped out because symptoms intensified, 4 others withdrew for non-medical reason related to economic concerns, domestic problems, or transportation issues. Two arms did not differ significantly with regard to missed doses, no patients missed more than 6 doses Adverse events: Relative frequencies of more than 200 adverse-event categories were impaired, no statistically significant differences between groups except in case of insomnia (higher in placebo), dry skin (higher in treatment) - this would be expected by chance as more than 200 comparisons were made

	and depression and anxiety dimension of SCL-90-R questionnaire. Groups imbalanced with respect to gender and possibly duration of symptoms. 80% reported sudden onset of illness, 47% had low grade fever at physical examination. Pts randomised according to two KPS strata: 20-39 and 40-60. Modified not to exclude certain psychiatric disorders (particularly depression)		

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Functional measure Measured by Karnofsky performance score, % change presented **Baseline values intervention group** **Baseline values control group** **Results in intervention group** +20 **Results in control group** 0 **Comments** p-value for comparison of median change using Mann-Whitney test = 0.023, remained significant when controlled for gender or duration of symptoms	**Outcome measured** Cognitive function Perceived cognitive deficit assessed by the SCL-90-R questionnaire, % change presented **Baseline values intervention group** **Baseline values control group** **Results in intervention group** +27.3 **Results in control group** +14.5 **Comments** p-value for comparison of median change using Mann-Whitney test = 0.05, remained significant when controlled for gender or duration of symptoms	**Outcome measured** Excerice duration Exercise treadmill testing, conducted according to standardised progressive exercise programme, % change reported **Baseline values intervention group** **Baseline values control group** **Results in intervention group** +10.3 **Results in control group** +2.1 **Comments** p-value for comparison of median change using ANCOVA of log transformed data with baseline as covariate = 0.007, remained significant when controlled for gender or duration of symptoms	**Outcome measured** Activity Activities of daily living assessed using Barthel's ADL index, % change reported **Baseline values intervention group** **Baseline values control group** **Results in intervention group** +23.1 **Results in control group** +14.1 **Comments** p-value for comparison of median change using ANCOVA with baseline as covariate = 0.034, remained significant when controlled for gender or duration of symptoms. Improvement in all 13 activity modules more marked among treatment group than placebo

Outcome 5	Outcome 6	Outcome 7	Outcome 8
Outcome measured Excerice & work Amount of work completed, assessed by treadmill test, % change presented **Baseline values intervention group** **Baseline values control group** **Results in intervention group** +11.8 **Results in control group** +5.8 **Comments** p-value for comparison of median change using ANCOVA of log transformed data with baseline as covariate = 0.011, remained significant when controlled for gender or duration of symptoms	**Outcome measured** Depression Depression and anxiety dimension assessed using SCL-90-R **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Changes in levels of depression and anxiety were similar in both treatment groups	**Outcome measured** Medication use Patient were asked to discontinue any concomitant medication use before start of treatment. **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** The use of three classes of drugs and all medications increased significantly in placebo group compared to treatment group	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments: Increases in Karnofsky scores were equivalent in patients presenting with and without HHV-6 reactivation			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Vollmer-Conna (1997)[41] **Study design** RCT **Level of evidence** 1+	**Number:** 99 **Adults or children?:** **Inclusion criteria:** Excluded if: pregnant, on any of following therapies (steroid medication, nonsteroidal anti-inflammatory drugs, immunomodulatory agents, choline esterase inhibitors), had previously received immunologic therapy, had a recent history of asthma **Exclusion criteria:** **Diagnosis/ case definition:** Australia **Age:** 16-73 (mean 40 years) **% Female:** 75 women, 24 men **Duration of illness:** 1-34 years (mean = 6 years) **Baseline functioning:** 23 patients were unable to participate in any work, 48 patients reported only 50% or less work attendance **Further details:** Acute viral like illness appeared to precipitate onset of CFS in 75 cases, serologic confirmation available for 23 of these cases	Immunoglobulin Patients received one of 3 different doses of immunoglobulin (0.5, 1 or 2g/kg) or placebo (1% albumin, 10% wt/vol maltose) in equivalent volume by intravenous infusion 3 infusions each lasting 24 hours were administered at monthly intervals, follow-up assessment 3 months after final infusion **Number of participants in each group** 73 received immunoglobulin (22 0.5g/kg, 28 1g/kg & 23 2g/kg), 26 received placebo	Withdrawals: 3 immunoglobulin recipients received only 1 infusion, 2 withdrew from study after severe constitutional symptom reaction to first infusion, one withdrew for personal reasons. One patient received only 2 immunoglobulin infusions as he developed vesiculopapular skin eruption. These patients followed up at 6 months after enrolment and analysed with other immunoglobulin recipients on an intention to treat basis Adverse events: No significant differences in occurrences of symptoms between different treatment groups

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Functional measure Measured by Karnofsky performance score (assessed by investigator), reflects ability of individuals to participate in daily activities on 100 point scale **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Improvement in scores for all 4 groups from pre to post-treatment assessment (F=36.74, p<0.001) however, no significant intergroup differences; irrespective of treatment given all groups showed same improvement	**Outcome measured** Quality of life assessed by patients using QAL visual analogue scale modified to include 10 aspects of physical or neuropsychological symptomatology typical of CFS **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Trend towards improvement in symptomatology across 3 measured occasions (pre, during and post-treatment), (F=6.62, p=0.012), did not differ significantly between different groups (p>0.09)	**Outcome measured** Mood Profile of mood states questionnaire completed by patients **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Significant increase in subjective energy from pre- to post- test was demonstrated (F=17.03, p<0.0001) which did not differ between the treatment groups (p>0.75)	**Outcome measured** Immune outcomes Absolute numbers of T suppressor/cytotoxic (CD8) cells, and T inducer (CD4) cells, DTH skin responses **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Significant linear increase in absolute numbers of CD8 cells demonstrated across 3 measurement occasions (F=17.8, p<0.0001), rate and or degree of increase did not differ between the different treatment groups (p>0.13), no linear trend evidence in CD4 cells, cell counts showed significant quadratic trend across measurement occasions (F=18.2, p<0.001) which did not differ between the different treatment groups (p>0.08), analysis of DTH skin responses did not produce any significant differences

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Zachrisson (2002)[50] **Study design** RCT **Level of evidence** 1+	**Number:** 98 **Adults or children?:** Adults **Inclusion criteria:** 6 months or more of full or part time sick leave. fibromyalgia (ACR criteria) **Exclusion criteria:** Patients with pathological blood values; patients with signs or symptoms of ongoing severe psychiatric or other somatic disorder; patients with autoimmune or rheumatological disorders. **Diagnosis/ case definition:** CDC (1994) **Age:** mean 49 yrs staph group, 47 years placebo group **% Female:** 100% **Duration of illness:** mean 11 years staph group, 12 years placebo group **Baseline functioning:** **Further details:** referred from primary care centres in Molndal, Sweden. Patients were allowed to continue with prescribed medication during the study as long as they were in a steady state. Physical examination and bloods were performed before study entry.	Staphylococcus toxoid Drug administered at increasing doses of 0.1ml, 0.2ml, 0.3ml, 0.4ml, 0.6ml, 0.8ml, 0.9ml and 1.0ml weekly, followed by booster doses of 1.0ml every 4 weeks Last injection given at week 24 and endpoint ratings performed at week 26. **Number of participants in each group** 49 in each	Withdrawals: 2 dropped out (one in each arm) before any assessment was made. 10 dropouts during study. Adverse events: slight local pain and reaction after injection in both groups. Headaches reported more often in treatment group (p<0.05). Overall side effects of the drugs were assessed at endpoint: 13 staph patients and 7 placebo patients had experienced side effects (p=0.14)

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Clinical Global Impression **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 32/49 responded favourably **Results in control group** 9/49 responded favourably **Comments** statistically significant difference (p<0.001); after withdrawal response rate was still significantly different	**Outcome measured** Changes in symptoms CPRS-15 **Baseline values intervention group** 34.1 (8.33) **Baseline values control group** 34.3 (8.61) **Results in intervention group** endpoint 24.1 (12.10), withdrawal (wk 32) 29.0 (12.22) **Results in control group** endpoint 30.4 (9.72), withdrawal (wk 32) 30.3 (10.42) **Comments**	**Outcome measured** Pain visual analogue scale **Baseline values intervention group** 6.2 91.69) **Baseline values control group** 6.2 (1.71) **Results in intervention group** endpoint 4.8 (1.98), withdrawal (wk 32) 5.9 (2.20) **Results in control group** endpoint 6.1 (2.10), withdrawal (wk 32) 6.2 (1.95) **Comments**	**Outcome measured** fibromyalgia impact questionnaire FIQ **Baseline values intervention group** 6.9 (1.14) **Baseline values control group** 6.8 (1.25) **Results in intervention group** endpoint 6.1 (1.55), withdrawal (wk 32) 6.4 (1.70) **Results in control group** endpoint 6.5 (1.75), withdrawal (wk32) 6.8 (1.46) **Comments** change in item 'feeling good' in favour of treatment group

3. Pharmacological interventions

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Blacker (2004)[52] **Study design** RCT **Level of evidence** 1+	**Number:** 434 **Adults or children?:** Adults **Inclusion criteria:** Aged 18-65 years, met CDC 1994 criteria for CFS, illness duration less than 7 years **Exclusion criteria:** psychiatric diagnosis, eating disorders, obesity, sleep disorders. History of inpatient psychiatric cae and/ or attempted suicide. Irritable bowel syndrome, peptic ulcer, severe asthma, endocrine or metabolic disease, HIV infection, neurological disease, known sensitivity to cholinergic agents, possible exposure to organophosphate compounds, diagnosis of Gulf War Syndrome, Pregnancy, breastfeeding, menstrual irregularities associated with fatigue. Use of concomitant medication and participantion in CBT or graded exercise programs was not permitted. **Diagnosis/ case definition:** CDC (1994) **Age:** mean 39.1 yrs 2.5mg group, 38.9 yrs 5mg group, 39.0 yrs 7.5mg group, 37.0 yrs 10mg group, 37.6 yrs placebo group **% Female:** 72% 2.5mg group, 71% 5mg group, 62% 7.5mg group, 62% 10mg group, 62% placebo group **Duration of illness:** less than 7 years **Baseline functioning:** not stated **Further details:** fibromyalgia (eligible for inclusion) Recruited from 35 centres in the UK, USA, Netherlands, Sweden and Belgium	galantamine hydrobromide Patients assigned to receive identical tablets of placebo or one of 4 doses of galantamine hydrobromide 3x per day (2.5mg, 5mg, 7.5mg or 10mg) Dose was titrated over a 3 to 8 week period. Total duration of treatment after titration period was 8 weeks. **Number of participants in each group** 89 received 2.5mg, 86 received 5mg, 91 received 7.5mg and 86 10mg. 82 received placebo.	Withdrawals: 130 patients withdrew. 422 patients provided valid data for inclusion in the ITT LOCF population. Adverse events: 389 patients reported adverse events, of which 88 withdrew. 15% of patients in the placebo group withdrew due to adverse events. Number of adverse events increased with higher doses of galantamine; fewer patients withdrew from the 2.5mg galantamine group or from the placebo group compared with groups receiving higher doses, although there was no statistically significant difference between the groups. Most common adverse events in all groups were nausea and headaches. There were 4 cases of emergent depression (3 in galantamine groups, including one suicide in 10mg group, and one in placebo group). The suicide was judged to be unrelated to the medication. Seven other serious adverse occurred but none were attributed to the study medication.

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Clinical Global Impression **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** The difference between galantamine and placebo response rates was in all cases less than 25% (prespecified level for clinical significance)	**Outcome measured** Fatigue Chalder Fatigue Rating Scale change score physical; mental **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 2.5mg 9.25; 6.46, 5mg 8.77, 5.89, 7.5mg 11.02, 7.74, 10mg 9.99; 6.60 **Results in control group** 9.86; 6.80 **Comments** no significant differences were seen between galantamine and placebo	**Outcome measured** Fibromyalgia Impact Questionnaire Change from baseline: physical; psychological; social score; global wellbeing **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 2.5mg -2.64; 1.19; 0.01; -77.84, 5mg -2.39; 0.93; 0.05; -88.65, 7.5mg -1.29; 0.48; 0.01; -29.92, 10mg 0.06; 0.75; 0.09; -60.67 **Results in control group** -1.06; 0.82; -0.03; -53.89 **Comments** no significant differences were seen between galantamine and placebo	**Outcome measured** Cognitive function Change from baseline: simple reaction time; choice reaction time; digit vigilance speed; articulatory working memory sensitivity index; spatial working memory sensitivity index; delayed word recall; word recognition sensitivity index; picture recognition sensitivity index **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 2.5mg -4.09; -19.25; -1.28; 0.008; 0.011; 7.60; 0.016; 0.022, 5mg 4.45; -1.73; -3.95; 0.02; 0.003; 4.30; 0.04; -0.04, 7.5mg 0.18; -9.11; 4.47; 0.01; 0.02; 5.98; 0.06; -0.02, 10mg -9.94; -17.70; 7.46; 0.03; 0.05; 3.90; 0.05; -0.003 **Results in control group** -19.07; -19.84; -2.90; -0.001; -0.002; 5.00; 0.028; 0.012 **Comments** No pattern of improvement for galantamine compared with placebo
Additional comments: Logistic regression analyses failed to identify any consistent factor predicting outcomes for measures including speed of onset, preceding episode of viral illness, duration of illness, type of clinic referral, primary CFS symptoms.			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Blockmans (2003)[65] **Study design** RCT **Level of evidence** 1+	**Number:** 80 **Adults or children?:** Adults **Inclusion criteria:** 100 consecutive patients meeting CDC 1994 criteria for CFS were included. **Exclusion criteria:** History of gastric or duodenal ulcer, arterial hypertension, glaucoma, diabetes mellitus. Pregnancy. **Diagnosis/ case definition:** CDC (1994) **Age:** mean 38 years **% Female:** 91% **Duration of illness:** median 30 months **Baseline functioning:** 31 currently working, 30 'on disability', 3 unemployed, 16 student, housewife, or retired **Further details:** All patients had laboratory evaluation, chest radiograph and psychiatric exam.	Hydrocortisone and fludrocortisone 5mg hydrocortisone and 50 micrograms 9-alfa-fludrocortisone versus placebo, given for 3 months each (crossover design) **Number of participants in each group** 43 received intervention first, 37 received placebo first	Withdrawals: 80 completed the study. 9 who were initially on active compound and 11 initially on placebo dropped out. Seven were lost to follow-up. Adverse events: Only one dropout due to adverse effects (acne and weight gain).

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Fatigue Visual analogue scale; abbreviated fatigue questionnaire **Baseline values intervention group** 6.8 (1.6); 6 (3) **Baseline values control group** 6.8 (1.6); 6 (3) **Results in intervention group** 6.6 (2.0); 8 (5) **Results in control group** 6.7 (2.1); 7 (5) **Comments** Results were reported pooled for all patients. No significant differences between active and placebo groups.	**Outcome measured** Wellbeing visual analogue scale **Baseline values intervention group** 5.0 (2.2) **Baseline values control group** 5.0 (2.2) **Results in intervention group** 5.0 (2.4) **Results in control group** 4.6 (2.6) **Comments** Results were reported pooled for all patients. No significant differences between active and placebo groups.	**Outcome measured** Hospital Anxiety and Depression Scale Anxiety; Depression **Baseline values intervention group** 10 (4); 9 (4) **Baseline values control group** 10 (4); 9 (4) **Results in intervention group** 9 (4); 8 (5) **Results in control group** 10 (4); 9 (4) **Comments** Results were reported pooled for all patients. No significant differences between active and placebo groups.	**Outcome measured** SF-36 physical; mental **Baseline values intervention group** 27.3 (12.3); 41.7 (18.4) **Baseline values control group** 27.3 (12.3); 41.7 (18.4) **Results in intervention group** 31.7 (18.2); 46.3 (21.0) **Results in control group** 30.4 (18.1); 42.3 (20.9) **Comments** Results were reported pooled for all patients. No significant differences between active and placebo groups.

Outcome 5	Outcome 6	Outcome 7	Outcome 8
Outcome measured Blood pressure supine; standing **Baseline values intervention group** 79/128; 82/127 **Baseline values control group** 79/128; 82/127 **Results in intervention group** 78/125; 82/124 **Results in control group** 80/126; 81/126 **Comments** Results were reported pooled for all patients. No significant differences between active and placebo groups.	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments: when outcomes were measured, an injection of 250micrograms ACTH was given and cortisol levels determined at 0, 30 and 60 minutes. There were no between-treatment differences in the 20 patients with the lowest baseline cortisol values and in the 20 patients with the lowest increase in 60-minute cortisol levels after ACTH injections.			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Cleare (1999)[61] **Study design** RCT **Level of evidence** 1++	**Number:** 32 **Adults or children?:** Adults **Inclusion criteria:** Exclusion criteria: any comorbid DSM psychiatric disorder, significant abnormalities on screening, hypocortisolism, illness >100 months, use of prescribed medication in the previous 2 months, medical contraindications for hydrocortisone, inability to attend hospital for screening or follow-up. **Exclusion criteria:** **Diagnosis/ case definition:** Oxford & CDC 1994 **Age:** mean 35.3yrs (range 19-58) **% Female:** 20 F, 12 M **Duration of illness:** Mean 36 (range 28-45) months. **Baseline functioning:** Mean baseline fatigue score 25.1 (23.7-26.5) points. Adrenal autoantibodies negative in all patients. **Further details:** 9 history of psychiatric illness All analysis done on 32 who were treated (not 35 who were randomised). Mean baseline fatigue score 25.1 (23.7-26.5) points. 2 hydrocortisone dose groups were analysed together. Patients from specialised CFS clinics in London and Cambridge. 19 patients had infection related onset. All patients had physical examination and standard lab tests, also baseline endocrine assessment. Semi-structured psychiatric examination done by trained psychiatrists to exclude additional psychiatric disorders	Hydrocortisone Crossover trial - randomly assigned to 1st treatment (hydrocortisone or placebo). 28 days each arm, 1 tablet per day. First 16 pts given 5mg hydrocortisone, remainder given 10mg. Looks like there was no washout period. 28 days on each treatment. **Number of participants in each group** 35 randomised, 32 treated (crossover trial)	Withdrawals: None dropped out from the 32 treated, however 3 randomised dropped out - 1 before receiving medication and 2 due to 'protocol violation'. Adverse events: 3 pts on hydrocortisone reported side effects (exacerbation of acne, nervousness, improvement in eczema), and one pt on placebo (episode of fainting)

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Fatigue 11 item self-administered fatigue scale scored according to likert 0,1,2,3 system to be sensitive to change. **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Mean change in fatigue scores: hydrocortisone group -7.2 (-10.3, -4.0); placebo group -3.3 (-5.3, -1.3). Paired comparison of hydrocortisone vs placebo showed mean benefit in favour of active treatment of 4.5 (1.2, 7.8) points, p=0.009. Results not affected by which treatment received first.	**Outcome measured** Clinical global impression clinician administered CGI scale **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** 7/32 in the hydrocortisone group improved compared with 2/32 on placebo.	**Outcome measured** Disability Work and social adjustment scale (WSAS) change scores **Baseline values intervention group** As above: combined measures **Baseline values control group** home activities 4.8; private leisure act 4.9; social leisure act 5.8; relationships 3.7; work 6.1 (mean 5.1) **Results in intervention group** home -0.6; private leisure -1.0; social leisure -1.1; relationships -0.6; work -0.8; mean -0.7 **Results in control group** home -0.04; private leisure 0.06; social leisure -0.3; relationships -0.3; work -0.2; mean -0.05 **Comments**	**Outcome measured** Disability Medical outcomes SF36 - physical function and role limitation subscales **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** No significant improvement overall.
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome measured Psychological assessment General Health Questionnaire (GHQ) **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** No results given	**Outcome measured** Symptom measure self-reported somatic symptoms **Baseline values intervention group** 16.9 **Baseline values control group** 17.2 **Results in intervention group** 14.3 (p=0.04) **Results in control group** 15.6 (p=0.21) **Comments**	**Outcome measured** endocrine variables hCRH test: basal ACTH; AUC ACTH; basal cortisol; AUC cortisol, IST test: basal ACTH; AUC ACTH; basal cortisol; AUC cortisol, 24-hour UFC **Baseline values intervention group** hCRH test: 90 (38); 28 (32); 497 (200); 193 (232), IST test: 80 (39); 84 (79); 442 (211); 465 (324), 24-h UFC 105 (51) **Baseline values control group** hCRH test: 90 (38); 28 (32); 497 (200); 193 (232), IST test: 80 (39); 84 (79); 442 (211); 465 (324), 24-h UFC 105 (51) **Results in intervention group** hCRH test: 92 (39); 19 (31); 410 (159); 263 (180), IST test: 86 (32); 115 (80); 343 (93); 541 (171), 24-h UFC 146 (93) **Results in control group** hCRH test: 93 (42); 22 (30); 442 (195); 230 (190), IST test: 78 (37); 83 (65); 420 (296); 498 (299), 24-h UFC 100 (51) **Comments** significantly higher UFC output in active treatment than in placebo group (p=0.003). No other significant differences between groups	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments: Results of endocrine assessments also given in the paper.			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Cleare (2002)[62] **Study design** RCT **Level of evidence** 1-	**Number:** 120? (unclear) **Adults or children?:** Not stated **Inclusion criteria:** not stated **Exclusion criteria:** not stated **Diagnosis/ case definition:** Not stated **Age:** not stated **% Female:** **Duration of illness:** not stated **Baseline functioning:** not stated **Further details:** possible hypocortisolism? (previous) study showed a significant reduction in 24 hour urinary free cortisol conference abstract only: many details missing	Hydrocortisone 5-10mg/day hydrocortisone replacement therapy, versus placebo **Number of participants in each group** not stated	Withdrawals: not stated Adverse events: not stated

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Fatigue scores details of scale not reported **Baseline values intervention group** **Baseline values control group** **Results in intervention group** There was a significantly greater reduction in fatigue scores in patients when on hydrocortisone compared to placebo. 28% of patients on hydrocortisone returned to normal population levels of fatigue **Results in control group** 9% of patients on placebo returned to normal population levels of fatigue **Comments**	**Outcome measured** Laboratory measures 24 hr Urinary free cortisol; human corticotropin releasing hormone, insulin stress test **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 24-hr urinary free cortisol was higher after active compared to placebo treatments but there was no effect on responses to human corticotropin releasing hormone and the insulin stress test. **Results in control group** **Comments** A differential effect was seen in patients who responded to treatment: in this group there was a significant increase in cortisol response to human corticotropin releasing hormone.	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Forsyth (1999)[57] **Study design** RCT **Level of evidence** 1+	**Number:** 26 **Adults or children?:** Adults **Inclusion criteria:** Subjects aged 20-70 years. Excluded if: fatigue could be explained by the presence of other illness, current substance or alcohol dependence, pre-existing and ongoing depression at time of onset of chronic fatigue, psychotic or bipolar disorders, patients with history of established medical condition that could be contributing to fatigue, use of antidepressants, lithium, neuroleptics and monoamine inhibitors generally considered exclusionary criteria **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1994) **Age:** 26-57 years (mean 39.6) **% Female:** 65% females **Duration of illness:** 1 to 16 years (mean 7.2) **Baseline functioning:** 100% of patients had fatigue, neurocognitive difficulties, sleep disturbance, 96% had post exertional malaise, 92% had headaches and muscle weakness, 85% had arthralgia, 81% had myalgias and history of allergy, 695 had swelling of lymph nodes **Further details:** Not stated Subjects allowed to continue taking prescribed medication. 25 patients Caucasian, 1 Afro-American. Patients referred by variety of physicians, self-referred or recruited from the Georgetown University Medical Center.	Oral NADH Received NADH/placebo at week 0 for 4 week period, at week 4 4-week wash out period begun in which no drug was given, at week 8 final 4-week period commenced - subjects crossed over to alternate regimen Given 10mg of NADH (2 5mg tablet formulation), took dosage of 2 tablets orally once a day in the morning about 45 before breakfast on an empty stomach with a glass of water **Number of participants in each group** 26 (cross-over trial). 35 initially enrolled.	Withdrawals: 2/35 subjects dropped out due to non-compliance. 9 were dropped from the analysis because they were using psychotropic drugs. Adverse events: No severe side effects were observed related to the study drug. Blood pressure and hand dynamometer were measured through study with no significant difference noted

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Symptom measure Symptom scoring system developed by authors. +-50 item questionnaire assessing symptoms of CFS, each scored on scale of 1 to 4, where 1 represented minimum severity and 4 maximum **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 8/26 showed 10% improvement, p-value for difference = <0.05 **Results in control group** 2/26 showed 10% improvement **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments: 35% of pts guessed correctly when asked which drug they thought they were on.			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Hickie (2000)[67] **Study design** RCT **Level of evidence** 1++	**Number:** 90 **Adults or children?:** Adults **Inclusion criteria:** Exclusion criteria: alternative mediacl diagnosis, alternative major psychiatric disorder (not major depression) or suicide risk, use of steroid medication or other immunomodulatory agents, hepatic dysfunction, recent alcohol or substance abuse, pregnancy or breastfeeding. Informed consent. **Exclusion criteria:** **Diagnosis/ case definition:** Australia **Age:** 18-65 (mean 42.2-44.9) **% Female:** 49 F, 41 M **Duration of illness:** mean 84.2-90.9 weeks **Baseline functioning:** Initial KPI scores (disability) mean 74-76. POMS subscale fatigue score 18.0. 31 cases major depression, 61 cases psychological distress, 27 cases abnormal delayed-type hypersensitivity skin repsonse. **Further details:** None stated. Recruited from infectious disease and immunology outpatient clinics in Australia. Lloyd criteria are similar to CDC 1994. - some details given - includes criteria of neuropsychiatric dysfunction: impairment of concentration and/or new onset of short-term memory impairment.	moclobemide (monoamine oxidase inhibitor) 300-600mg/day moclobemide or placebo - identical 150mg tablets Initially 2 tablets per day, increased in week 2 to 3 tablets then to 4 tablets if tolerated. Intermittent night doses of short-acting benzodiazepine allowed. **Number of participants in each group** 47 in moclobemide arm, 43 in placebo	Withdrawals: 6 in placebo group and 7 in moclobemide group. 2 withdrew with no explanation, 1 in moclobemide withdrew due to psychotic symptoms, others withdrew due to side effects including agitation, headache, insomnia, gastrointestinal problems, increased malaise and anxiety. Adverse events: see 'drop outs'.

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Global improvememnt (self-assessed) No details of scales given **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 24/47 **Results in control group** 14/43 **Comments** ITT analysis with last observation carried forward (LOCF). OR 2.16 (95% CI 0.9, 5.1)	**Outcome measured** Disability Karnofsky performance index score **Baseline values intervention group** 74.3 (5.0) **Baseline values control group** 75.9 (4.5) **Results in intervention group** change score +0.86 (1.2) **Results in control group** change score +0.58 (1.3) **Comments** mean difference between groups 0.28 (-0.2, 0.8), not significant. ITT, LOCF.	**Outcome measured** Mood POMS subscale scores: fatigue, vigour, depression **Baseline values intervention group** fatigue 18.0 (5.6); vigour 8.2 (5.3); depression 12.9 (13.4) **Baseline values control group** fatigue 18.0 (5.8); vigour 8.8 (5.1); depression 14.1 (12.2) **Results in intervention group** change scores: fatigue -0.05 (0.37); vigour +0.51 (1.2); depression -0.06 (1.0) **Results in control group** change scores: fatigue -0.01 (0.3); vigour 0.00 (1.1); depression -0.08 (0.7) **Comments** mean difference between groups: fatigue 0.04 (-0.2, 0.1, n.s.), vigour 0.52 (0.1,1.0, significant), depression 0.07 (-3.0, 0.5, n.s.). ITT, LOCF.	**Outcome measured** Immunologic CD4 T cell count, CD8 T cell count, size of delayed type hypersensitivity skin response (mm). **Baseline values intervention group** CD4 0.89 (0.31); CD8 0.83 (0.26) **Baseline values control group** CD4 0.05 (0.04); CD8 0.51 (0.15) **Results in intervention group** change scores: CD4 +0.03 (0.29); CD8 +0.01 (0.19); skin test 0.00 (0.73) **Results in control group** change scores: CD4 +0.07 (0.32); CD8 +0.03 (0.12); skin test -0.10 (0.56) **Comments** mean differences between groups: CD4 0.04 (-0.2, -.1, ns); CD8 0.03 (0.1, 0.04, signficant); skin test 0.10 (-0.2, 0.4, ns). CD4 and CD8 n=44 moclobemide, 34 placebo. skin test n=44 moclobemide, 35 placebo. ITT, LOCF
Additional comments: standardised units of improvement were used for change scores (which take into account placebo response). Subgroup analysis: general psychological distress and major depression did not affect response. Impaired immune responsive patients demonstrated most impressive difference between groups on KPI.			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Kakumanu (2001)[66] **Study design** RCT **Level of evidence** 1+	**Number:** 28 **Adults or children?:** Not stated **Inclusion criteria:** Diagnosis of CFS plus rhinitis symptoms **Exclusion criteria:** not stated **Diagnosis/ case definition:** Not stated **Age:** not stated **% Female:** not stated **Duration of illness:** not stated **Baseline functioning:** not stated **Further details:** not stated conference abstract only	Topical nasal corticosteroids 8 wks topical nasal corticosteroid, or 4wk TNC and 4 wk placebo, or 4wk placebo and 4wk TNC 8 wk placebo **Number of participants in each group** 7	Withdrawals: not stated Adverse events: not stated

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: daytime sleepiness **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** "did not significantly improve when CFS patients with rhinitis were treated with topical nasal corticosteroids"	**Outcome measured** fatigue, post-exertional fatigue **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** severity did not improve with treatment	**Outcome measured** muscle pain **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** severity did not improve with treatment	**Outcome measured** daily activity **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** severity did not improve with treatment

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
McKenzie (1998)[60] **Study design** RCT **Level of evidence** 1+	**Number:** 70 **Adults or children?:** Adults **Inclusion criteria:** Men and women aged 18-55. Illness began over a period of 6 weeks or less, and had no contraindications to systemic steroid. No other acute or chronic medical or psychiatric condition that required ongoing or intermittent medication. Women needed to practice effective means of birth control and have a negative pregnancy test at enrolment. Active depression that was of such severity to warrant treatment precluded enrolment **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1988) **Age:** mean 36.7 (sd=7.2) in HYDROCORTISONE GROUP, 38.3 (SD=7.5) in placebo group **% Female:** 20% male **Duration of illness:** Mean 46.9 (sd=27.3) months in hydrocortisone group, 59.9 (sd=31.7) in placebo group **Baseline functioning:** Similar in both groups, 73% impaired employment **Further details:** None stated Withheld prescribed medication for duration of study and for 2-6 weeks prior to the study starting Diagnosis ascertained by patient history routine physical examination and laboratory tests to exclude other relevant diagnoses	Hydrocortisone Told to take placebo/hydrocortisone pills equivalent to 16mg/m2 of body surface area per day, 20-30mg every morning at about 8am and 5 mg every day at 2pm for 12 weeks **Number of participants in each group** 35 in each arm	Withdrawals: 7 patients withdrew from trial 3 in each group as considered that intervention was ineffective, and one in placebo group because of a rash Adverse events: 21 adverse reactions identified, 3 of which occurred significantly more frequently in treatment group: increased appetite, weight gain and difficulty in sleeping, actual patient weights confirmed reports

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: General health Patients recorded current Wellness score, single item global health score ranging from 0 (worse ever felt) to 100 (best ever felt). Mean change in scores presented **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 6.3 (sd=11.7), p-value for difference in change = 0.06 (value calculated from 2 sided Wilcoxon rank sum test) **Results in control group** 1.7 (sd=8.8) **Comments** The proportions of patients reporting improvement of at least 5, 10 or 15 points on global wellness scale were greater for hydrocortisone than placebo (5 point: 53% v 29%, p=0.04; 10 point: 33% v 14%, p=0.07; 15 points: 20% v 6%, p=0.08)	**Outcome measured** Mood Patients completed profile of mood states questionnaire **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Anger, anxiety, confusion, depression, fatigue and vigour assessed, none showed significant differences in improvement at the 5% level between placebo and active treatment	**Outcome measured** Symptom measure Patients completed symptom checklist-90-R. Mean change in scores for general severity index presented **Baseline values intervention group** **Baseline values control group** **Results in intervention group** -0.1 (sd=0.2), p-value for difference between 2 groups = 0.20 (value calculated from 2 sided Wilcoxon rank sum test) **Results in control group** -0.1 (sd=0.2) **Comments**	**Outcome measured** Symptom measure Sickness impact profile **Baseline values intervention group** **Baseline values control group** **Results in intervention group** -2.5(sd=6.4)p-value for difference between 2 groups = 0.85 (value calculated from 2 sided Wilcoxon rank sum test) **Results in control group** -2.2 (sd=6.8) **Comments**
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome measured Depression Beck depression inventory **Baseline values intervention group** **Baseline values control group** **Results in intervention group** -2.1 (sd=5.1) **Results in control group** -0.4 (sd=4.1) p-value for difference between 2 groups = 0.17 (value calculated from 2 sided Wilcoxon rank sum test) **Comments**	**Outcome measured** Activity 10 point activity scale developed by authors **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 0.3 (sd=1.1) p-value for difference between 2 groups = 0.32 (value calculated from 2 sided Wilcoxon rank sum test) **Results in control group** 0.7 (sd=1.4) **Comments**	**Outcome measured** Depression Patients interviewed by psychiatric specials who administer Hamilton Depression Rating scale **Baseline values intervention group** **Baseline values control group** **Results in intervention group** -0.8 (sd=3.8) p-value for difference between 2 groups = 0.25 (value calculated from 2 sided Wilcoxon rank sum test) **Results in control group** 0.1 (sd=2.9) **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments:			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Moorkens (1998)[56] **Study design** RCT **Level of evidence** 1-	**Number:** 20 **Adults or children?:** Adults **Inclusion criteria:** GH levels as above. Excluded if: GH response <3ug/L, pituitary disease, pregnancy, acute sever illness in last 6 months, liver renal or cardiopulmonary disease, diabetes mellitus, hypertension, malignancy, BMI>28, previous GH therapy, life expectancy <5yrs, hypersensitive to methyl-cresol, suspected poor compliance, chronic medication **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1994) **Age:** 30-60 years **% Female:** 7 M, 13 F **Duration of illness:** **Baseline functioning:** Not stated. **Further details:** None stated Recruited from CFS clinic at Antwerp University Hospital. All had nocturnal peak levels of GH <10ug/L	Growth hormone 1. Growth hormone 6.7 ug/kg/day (0.02 IU/kg/day) or 2. placebo 12 weeks, double blind **Number of participants in each group** 10	Withdrawals: 3 withdrew - 1 due to lack of motivation, 1 due to anxiety, 1 due to nervousness. Not stated which group they were in, Adverse events: None stated.

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Physical Weight, muscle strength, skinfold thickness, fat mass, fat free mass, total body water, BMI **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** No significant changes from baseline. Not stated whether there was a significant difference between the placebo group and the treated group after 12 weeks.	**Outcome measured** Laboratory measures serum IGF-1, thyrotrophin, free tri-iodothyronine, free thyroxine, prolactin, cortisol, follicle-stimulating hormone, luteinising hormone, testosterone, sex-hormone-binding globulin, Lp(a), amino acids. **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** only reported after 12 months (following 9 month open label administration)	**Outcome measured** Quality of life Nottingham Health Profile (NHP) and specifically designed questionnaire for quality of life assessment in GH-deficient adults (QoL-AGHDA) **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** only reported after 12 months (following 9 month open label administration)	**Outcome measured** Return to work **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** only reported after 12 months (following 9 month open label administration)

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Morriss (2002)[70] **Study design** RCT **Level of evidence** 1-	**Number:** 10 (plus 10 healthy controls) **Adults or children?:** Adults **Inclusion criteria:** aged 18-60, meeting CDC 1994 criteria for CFS **Exclusion criteria:** ICD-10 psychiatric disorder; taking psychotropic medication, oral contraceptives, steroids, thyroxine, bromocriptine and anti-hypertensive medication in previous 15 days; BMI<15 or >30; migraine; pregnancy or breast feeding. **Diagnosis/ case definition:** CDC (1994) **Age:** mean 46 years **% Female:** 50% **Duration of illness:** median 75 months (range 17-168 months) **Baseline functioning:** fatigue 31.7 points (Chalder et al scale), cognitive failures questionnaire 57.8 points, HAD depression 5.5, HAD anxiety 5.5 **Further details:** not stated Consecutive attenders at a medical outpatient centre for CF at a general UK hospital were invited to participate if they met CDC 1994 criteria for CFS Screened by a research psychiatrist.	Clonidine challenge test High dose clonidine (2.5 mg/kg) and placebo (10ml normal saline over 5 mins) given intravenously in random order **Number of participants in each group** 10 (crossover design)	Withdrawals: one patient started fluoxetine (given by GP) between tests and received only the placebo challenge Adverse events:

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Executive function tests Stockings of Cambridge. Minimum moves; initial thinking time; subsequent thinking time. RVIP: reaction time; alpha. ID/ED set-shift: IDS errors; EDS errors. Spatial working memory: between-search errors; strategy score **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 9.00 (2.18); 7.99 (4.34); 1.38 (2.46). 5.00 (1.52); 0.92 (0.05). 0.44 (0.73); 1.78 (1.56); 7.09 (4.21); 31.56 (5.96) **Results in control group** 10.22 (2.39); 9.27 (4.13); 1.89 (3.07). 5.15 (1.22); 0.92 (0.04). 0.22 (0.44); 4.44 (6.64). 9.26 (6.82); 31.78 (6.38) **Comments** Clonidine decreased initial thinking time on Stockings of Cambridge test ($p<0.001$). It is unclear whether the clonidine and placebo groups have been compared or whether it is a within group (before/ after clonidine) comparison.	**Outcome measured** Mnemonic function tests Pattern recognition: number correct; latency correct. Spatial recognition: number correct; latency correct. Spatial span: length; errors stage 5. DMTS: simultaneous correct; 0s delay; 4s delay; 2s delay. Paired-associate learning: sets completed; first trial correct; memory score **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 22.3 (1.3); 2.01 (0.30). 15.2 (2.9); 2.10 (0.44). 6.40 (1.26); 0.22 (0.44). 9.00 (1.66); 7.78 (2.11); 7.67 (1.50); 6.56 (1.69). 8.89 (0.33); 5.89 (1.05); 21.7 (6.6) **Results in control group** 21.4 (2.2); 1.98 (0.27). 15.3 (2.1); 1.92 (0.33). 6.10 (1.20); 0.33 (1.00). 9.22 (1.09); 8.69 (0.71); 7.89 (1.96); 7.78 (1.39). 8.89 (0.33); 6.11 (1.05); 24.7 (5.8) **Comments** There were no significant effects of clonidine on any mnemonic function task and no interaction with CFS diagnosis.	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Natelson (1998)[68] **Study design** Controlled trial **Level of evidence** 2+	**Number:** 25 **Adults or children?:** Not stated **Inclusion criteria:** Patients had to report symptom severities of >=3. Exclusion criteria: unable to visit centre when required, history of serious psychiatric problems in 5 years prior to study, score of 27 or more on CES-study of depression, pregnancy, use of antidepressant drug, abnormalities in serum chemistries **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1988) **Age:** Not stated **% Female:** Not stated **Duration of illness:** Not stated **Baseline functioning:** Not stated **Further details:** Not stated All patients were from the University CFS centre identified serially Only 7 minor symptoms were require for entry into study	Selegiline (Antidepressant) Trial lasted 6 weeks, for first 2 weeks all subjects took 2 placebo pills per day, next 2 weeks took 1 5mg tablet and 1 placebo for final 2 weeks took 2 5mg tablets **Number of participants in each group** 25 patients (one treatment arm only)	Withdrawals: 6 patients did not complete the trial: 2 never started (1 because of elevated liver enzyme), 4 dropped out in placebo phase (3 for symptoms, 1 for not returning phone calls) Adverse events: None stated but can't be sure about the 3 that dropped out for symptoms in the placebo phase

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Functional measure Functional status questionnaire: data on 9 variables assessed **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Wilcoxon matched paired tests of the difference in patients response to placebo compared to drug: Sexual relations were improved for the 12 subjects responding to this question ($p<0.03$), other 8 factors showed no significant differences. Most of the variables from the FSQ did not change for the plurality of patients at either time point studied	**Outcome measured** Mood Profile of mood states questionnaire (POMS), 6 variables were assessed including fatigue, vigour, depression and confusion **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Wilcoxon matched paired tests of the difference in patients response to placebo compared to drug: Tension/anxiety was reduced ($p<0.01$) and vigour was improved ($p=0.004$), other 2 factors showed no significant differences. During active phase the majority of patients showed improvement during placebo phase of the treatment on all 6 scales, on placebo majority showed improvement on 2 scales and worsening on 4 scales	**Outcome measured** Depression Centers for Epidemiological Studies of Depression (CES-D), pencil and paper test for depression used **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Wilcoxon matched pair tests of the difference in patients response to placebo compared to drug showed no significant differences. Most of the patients showed improvement in depression scores on drug, but worsening on placebo	**Outcome measured** Illness severity Illness severity scale (modification of Karnofsky, expanding areas of mild to moderate disability) used **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Wilcoxon matched pair tests of the difference in patients response to placebo compared to drug showed no significant differences. Most of the variables from this scale did not change for the plurality of patients at either time point studied

Outcome 5	Outcome 6	Outcome 7	Outcome 8
Outcome measured Fatigue Fatigue severity scale used **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Wilcoxon matched pair tests of the difference in patients response to placebo compared to drug showed no significant differences. Most of the patients showed improvement on drug and worsening on placebo.	**Outcome measured** Symptom measure 16-question symptom severity checklist used **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Wilcoxon matched pair tests of the difference in patients response to placebo compared to drug showed no significant differences. Most of the patients showed improvement on both drug and placebo	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Natelson (1996)[54] **Study design** RCT **Level of evidence** 1-	**Number:** 24 **Adults or children?:** Adults **Inclusion criteria:** Exclusion criteria included inability to visit center when required, history of serious psychiatric problems in the 5 years prior to study, or score of 27+ on the CES-D, pregnancy, inability to follow diet/drug restrictions, unwillingness to stop taking drugs or dietary supplements that produce interactions with phenelzine **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1988) **Age:** 37.9 (se =2.6) in drug group, 31.2 (se=2.9) in placebo group **% Female:** 9 women in drug group, 6 women and 3 men in placebo group **Duration of illness:** Not stated **Baseline functioning:** Not stated **Further details:** None stated Not stated Only 7 minor symptoms were required for entry into trial. All patients also filled CDC 1994 criteria	Phenelzine 6 weeks duration, 1st 2 weeks all took placebo, next 2 weeks 2/3 took one 15mg phenelzine tablet alternated with placebo, in last 2 weeks took 15mg phenelzine every day, other 1/3 continued with placebo **Number of participants in each group** 15 in active treatment, 9 in placebo, 9 in each group evaluated	Withdrawals: 6 patients, all from active treatment group, dropped out: 1 because of unreliability, 2 dropped out during placebo phase in period of trial, 3 dropped out because of unpleasant symptoms Adverse events: 3 patients dropped out due to adverse effects when on full dose of phenelzine

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Functional measure Functional status questionnaire: data on 11 variables assessed **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Wilcoxon matched pair analysis of change in score from baseline (after first 2 weeks on placebo) to final score (after last 2 weeks of treatment) showed no significant differences. A plurality of patients reported no change for most of the tests comprising the FSQ	**Outcome measured** Mood Profile of mood states questionnaire (POMS), 6 variables were assessed including fatigue, vigour, depression and confusion **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Wilcoxon matched pair analysis of change in score from baseline (after first 2 weeks on placebo) to final score (after last 2 weeks of treatment) showed no significant differences.	**Outcome measured** Depression Centers for Epidemiological Studies of Depression (CES-D), pencil and paper test for depression used **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Wilcoxon matched pair analysis of change in score from baseline (after first 2 weeks on placebo) to final score (after last 2 weeks of treatment) showed no significant differences.	**Outcome measured** Illness severity Illness severity scale (modification of Karnofsky, expanding areas of mild to moderate disability) used **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Wilcoxon matched pair analysis of change in score from baseline (after first 2 weeks on placebo) to final score (after last 2 weeks of treatment) showed no significant differences.
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**

Outcome measured Fatigue Fatigue severity scale used **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Wilcoxon matched pair analysis of change in score from baseline (after first 2 weeks on placebo) to final score (after last 2 weeks of treatment) showed no significant differences.	**Outcome measured** Symptom measure 16-question symptom severity checklist used, 0-4 scale **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Wilcoxon matched pair analysis of change in score from baseline (after first 2 weeks on placebo) to final score (after last 2 weeks of treatment) showed no significant differences.	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments: Out of the 20 tests there were 11 tests for which a plurality of drug-related patients improved and none for which a plurality worsened, there were 5 tests for which a plurality of placebo-treated patients improved and 4 tests for which a plurality worsened			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Olson (2003)[69] **Study design** RCT **Level of evidence** 1-	**Number:** 20 **Adults or children?:** Adults **Inclusion criteria:** Diagnosed with CFS using CDC 1994 criteria, normal results for an overnight sleep study, mean daytime sleep latency of more than 7 minutes. **Exclusion criteria:** History of alcohol or other substance abuse, epilepsy, myocardial infarction, current hypertension, cardiac arrhythmia, angina, coeliac disease, psychiatric diagnosis (other than depression). Use of antidepressant drugs was not permitted. **Diagnosis/ case definition:** CDC (1994) **Age:** mean 32.1 yrs dexamphetamine group, 39.7 yrs placebo group **% Female:** 60% dexamphetamine group, 70% placebo group **Duration of illness:** mean 7.1 yrs dexamphetamine group, 5.6 yrs placebo group **Baseline functioning:** 80% employed. **Further details:** Recruited in Australia between 1998 and 1999 Diagnosed by a single physician who was believed to see most patients suspected of CFS in Newcastle, Australia.	dexamphetamine All initially took one 5mg tablet twice daily. After one week does was adjusted up or down (10 - 30mg, highest actual dose 20mg) versus placebo. 6 weeks duration. **Number of participants in each group** 10 in each arm	Withdrawals: none reported. Adverse events: Five patients in dexamphetamine group reported reduced food consumption, three reported weight loss. One patient receiving placebo reported reduced food consumption and five reported impaired balance. Common side effects such as tremor, palpitations, dry mouth, were not reported by patients in either group.

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Fatigue Fatigue Severity Scale **Baseline values intervention group** 6.1 (0.7) **Baseline values control group** 5.9 (1.0) **Results in intervention group** 4.7 (1.2); mean change -1.45 (SD 1.09) **Results in control group** 5.9 (0.9); mean change -0.03 (SD 1.11) **Comments** difference in mean change between groups statistically significant (p<0.02)	**Outcome measured** SF36 scores physical functioning; physical role; bodily pain; social functioning; emotional role; vitality; general health; mental health; physical summary; mental summary **Baseline values intervention group** 57.5; 22.5; 54.9; 46.2; 63.3; 23.0; 48.0; 68.8; 35.6; 40.9 **Baseline values control group** 49.0; 12.5; 46.7; 37.5; 66.7; 15.5; 46.5; 62.8; 32.3; 39.1 **Results in intervention group** 65.0; 52.5; 62.7; 58.8; 66.7; 40.0; 47.9; 71.2; 40.8; 43.4 **Results in control group** 54.0; 20.0; 51.9; 50.0; 76.7; 23.5; 53.0; 65.2; 34.6; 42.6 **Comments** no significant differences between groups for any variables	**Outcome measured** sleep latency **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 13.0 minutes (95% CI: 9.1, 16.9 minutes) **Results in control group** 11.8 minutes (95% CI: 9.1, 14.4) **Comments** no change in either group.	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Peterson (1998)[63] **Study design** RCT **Level of evidence** 1++	**Number:** 25 **Adults or children?:** Not stated **Inclusion criteria:** Patients excluded if fatigue severity during previous month of less than 5, taking fludrocortisone or another medication that could confound interpretation of results **Exclusion criteria:** **Diagnosis/ case definition:** CDC 94 & 88 **Age:** 39.7+-10.9 **% Female:** 76% female **Duration of illness:** 7.0 (sd=4.9) **Baseline functioning:** At initiation of treatment in both arms severity of most of the symptoms associated	Fludrocortisone Dose: fludrocortisone acetate 0.1mg 1 tablet orally, if no improvement dose doubled after 2 weeks (done for 8 patients on drug, 11 on placebo) Patients received fludrocortisone or placebo for 6 weeks, followed by 6 week wash out period then entry into opposite arm of the study **Number of participants in each group** 25 in each	Withdrawals: Five patients dropped out of study: 3 fludrocortisone, one placebo - due to worsening symptoms and surgery (1pt). One dropped out during washout due to family problems. Adverse events: None reported

	with CFS was high. **Further details:** None stated All subjects were white. Onset of illness described as acute infection disease like episode in 22/25 patients. Patients already enrolled in research programmes at Hennepin County Medical Center, Minneapolis or from Park Nicollett Clinic CFS Program, Min		

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Symptom measure 10 cm visual analogue scale with 0 being no problem to 10 of worst it could be **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** No significant differences in change in symptom measures (Fatigue, unrefreshing sleep, muscle pains, inability to concentrate, headaches, forgetfulness, confusion, joint pains, painful lymph nodes, sore throat, distance before exhausted, light headedness, depression) in fludrocortisone and placebo groups	**Outcome measured** Functional measure 36 item medical short form health survey used to assess functional status **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** No significant differences in change in functional status measurements (Physical, social, emotional and physical role limitations, emotional well-being, pain, energy or fatigue and general well-being) in fludrocortisone and placebo groups	**Outcome measured** Mood Mood state was assessed using the Positive and negative affect scale **Baseline values intervention group** 22.9 (sd=6.0) **Baseline values control group** 22.7 (sd=6.3) **Results in intervention group** 22.7 (sd=8.3) **Results in control group** 21.7 (6.7) **Comments**	**Outcome measured** Cognitive function Speed of cognitive function assessed using Hick paradigm reaction time **Baseline values intervention group** 0.35 (sd=0.05) **Baseline values control group** 0.37 (sd=0.07) **Results in intervention group** 0.35 (sd=0.07) **Results in control group** 0.36 (sd=0.08) **Comments**

Outcome 5	Outcome 6	Outcome 7	Outcome 8
Outcome measured Excerice & work Duration of walking on a treadmill (mins) at 1mph until feeling exhausted for a maximum of 30 mins **Baseline values intervention group** 19.3 (sd=11.2) **Baseline values control group** 20.0 (sd=11.7) **Results in intervention group** 22.8 (sd=9.2) **Results in control group** 20.2 (sd=11.5_ **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Rowe (2001)[64] **Study design** RCT **Level of evidence** 1++	**Number:** 100 **Adults or children?:** Adults **Inclusion criteria:** Nneurally mediated hypotension (NMH) established during 2 stage tilt table test. 18-50 years old. Participants' physicians had to confirm that participant would be able to tolerate study procedures. Had to score =<65 (moderate) on global wellness scale (out of 100). Excluded if had a history of conditions that could be exacerbated by fludrocortisone or tilt table testing, if had ever taken fludrocortisone at dose of =>0.1mg/day for 2 or more weeks,or if had taken following drugs in previous 2 weeks: tricyclic antidepressants >25mg/day, SSRIs, trazodone, diureticcs, oral mineralocorticoids or glucocorticoids, other drugs used in treatment of NMH, systemic anti-fungal azoles, sumatriptan, kutapressin, coenzyme Q10, niacin, vitamin B12 injections. Also excluded if enrlled in another CFS study, had depression or other psychiatric diagnoses, or abused drugs or alcohol. **Exclusion criteria:** **Diagnosis/ case definition:** CDC 1994 **Age:** mean 36.2(7.4) fludrocortisone group; 37.3(9.3) placebo group **% Female:** not stated. **Duration of illness:** mean 6.0(4.9) years in placebo group; 6.9(6.4) years in fludrocortisone group. **Baseline functioning:** All able to walk withut assistance. 53-56% currently working. Baseline wellness score 40.7(16.3) placebo group; 46.8(16.0) fludrocortisone group. **Further details:** neurally mediated hypotension 70-72% had duration of illness => 3 years. Participants recruited from registry of subjects who had participated in other CFS studies at NIH and from notices in patient publications, newspapers and the internet. clinical evaluation.	fludrocortisone Duration: 9 weks treatment period; follow up at 11 weeks. Fludrocortisone 0.025mg/day for 1 week, then 0.5mg/day for 1 week then 0.1mg/day for 7 weeks. Placebo capsules given in identical sequence. Placebo capsules contained only filler (methylcellulose) **Number of participants in each group** 50	Withdrawals: 21 overall: 8 placebo(1 developed hypertension, 1 refused to comply, 1 developed panic and tachcardia, 1 had increased fatigue, 1 had severe lightheadedness, fatigue and diaphoresis,3 were unimproved), 13 fludrocortisone (1 developed hypertension, 1 refused to comply, 4 developed depression, 1 had worse headaches, 2 had new abdominal disconfort, 1 had unrelated medical illness, 1 was found to have major depression and 2 had worsening symptoms). Adverse events: Noone had a change I systolic BP of more than 40mmHg. Weight gain was not significant. No patient developed depression requiring antidepressant medication during the treatment period. Side effects did not seem to be significantly better or worse in either group.

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Improvement at least 15 point improvement in global Wellness scores **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 14% improved **Results in control group** 10% improved **Comments** ITT analysis. No difference in those who had CFS <3 years or who were younger than 30 years.	**Outcome measured** Wellness global wellness scale score (o-100, 0 bad, 100 good) **Baseline values intervention group** 46.8 (16.0) **Baseline values control group** 40.7 (16.3) **Results in intervention group** 50.4 (18.2) **Results in control group** 43.1 (17.6) **Comments** p baseline = 0.06; p on treatment = 0.07.	**Outcome measured** fatigue Wood mental fatigue index **Baseline values intervention group** 16.3(9.7) **Baseline values control group** 18.3(8.2) **Results in intervention group** 14.1(10.9) **Results in control group** 13.3(9.6) **Comments** p baseline 0.28; p final 0.73	**Outcome measured** depression BDI **Baseline values intervention group** 14.7(8.2) **Baseline values control group** 15.0(5.5) **Results in intervention group** 10.4(7.2) **Results in control group** 10.8(6.8) **Comments** p baseline 0.82; p final 0.82
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome measured mood POMS vigour and fatigue subscales **Baseline values intervention group** vigour 7.9(4.7); fatigue 19.6(5.1) **Baseline values control group** vigour 6.7(4.3); fatigue 21.3(4.6) **Results in intervention group** vigour 8.8(6.1); fatigue 16.2(7.3) **Results in control group** vigour 8.6(6.7); fatigue 16.4(7.9) **Comments** vigour p baseline 0.2; p final 0.91. Fatigue p baseline 0.08; p final 0.93	**Outcome measured** General health SF36 physical function and mental health **Baseline values intervention group** PF: 54.8(22.5); MH: 63.7(18.1) **Baseline values control group** PF: 45.1(22.7); MH 66.3(16.3) **Results in intervention group** PF: 58.9(21.9); MH: 68.6(19.1) **Results in control group** PF: 51.4(27.8); MH: 69.8(16.3) **Comments** PF p baseline 0.04, p final 0.18. MH p baseline 0.45, p final 0.75	**Outcome measured** activity Duke Activity Status Index **Baseline values intervention group** 7.8(9.3) **Baseline values control group** 5.0(6.2) **Results in intervention group** 9.2(10.6) **Results in control group** 6.7(7.3) **Comments** p baseline 0.09, p final 0.23	**Outcome measured** tilt test outcomes NMH in stage 1, 2 (N) **Baseline values intervention group** 34, 16 **Baseline values control group** 33, 17 **Results in intervention group** 20, 6 **Results in control group** 17, 14 **Comments** stage 1 p baseline 0.83, final 0.16

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Santaella (2004)[58] **Study design** RCT **Level of evidence** 1-	**Number:** 20 analysed **Adults or children?:** Adults **Inclusion criteria:** Patients with CFS referred to the Clinical Immunology Clinic. Aged 18 years or older. **Exclusion criteria:** Any condition known to cause an immunodeficiency state or that could be accountable for symptoms such as malaise and fatigue **Diagnosis/ case definition:** CDC (1988) **Age:** mean 31 years **% Female:** 90% **Duration of illness:** not stated **Baseline functioning:** 7 employed, 13 unemployed. Baseline symptom score was very high (3.7 out of 4) **Further details:** 15 had other medical conditions (allergies, diabetes, migraine, depression, anxiety, bronchiectasis 16 reported stress, viral illness as 'co-events' related to onset of illness. 45% were taking medication including diabetes medication, antidepressants, anxiolytic agents or antihistamines	Oral NADH Oral therapy with reduced nicotinamide adenine dinucleotide, initial dose 5mg, increased to 10mg if symptoms did not improve versus nutritional supplements and psychological therapy, for 24 months. **Number of participants in each group** 12 in NADH group, 8 in control group	Withdrawals: 31 patients were randomised but 11 dropped out before 12 months, and only 20 were included in the analysis Adverse events: no adverse events were reported by participants taking NADH

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: symptom score questionnaire scale from 1 to 4 (1 minimum, 4 maximum severity) **Baseline values intervention group** 3.8 (0.4) **Baseline values control group** 3.4 (0.5) **Results in intervention group** Trimester 1 2.2, Trimester 2 2.0, Trimester 3 2.0, Trimester 4 1.9 **Results in control group** doesn't seem to be reported – seems ot be the same in both groups at 12 months (1.9) **Comments** No significant difference between groups	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Snorrason (1996)[51] **Study design** RCT **Level of evidence** 1-	**Number:** 49 **Adults or children?:** Adults **Inclusion criteria:** CFS patients with minor psychiatric symptoms including depression and anxiety eligible for inclusion. Patients with medical conditions known to produce symptoms of fatigue, or those with major pschiatirc diagnosis defined by DSM-III-R rinterview excludued. **Exclusion criteria:** **Diagnosis/ case definition:** Not stated **Age:** 18 - 67, mean 43.4 on galanthamine, 44.5 on control **% Female:** 7 male, 42 female **Duration of illness:** 13.7 years on galanthamine, 11.8 on placebo **Baseline functioning:** Not stated **Further details:** Not stated Patients selected from University outpatient clinic and rheumatologicial outpatient clinic. Symptoms of fatigue occurring for more than 50% of waking hours and lasting more than 6 months, major sleep disturbances and myalgia. Patients taken off all medication 2 weeks prior to entering trial	Galanthamine hydrobromide (a selective acetylcholinesterase inhibitor) Galanthamine hydrobromide 10 mg t.I.d., reached by schedule of escalating dosage, or matched treatment with placebo tablets. Optional cross-over trial. Patients who failed to improve or whose symptoms worsened after 2 weeks on treatment swiched to alternative treatments, patients assessed 1,2, 4 and 8 weeks after change in treatment. If no improvement evident after 2 weeks on second treatment patients reverted to pretrial therapy. **Number of participants in each group** 49 patients, 25 initially on galanthamine, 24 on placebo.	Withdrawals: 5 patients (3 active, 2 placebo) did not progress past first 2 weeks of trial. After first 2 weeks 24 patients changed to alternative therapy (21 from placebo, 3 frm galanthamine) at end of week 2. P<0.0001 Adverse events: In 30% of patients dosage was reduced becasuse of adverse effects, mainly nausea. 30% of patients on galanthamine suffered mild nausaea at onset of treatment, disapeared with time. 4 patients had severe nausea on only 5mg. 9 reported headahced, 3 had severe headaches, 1 withdrew from trial. Dizziness occurred in 4 patients, 1 withdrew from stuy. 1 patient complained of mightmares. 2 patents developed redness and itching of skin around eyes on 10mg, dissapeared when reduced to 5mg, 2 patients duffered from profuse sweating, diarrhoea, vomiting, confusion and hallucinations at 20mg dose

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Sleep Sleep disturbance, measured on 3 visual analogue scales at 2 weeks **Baseline values intervention group** 7.52 (1.87) **Baseline values control group** 7.77 (1.37) **Results in intervention group** 7.00 (2.35) **Results in control group** 6.66 (2.49) **Comments** Average scores (smaller score less impaired) and sd presented.	**Outcome measured** Fatigue Measured on 4 visual analogue scales at 2 weeks **Baseline values intervention group** 7.72 (1.37) **Baseline values control group** 7.41 (1.58) **Results in intervention group** 7.25 (2.10) **Results in control group** 7.11 (1.35) **Comments** Average scores (smaller score less impaired) and sd presented.	**Outcome measured** Myalgia Measured on 2 visual analogue scales at 2 weeks **Baseline values intervention group** 8.57 (1.56) **Baseline values control group** 8.56 (1.72) **Results in intervention group** 7.52 (1.97) **Results in control group** 7.99 (1.26) **Comments** Average scores (smaller score less impaired) and sd presented.	**Outcome measured** Cognitive function Memory, measured on 1 visual analogue scale **Baseline values intervention group** 4.86 (3.21) **Baseline values control group** 5.22 (2.83) **Results in intervention group** 5.63 (3.16) **Results in control group** 4.72 (2.46) **Comments** Average scores (smaller score less impaired) and sd presented.
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome measured Work Work capacity/satisfaction, measured on 2 visual analogue scales at 2 weeks **Baseline values intervention group** 4.81 (1.72) **Baseline values control group** 5.25 (1.91) **Results in intervention group** 4.92 (2.15) **Results in control group** 5.09 (1.67) **Comments** Average scores (smaller score less impaired) and sd presented.	**Outcome measured** Dizziness 2 visual analogue scales, at 2 weeks **Baseline values intervention group** 3.95 (2.60) **Baseline values control group** 2.95 (2.77) **Results in intervention group** 4.26 (2.77) **Results in control group** 3.54 (3.12) **Comments** Average scores (smaller score less impaired) and sd presented.	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments: Results after 2 weeks only considered as after this nearly all placebo group switched to treatment. Other outcomes were measured (anxiety, mood disturbance, psychometric tests) but only reported for galanthamine group. All omparisons before after rather than between groups.			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Tiev (1999)[53] **Study design** RCT **Level of evidence** 1+	**Number:** 326 **Adults or children?:** Adults **Inclusion criteria:** Age more than 18 years. Patients with ongoing infection (e.g. chronic hepatitis), those who had experienced a traumatic situation in the previour quarter (e.g. bereavement), those with ongoing chronic illness with severe prognosis (e.g. cancer, aids, psychiatric or depressive illness), those with liver, renal endcrinological, cardiovascular, metabolic or auto-immune diseases requiring hospitalisation or surgical intervention were excluded. Women who were or were trying to become pregnant and chronic ethyliques (???) were also excluded. **Exclusion criteria:** **Diagnosis/ case definition:** Not stated **Age:** 42.4 (sd=15.5), range = 18-87 **% Female:** 36% female **Duration of illness:** 27 days to 2 years. **Baseline functioning:** No difference in baseline functioning as measured by the MFI fatigue scale. **Further details:** Not stated Patients recruited by 120 GPs. Patients had to stop taking medications which were psychostimulants, anti-asthenics or substances prescribed with these goals 15 days before treatment started. Antidepressives, medications with neurological or psychiatric aims, and muscle relxants had to be stopped at least one month before treatment started. Corticoids had to be stopped between and 1 and 3 weeks before inclusion in the study. Paitnets suffering from chronic postinfectious fatigue (CPIF). Febrile episode (after the dissapearance of the initial infection - flu, bronchitis, common cold, gastro-enterisits etc.) accompanied by persitant fatigue. A score greater than 12 on the "general fatigue" section of the MFI scale (validated multidimentional fatigue scale)m and more than 3 symptoms out of 12 on the Ferreri inhibition scale.	Sulbutiamine 3 groups: A: 400mg sul daily; B: 600 mg sul daily; C: placebo for 28 days **Number of participants in each group** A=106; B=111; C=109	Withdrawals: 16 patients dropped out, 5 on sul 400mg, 4 on sul 600 mg and 7 on placebo. One in each group dropped out because of non-serious side effects. 6 patients in placebo group sopped because they wanted to, 1 patient in 600mg and one n 400mg sul group judged the treatment not to work so stopped, 2 patients in 400 mg sul were not observed and 2 patients were lost to follow-up. Adverse events: 9 patients in su 400mg experienced side effects, 6 in 600mg su group and 12 in placebo, side effects included agitation, palpitations, diarrhoea, cystitits, bronchitis, arthritic pain, back pain, asthma, abdominal pain, insomnia, constipation, gastro-enteritis, diffuse pain, sinusitis, headahce, renal coli, vertigo, pharyngitis, tracheitis.

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Fatigue Fatigue as measured by MFI score, divided into general fatigue, physical fatigue, activity, motivation, and psychological fatigue. Combined results presented as mean (sd) **Baseline values intervention group** 400mg: 16.7 (2.3) 600mg: 16.8 (2.3) **Baseline values control group** 16.6 (2.2) **Results in intervention group** 400mg: 8.6 (3.4) 600mg: 8.9 (3.8) **Results in control group** 8.9 (3.3) **Comments** No significant difference in change between the groups. No significant difference in change when types of fatigue analysed separately, or after 7 days instead of after 28 days (results presented).	**Outcome measured** Clinical global impression Global impression of severity of illness (CGI item 1). Reported as mean change (sd) **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 400 mg: -2.06 (1.48); 600 mg: 1.98 (1.51) **Results in control group** -1.91 (1.42) **Comments** None of the items (item 1(above), impression of therapeutic effect, therapeutic index, or impression of side effects) showed differences in improvement between the placebo and treatment groups	**Outcome measured** Activity Baecke's measure of activity, divided into work, sport and leisure activity **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** No difference in change in scores between the groups	**Outcome measured** Illness severity Ferreri's score of incapacity, reported as mean change (sd) **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 400 mg: -12.9 (8.8) 600mg: -12.5 (9.1) **Results in control group** -12.1 (7.9) **Comments** There were no significant differences between treatment groups
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome measured fatigue EVA scale **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 400 mg: -4.5 (2.3) 600mg: -4.7 (2.3) **Results in control group** -4.3 (2.2) **Comments** No significant differences between the groups	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments:			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Vercoulen (1996)[55] **Study design** RCT **Level of evidence** 1+	**Number:** 48 depressed and 59 non-depressed **Adults or children?:** Adults **Inclusion criteria:** Randomly selected from researchers CFS database, acquired through self-referral, or referral by family doctors to the outpatient clinic at hospital in Nijmegen. Fatigue for more than 1 year with substantial impairment to their daily life (score >=35 on subjective fatigue questionnaire), depressed patients had to have score on depression index of 16 or more, non-depressed patients had to be 10 or less. Exclusion criteria: psychiatric diagnosis other than depression, pregnancy or lactation, lack of contraception in women of childbearing age, previous exposure to fluoxetine in formal clinical trial, previous lack of response to fluoxetine, participation in recent clinical trials, use of prescribed mediation other than incidental analgesics that could not be stopped, current psychotherapy **Exclusion criteria:** **Diagnosis/ case definition:** Oxford **Age:** Mean 38-40 **% Female:** 80F, 27M **Duration of illness:** Median 5-6 years range 1-30 years **Baseline functioning:** Fatigue for more than 1 year with substantial impairment to their daily life (score >=35 on subjective fatigue questionnaire), depressed patients had to have score on depression index of 16 or more, non-depressed patients had to be 10 or less. **Further details:** None stated Participants all on one CFS database at one hospital. No further details	Fluoxetine Fluoxetine (20mg)/placebo capsules taken once a day for 8 weeks **Number of participants in each group** 53 in placebo, 54 in treatment arm	Withdrawals: 15% of treatment group stopped treatment because of side effects compared to 4% in placebo group. 11 pts dropped out altogether: 9/54 in treatment group and 12/53 in placebo group. Adverse events: Two patients on placebo dropped out because of adverse effects (skin reactions and headaches), in treatment group 3 dropped out because of skin reactions, 1 heamatoma, 2 nausea, 2 headache. After 2 & 6 weeks of treatment no differences between actively treated and placebo groups in frequency of any possible side-effects. At end of treatment more fluoxetine patients complained of tremor and perspiration

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Fatigue Subjective fatigue score, fatigue measured 4 times a day on 4 point scale, completed self-observation list 12 days before treatment and 12 days before follow-up testing **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** No difference between fluoxetine treated group and placebo groups in the change from pre-treatment to post-treatment for any primary outcome measure assessing subjective fatigue. Mean difference between fluoxetine and placebo were: -0.164 (95% CI -0.64, 0.31) - not clinically meaningful.	**Outcome measured** Depression **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** No difference between fluoxetine treated group and placebo groups in the change from pre-treatment to post-treatment for any primary outcome measure assessing subjective depression. Mean difference between fluoxetine and placebo were: -0.186 (95% CI -0.35, -0.02) - not clinically meaningful	**Outcome measured** Recovery change in status **Baseline values intervention group** **Baseline values control group** **Results in intervention group** Depressed: 1 improved, 12 unchanged, 8 worse. Non-depressed: 2 improved, 13 unchanged, 8 worse. **Results in control group** depressed: 3 improved, 14 unchanged, 6 worse. Non-depressed: 3 improved, 21 unchanged, 4 worse. **Comments** No patient reported complete recovery, no effects on self-reported change at follow-up testing	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments: No difference between fluoxetine treated group and placebo groups in the change from pre-treatment to post-treatment for any primary outcome measure assessing psychological well-being, functional impairment, physical activity, sleep disturbances, neuro-psychological functioning, social interactions or cognitions.			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Williams (2002)[59] **Study design** RCT **Level of evidence** 1-	**Number:** 30 **Adults or children?:** Adults **Inclusion criteria:** **Exclusion criteria:** **Diagnosis/ case definition:** Oxford **Age:** mean 44.5 years **% Female:** 57% **Duration of illness:** mean 3.6 years **Baseline functioning:** **Further details:** 62 patients who met CFS Oxford criteria were initially identified by screening in clinics at two hospitals in Liverpool and patient-based CFS groups in NW England. Detailed enquiry and physical examination ruled out underlying causes of fatigue. Haematological and biochemical screening carried out with specific screening tests where appropriate.	melatonin vs phototherapy Melatonin (5mg in the evening) and phototherapy (2500 Lux for 1 hour in the morning) each given for 12 weeks in random order, separated by a washout period **Number of participants in each group** 30	Withdrawals: 42 patients entered the study but only 30 completed it. Reasons for withdrawal included the time and social demands of the study (n=10) and change of employment (n=2) Adverse events:

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Symptoms VAS; SF-36 **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** marginal improvement of sleep disturbance (p=0.03) with phototherapy; worsening of bodily pain (p=0.044), increased vitality (p=0.016) and improved mental health (p=0.046) with melatonin	**Outcome measured** Mental fatigue Mental fatigue inventory **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** no significant treatment effects	**Outcome measured** Hospital Anxiety and Depression Scale **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** no significant treatment effects	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

4. **Supplements**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Behan (1990)[31] **Study design** RCT **Level of evidence** 1++	**Number:** 63 **Adults or children?:** Adults **Inclusion criteria:** Patients selected because of severity of symptoms, symptoms present for 1-3 years, all symptoms followed definite viral infection **Exclusion criteria:** **Diagnosis/ case definition:** Not stated **Age:** 21-63 (mean 40) **% Female:** 27 men, 36 women **Duration of illness:** 1-3 years **Baseline functioning:** Not stated **Further details:** None stated A febrile illness with upper respiratory or gastrointestinal symptoms of such severity that the patient was confined to bed for several days was the precipitating factor in all cases, all patients also complained at some time of palpitations, shooting pains in the chest and unsteadiness all patients diagnosed with post-viral fatigue syndrome, symptoms included overwhelming fatigue made worse by exercise, myalgia and depression with poor concentration and short-term memory. All had been investigated to exclude other possible conditions	Essential fatty acids Patients took 8 capsules per day of either active preparation or placebo divided into 4 doses for 3 months, patients told to swallow capsules whole as the oils tasted slightly different Patients received either essential fatty acids or placebo - liquid paraffin. Each capsule contained 36mg gamma-linolenic acid (GLA), 17mg of eicosapentaenoic acid (EPA), 11mg of docosahexaenoic acid (DHA) and 255mg of linoleic acid, placebo contained 50mg linoleic acid in liquid paraffin. 10 IU of vitamin E was present in all capsules **Number of participants in each group** 39 to treated group, 24 in placebo	Withdrawals: No drop-outs Adverse events: No adverse effects stated

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Symptom measure Following symptoms scored from 0-3 (0=absent to 3=severe): fatigue, myalgia, dizziness, poor concentration and depression, symptom scores combined to give index of disease severity **Baseline values intervention group** 1.9 **Baseline values control group** 1.8 **Results in intervention group** 2.8 **Results in control group** 2.0 **Comments** Mean difference between treatments = 0.7, p<0.001 (calculated using Mann Whitney non-parametric test). Significant difference in improvement for all 5 symptoms assessed with those in treatment group showing a greater improvement	**Outcome measured** General health Patients overall condition evaluated as to whether felt worse, unchanged or better compared to baseline, made by doctor in consultation with the patient **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 0 worse, 15% unchanged, 85% improved (p of difference between 2 groups using likelihood ratio test <0.0001) **Results in control group** 9% worse, 75% unchanged, 17% improved **Comments**	**Outcome measured** Fatty acid concentration Fatty acid concentration of erythrocyte membrane phospholipids **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Compared with normal controls at the beginning of the trial all patients with PFS had significantly reduced levels of total EFAs, during the trial both actively treated and placebo groups showed a tendency to return towards normal values but in placebo groups shifts were significant only for adrenic acid and oleic acid, in group treated with essential fatty acids shifts towards normal were substantially greater and most were statistically significant	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Brouwers (2002)[79] **Study design** RCT **Level of evidence** 1-	**Number:** 53 **Adults or children?:** Adults **Inclusion criteria:** CDC 1994 criteria, minimum age 18 yrs. Patients were included when they had both high fatigue severity scores (CIS-fatigue >=40) and high disability scores (SIP8-total >=750). **Exclusion criteria:** Pregnant/ lactating women; people with lactose intolerance; people using experimental medication. During the trial patients were not allowed to take vitamins and minerals other than the trial supplements. **Diagnosis/ case definition:** CDC (1994) **Age:** mean 40 yrs supplement group, 38.9 yrs placebo group **% Female:** 74% supplement group, 65% placebo group **Duration of illness:** median 8.0 yrs supplement group, 4.5 yrs placebo group **Baseline functioning:** see 'results' **Further details:** not stated Recruited from a database of Dept of General Internal Medicine, University Medical Center Nijmegen, Netherlands	polynutrient supplement nutritional supplement containing several vitamins, minerals and (co)enzymes, specifically designed to have high antioxidative capacity. Composition reported in the paper. Placebo identical in appearance to supplement (125ml packages) **Number of participants in each group** 27 in supplement arm, 26 in placebo arm	Withdrawals: Five dropped out: three in the supplement group due to nausea, two for other reasons (1 in each group) Adverse events: see 'dropouts'

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: CIS fatigue score **Baseline values intervention group** 51.4 (4.2) **Baseline values control group** 51.3 (3.6) **Results in intervention group** 48.6 (7.4) **Results in control group** 48.2 (7.6) **Comments** CIS score <40 at follow-up: 15% in supplement group; 16% in placebo group	**Outcome measured** Number of CDC symptoms **Baseline values intervention group** 6.7 (2.1) **Baseline values control group** 7.0 (2.0) **Results in intervention group** 6.7 (1.8) **Results in control group** 7.5 (1.5) **Comments**	**Outcome measured** Functional impairment (SIP8) score **Baseline values intervention group** 1911 (666) **Baseline values control group** 1811 (683) **Results in intervention group** 1650 (543) **Results in control group** 1710 (644) **Comments**	**Outcome measured** Actometer score higher scores indicate higher levels of physical activity **Baseline values intervention group** 62.9 (17.9) **Baseline values control group** 65.8 (19.4) **Results in intervention group** 57.2 (14.6) **Results in control group** 65.6 (22.4) **Comments**
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome measured Daily Observed Fatigue score **Baseline values intervention group** 8.1 (2.2) **Baseline values control group** 7.8 (2.7) **Results in intervention group** 7.7 (2.4) **Results in control group** 7.2 (2.3) **Comments**	**Outcome measured** Self-reported improvement at follow-up **Baseline values intervention group** **Baseline values control group** **Results in intervention group** Completely recovered 0%; improved 20%; similar 76%; worse 4% **Results in control group** Completely recovered 0%; improved 16%; similar 68%; worse 1% **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments: none of the outcome measures showed significant differences between supplement and placebo			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Cox (1991)[76] **Study design** RCT **Level of evidence** 1++	**Number:** 34 **Adults or children?:** Adults **Inclusion criteria:** Duration of illnes greater than 6 months less than 18 months. Informed consent. **Exclusion criteria:** **Diagnosis/ case definition:** Australian **Age:** 18-56, mean 36 & 37 **% Female:** 11 male, 23 female **Duration of illness:** 6-18 months **Baseline functioning:** 2 groups similar with respect to baseline details (sex, age, packed red cell volume, Mean Nottingham health profile score, and magnesium concentration of placema, whole blood and red blood cell) **Further details:** Not stated Patients recruited from Centre for Study of Complementary medicine and from GPs in Southampton No further detials	magnesium 50% magnesium sulphate (1g in 2ml) or placebo (2ml injectable water). Given as intramuscular injection in the gluteal region every week for 6 weeks. **Number of participants in each group** 15 patients on active treatment (17 randomised) and 17 in control group.	Withdrawals: 4 patients excluded before randomisation as did not satisfy diagnostic criteria. 2 treatment group patients dropped out, generalised rash developed in 1 patient, and the other could not get the co-opertion of his GP. Adverse events: Not stated

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4

Outcome measured: General health Nottingham health profile score (energy, pain emotional reactions, sleep, social isolation, physical mobility) **Baseline values intervention group** 284.9 (sd=71.5) **Baseline values control group** 261.1 (sd=91.6) **Results in intervention group** Change in score: -143.51 **Results in control group** Change in score: -24.74 **Comments** p-value for the change between the groups = 0.001. Difference in change between the groups was also significant for enery, pain and emotional reactions but not for social isolation, sleep or physical mobility.	**Outcome measured** Laboratory measures Change in magnesium concentrations of plasma, whole blood and red blood cells (mmol/l) **Baseline values intervention group** Plasma: 0.80(sd=0.082) Whole blood: 0.99 (sd=0.07), Red blood cell: 1.29 (0.079) **Baseline values control group** Plasma: 0.81(sd=0.058) Whole blood: 1.00 (sd=0.046), Red blood cell: 1.28 (0.067) **Results in intervention group** Change after treatment: Plasma: 0.09(sd=0.09) Whole blood: 0.29 (sd=0.09), Red blood cell: 0.57 (0.19) **Results in control group** Change after treatment: Plasma: 0.08(sd=0.07) Whole blood: 0.04 (sd=0.048), Red blood cell: -0.018 (0.06) **Comments** 1 person in treatment group refused to give blood so n=14 Before treatment only 1 person in treatment group had red cell magnesium concentration within the normal range compared with none in group B, after treatment red cell magneisum was within the normal range in all group A patients but in only 1 group B patient.	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
de Becker (2001)[83] **Study design** Controlled trial **Level of evidence** 2-	**Number:** 90 **Adults or children?:** Not stated **Inclusion criteria:** CFS (1988 and/or 1994 CDC definition). Not allowed to take medication other than minor pain relievers and homeopathic medication. **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1994) **Age:** not stated **% Female:** not stated **Duration of illness:** not stated **Baseline functioning:** not stated **Further details:** none stated conference abstract; many details missing or CDC 1988	acclydine and amino acids first 4 weeks acclydine 250mg/ 4x per day in combination with amino acids, 2nd 4 weeks 250mg acclydine twice per day in combination with amino acids versus placebo **Number of participants in each group** not stated	Withdrawals: Adverse events:

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Clinical Global Impression **Baseline values intervention group** **Baseline values control group** **Results in intervention group** improvement in the active gorup at week 4 (p<0.004) and at week 8 (p<0.0003) **Results in control group** no significant changes at week 4 or week 8 **Comments** comparison seems to have been made within rather than between groups.	**Outcome measured** Improvement in symptoms **Baseline values intervention group** **Baseline values control group** **Results in intervention group** 54% **Results in control group** 16% **Comments**	**Outcome measured** IGF-1 levels **Baseline values intervention group** **Baseline values control group** **Results in intervention group** increased significantly at week 4 and week 8 compared to placebo group (p<0.0002) **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Kaslow (1989)[77] **Study design** RCT **Level of evidence** 1-	**Number:** 15 **Adults or children?:** Adults **Inclusion criteria:** Not stated **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1988) **Age:** 30 to 48 **% Female:** 3 male, 11 female **Duration of illness:** Not stated **Baseline functioning:** Karnofsky (functional status) score at baseline ranged from 50 to 80, all subjects had experienced previous treatment failures or had not tried any treatment. Normal values for blood tests, minor symptom scores 6-10, 9 had fever **Further details:** Not stated Not stated Not stated	Liver extract - folic acid - cyanocobalamin (LEFAC) Extract of bovine liver (10ug/mL, cyanocobalamin equivalent) with folic acid (0.4mg/mL) and cyanocobalamin (100ug/mL) 2. Placebo (no further details) Self administration of 2mL (weekly supply given, number of doses not stated) intramuscular injection containing either LEFAC or placebo, for 1 week then changed over to other preparation - did not know which was which **Number of participants in each group** 15 in each arm (cross-over trial), only 14 evaluated	Withdrawals: 1 subject dropped out - subject that dropped out completed treatment but did not return questionnaire Adverse events: None stated

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Activity Daily activity - subset of Karnofsky score (Functional status questionnaire) **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** No difference in activity score after LEFAC (p=0.73) or placebo (p=0.48) versus score on entry or in score after LEFAC versus placebo (0.53).	**Outcome measured** Psychological assessment Mental health - subset of Karnofsky score **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** No difference in mental health score after LEFAC (p=0.19) versus score on entry or in score after LEFAC versus placebo (0.55), but was significant after placebo (p=0.01) versus score on entry. Placebo group improved but not significantly more than LEFAC group at end of trial.	**Outcome measured** energy Energy levels measured using Likert scales from 1 to 10 **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Significant difference in energy score after LEFAC (p=0.03) and placebo (p=0.02) versus score on entry but not in score after LEFAC versus placebo (0.72).	**Outcome measured** Symptom measure Symptoms measured using Likert scales from 1 to 10 **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** No difference in symptom score after LEFAC (p=0.13) versus score on entry or in score after LEFAC versus placebo (0.92), but was significant after placebo (p=0.03) versus score on entry. Placebo group improved but not significantly more than LEFAC group at end of trial.
Additional comments: Trial continued for further 2 weeks during which time all subjects that continued (n=11) were given LEFAC and knew that they were getting this. Significant improvements were found in all outcomes assessed above compared to scores on entry into the study (p=0.036, 0.01, 0.002 and 0.01 respectively)			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Martin (1994)[78] **Study design** Controlled trial **Level of evidence** 2+	**Number:** 42 **Adults or children?:** Not stated **Inclusion criteria:** Coxsackie B antibodies present **Exclusion criteria:** **Diagnosis/ case definition:** Author's own **Age:** F mean 41.6(14.5), M mean 37.3(9.1) **% Female:** 13 M, 37 F **Duration of illness:** 3 to 120 months, mean 27 months **Baseline functioning:** Not stated (other than baseline values of results - see below) **Further details:** None stated All from one GP practice: Brechin & district 2 of following 3 criteria present for at least 3 months: Muscle pain, Mental/physical fatigue at rest or on minimal exercise, persisting/relapsing course of illness and following 2 criteria fulfilled: patient well before illness, exclusion of other cause of symptoms	Supplements Vitamin and mineral mixture or placebo, 2 tablets taken 4 times a day, contained mix of 35 vitamins and minerals Cross over trial with active ingredient/placebo taken for 3 months and then other taken for further 3 months. No washout. **Number of participants in each group** 21 in each arm. Only 19 completed full crossover trial.	Withdrawals: 30 patients (15 in each group) completed 3 months of treatment, 19 (10 in one group, 9 in other) completed 6 months of treatment Adverse events: None stated

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: General health GHQ questionnaire, rated on 4 point scale, completed by patients **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Data provided on graph cannot be read accurately, graphs not labelled clearly. Analysis of variance showed no differences for the two treatment groups, results not reported clearly, p-values not reported, only states that were not significant	**Outcome measured** Physical Physical questionnaire devised by authors, same structure as GHQ used, completed by patients **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Data provided on graph cannot be read accurately, graphs not labelled clearly. Analysis of variance showed no differences for the two treatment groups, results not reported clearly, p-values not reported, only states that were not significant	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Ockerman (2000)[81] **Study design** RCT **Level of evidence** 1+	**Number:** 22 **Adults or children?:** Adults **Inclusion criteria:** CFS diagnosed according to CDC 1994 criteria, aged 18-70 years, symptom score of 49 or more for 13 symptoms and 5 or more for total wellbeing (to include only relatively serious cases) **Exclusion criteria:** smoking, active dental treatment, electrical hypersensitivity, pollen allergy, other diseases of importance, use of drugs or antioxidants, other medical treatment. **Diagnosis/ case definition:** CDC (1994) **Age:** mean 50 years **% Female:** 86% **Duration of illness:** not stated **Baseline functioning:** not stated (relatively serious cases?) **Further details:** not stated	pollen extract 3 months treatment with pollen and pistil extract, 7 tablets per day taken in one dose, versus 3 months placebo tablets. Crossover trial, 2 week washout period in between treatments. Only ten patients had both treatments: 6 patients had placebo in both treatment periods and 6 patients had pollen extract in both treatment periods. **Number of participants in each group** 22	Withdrawals: One person moved away between treatment periods. Adverse events: No clear side effects with the exception of 'slight intestinal inconvenience' for a few days in 1 or 2 patients.

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Total well-being patient rating scale (0-10) **Baseline values intervention group** 7.14 **Baseline values control group** 6.66 **Results in intervention group** 5.48 **Results in control group** 6.45 **Comments** statistical comparisons made within groups (before/ after), not between groups	**Outcome measured** Fatigue; fatigability patient rating scale (0-10) **Baseline values intervention group** 7.95; 6.90 **Baseline values control group** 7.32; 7.59 **Results in intervention group** 7.52; 6.60 **Results in control group** 7.14; 7.45 **Comments** statistical comparisons made within groups (before/ after), not between groups	**Outcome measured** sleep problems patient rating scale (0-10) **Baseline values intervention group** 6.56 **Baseline values control group** 7.42 **Results in intervention group** 6.32 **Results in control group** 7.33 **Comments** statistical comparisons made within groups (before/ after), not between groups	**Outcome measured** depression patient rating scale (0-10) **Baseline values intervention group** 5.90 **Baseline values control group** 6.70 **Results in intervention group** 5.16 **Results in control group** 6.60 **Comments** statistical comparisons made within groups (before/ after), not between groups
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome measured intestinal problems patient rating scale (0-10) **Baseline values intervention group** 4.52 **Baseline values control group** 4.14 **Results in intervention group** 3.95 **Results in control group** 3.86 **Comments** statistical comparisons made within groups (before/ after), not between groups	**Outcome measured** cold hands and/or feet Patient rating scale (0-10) **Baseline values intervention group** 3.87 **Baseline values control group** 3.91 **Results in intervention group** 3.61 **Results in control group** 3.81 **Comments** statistical comparisons made within groups (before/ after), not between groups	**Outcome measured** odour sensitivity patient rating scale (0-10) **Baseline values intervention group** 4.21 **Baseline values control group** 4.07 **Results in intervention group** 3.69 **Results in control group** 4.03 **Comments** statistical comparisons made within groups (before/ after), not between groups	**Outcome measured** erythrocyte fragility patient rating scale (0-10) **Baseline values intervention group** 19.5 **Baseline values control group** 20.8 **Results in intervention group** 17.3 **Results in control group** 21.2 **Comments** statistical comparisons made within groups (before/ after), not between groups
Additional comments:			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Rothschild (2002)[82] **Study design** RCT **Level of evidence** 1-	**Number:** 70 **Adults or children?:** Adults **Inclusion criteria:** People aged between 25 and 60 years, chronic exhaustion >6 months, imbalanced immune system, recurrent random muscle soreness. **Exclusion criteria:** Treatment with tranquilisers, antidepressants, steroids and/or chemotherapeutic drugs or prescription medicines in preceding 3 months. Anyone declare din a critical condition by a licensed health practitioner, or people with acute infectious disease, diabetes, cardiovascular illness, renal condition or other immediately life-threatening pathology. People who responded allergically to any component of RM-10 or who were alcoholics or drug addicts. Trauma in preceding 3 months. **Diagnosis/ case definition:** CDC 1994 **Age:** not reported **% Female:** 64% **Duration of illness:** not reported **Baseline functioning:** not reported **Further details:** Diagnosis by physicians after physical examination, symptoms scoring, blood workups.	RM-10: a mix of ten medicinal mushrooms plus aloe vera and cat's claw, processed and fermented. 3 caplets taken 3 times daily before meals. Vs placebo Duration: 120 days **Number of participants in each group:** 35 in each group	Withdrawals: 2 droped out of RM10 group, results not reported for placebo group Adverse events: No adverse effects stated

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: symptoms **Results in intervention group** 8/33 asymptomatic at end of treatment period, 14/33 improved by >=60%, 8/33 improved by 40%. None worsened. **Results in control group** Half reported no effect and half worsened. **Comments**	**Outcome measured:** other **Results in intervention group** 21 patients noticed definite improvements in health difficulties and reduction of arthritic pain. **Results in control group** Not reported **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments: Laboratory values reported for RM10 group but not for placebo group (so have not extracted them)			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Stewart (1987)[80] **Study design** RCT **Level of evidence** 1-	**Number:** 12 **Adults or children?:** Not stated **Inclusion criteria:** Not stated **Exclusion criteria:** **Diagnosis/ case definition:** Not stated **Age:** Not stated **% Female:** Not stated **Duration of illness:** Mean 7 years, range 2.5 to 16 years **Baseline functioning:** Wide variability in subjects of their condition, and also variable from one day to the next **Further details:** Not stated Diagnosed cause was judged to be a virus in 7 cases and 245T poisoning in 3, most subjects had tried almost all available treatments Subjects diagnosed as having ME by their GPS and the study authors (no further diagnosis details)	Supplements For 1st week no supplements given to either group, one group of subjects given supplements for 3 weeks. After first 3 weeks crossed over treatment arms for further 3 weeks 2 multidigestive enzymes ("Vita fit" multidigestive formula) per meal, 3 capsules to be taken away from protein (Vita fit "immune boost", "Adrenal Support", "Cascara Sagrade") three times a day, other group received placebo capsules of similar colour and smell containing non-allergenic lactose-sugar free fillers **Number of participants in each group** 12 (cross-over trial)	Withdrawals: 2 subjects dropped out Adverse events:

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Fatigue Degree of tiredness on first arising in morning, severity of tiredness in day, work output & general feeling of wellness, degree of digestion at each meal, ease of bowel movements, degree of muscle/joint aching, ability to concentrate recorded by subjects, no details on scales used **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** 5/8 subjects showed reduction in tiredness and improvement in well-being accompanying better digestion, for one other digestion improved but no effect on tiredness, in 1 subject improvement in tiredness occurred during follow-up period, for one other subject digestion improved, tiredness did not but overall condition did. Average % improvement in tiredness was 33% for 7 subjects that showed positive change on this measure. During control conditions only 2 subjects showed improvement (this was in first 3 week section of study) of 36% and 17%, one subject got worse by 23%. Two subjects in control condition showed decrease in digestive scores (11% and 42% decrease), 2 subjects maintained their improvement from experimental to control phase & 2 continued to improve	**Outcome measured** bowel movements **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** cascare caused increase in bowel movements for nearly all subjects over experimental condition, increased bowel movements nearly always accompanied improvement in digestion. For 8 subjects showing digestive improvement, average improvement was 35%.	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Vermeulen (2004)[84] **Study design** RCT **Level of evidence** 1+	**Number:** 90 **Adults or children?:** Adults **Inclusion criteria:** CFS according to CDC 1994 criteria **Exclusion criteria:** Patients with an evident underlying organic cause, substance misuse or severe psychiatric disorder. **Diagnosis/ case definition:** CDC (1994) **Age:** mean 37 yrs ALC, 38 yrs PLC, 42 yrs combined group **% Female:** 77% each group **Duration of illness:** median 5.5 yrs ALC, 3.0 years PLC, 6.0 yrs combined group **Baseline functioning:** not reported **Further details:** not stated recruited from the polyclinic at the CFS Research Centre, Amsterdam. Structured interview, physical examination and extensive laboratory tests were carried out.	pharmacological 2g/day acetyl-L-carnitine, versus 2g/day propionyl-L-carnitine versus 2g of each (combined), for 24 weeks **Number of participants in each group** 30	Withdrawals: 8 patients withdrew due to side effects, another 8 stopped because they experienced no effect of the treatment: 4 in ALC group, 1 in PLC group and 3 in the combined group. Two patients stopped for reasons unrelated to treatment, Adverse events: 8 patients withdrew due to side effects: 3 in the Alc group, 2 in PLC group and 3 in combined group.

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Clinical Global Improvement Patient-rated **Baseline values intervention group** n/a **Baseline values control group** n/a **Results in intervention group** ALC Number improved: 8 weeks 13, 16 weeks 14, 24 weeks 17. PLC Number improved: 8 weeks 15, 16 weeks 19, 24 weeks 16. Combined ALC + PLC number improved: 8 weeks 10, 16 weeks 11, 24 weeks 11 **Results in control group** **Comments** 2 weeks following the end of therapy, no patients in any group rated themselves as improved.	**Outcome measured** General fatigue Multidimensional fatigue inventory (MFI-20) **Baseline values intervention group** ALC 17.6 (2.1); PLC 18.0 (2.4); combined 19.0 (1.5) **Baseline values control group** **Results in intervention group** ALC 8 weeks 16.7 (3.5), 16 weeks 16.5 (4.1), 24 weeks 15.9 (4.2); PLC 8 weeks 17.0 (2.9), 16 weeks 15.7 (4.0), 24 weeks 16.5 (3.1); Combined 8 weeks 18.0 (2.8), 16 weeks 16.9 (3.2), 24 weeks 17.3 (3.3) **Results in control group** **Comments** Significant improvements in PLC (p=0.004) and combined group (p=0.000)	**Outcome measured** Physical fatigue MFI-20 **Baseline values intervention group** ALC 16.9 (2.6), PLC 17.4 (3.0), combined 17.9 (2.2) **Baseline values control group** **Results in intervention group** ALC 8 weeks 16.5 (3.6), 16 weeks 15.8 (4.4), 24 weeks 15.7 (4.4); PLC 8 weeks 16.5 (3.0), 16 weeks 15.8 (4.0), 24 weeks 16.4 (3.2); Combined 8 weeks 17.3 (2.9), 16 weeks 16.1 (3.5), 24 weeks 16.5 (3.4) **Results in control group** **Comments** Not significantly improved in PLC group (p=0.069)	**Outcome measured** Mental fatigue MFI-20 **Baseline values intervention group** ALC 16.4 (2.8), PLC 15.1 (3.4), combined 15.3 (3.7) **Baseline values control group** **Results in intervention group** ALC 8 weeks 15.1 (3.2), 16 weeks 15.0 (2.9), 24 weeks 15.1 (3.6); PLC 8 weeks 15.1 (3.2), 16 weeks 13.8 (4.1), 24 weeks 13.9 (3.5); combined 8 weeks 14.3 (4.1), 16 weeks 14.2 (4.0), 24 weeks 14.6 (4.0) **Results in control group** **Comments** Significantly improved in ALC group (p=0.015)
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome measured Attention concentration Stroop test **Baseline values intervention group** median (IQR): ALC 46 (37-67), PLC 33 (24-49), combined 40 (28-54) **Baseline values control group** **Results in intervention group** median (IQR) ALC 8 weeks 38 (29-51), 16 weeks 38 (26-52), 24 weeks 38 (27-51); PLC 8 weeks 36 (25-41), 16 weeks 33 (22-40), 24 weeks 32 (24-40); combined 8 weeks 39 (28-47), 16 weeks 39 (27-47), 24 weeks 37 (27-42) **Results in control group** **Comments** Attention concentration score improved significantly in all groups	**Outcome measured** Pain McGill Pain Questionnaire-Dutch Language Version (MPQ-DLV) **Baseline values intervention group** Median (IQR): ALC 27 (13-57), PLC 45 (24-63), combined 37 (14-68) **Baseline values control group** **Results in intervention group** ALC 8 weeks 19 (3-44), 16 weeks 17 (0-44), 24 weeks 20 (6-56); PLC 8 weeks 47 (13-69), 16 weeks 25 (0-68), 24 weeks 25 (13-54); combined 8 weeks 26 (7-72), 16 weeks 33 (7-55), 24 weeks 38 (9-69) **Results in control group** **Comments** None of the treatments had significant effect on the pain scores	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Warren (1999)[75] **Study design** RCT **Level of evidence** 1++	**Number:** 50 **Adults or children?:** Adults **Inclusion criteria:** Not pregnant, not receiving EFA supplements. Beck Depression Inventory score <30 at entry. Aged 18-65. **Exclusion criteria:** **Diagnosis/ case definition:** Oxford **Age:** 18-59 years, mean 37.1(11.9) **% Female:** 21 M, 29 F **Duration of illness:** Mean 4.0 (2.7) years **Baseline functioning:** No significant differences between treatment and placebo groups w.r.t. physical symptoms, Beck scores or erythrocyte fatty acid profiles. **Further details:** None stated Participants were selected from 98 consecutive referrals to a regional infectious diseases unit. Full physical, psychiatric and blood screen took place before they were entered into the study. Diagnosis confirmed by physicians in outpatient setting.	Essential fatty acids 1. Efamol Marine 2x 500mg capsules taken 4 times a day. 2. Placebo (same number of capsules containing sunflower oil) Treatment duration = 3 months. Efamol Marine = evening primrose oil + concentrated fish oil. Each capsule contains 36mg gamma-linoleic acid (GLA), 17mg eicosapentanoic acid (EPA), 11mg docosahexanoic acid (DHA) and 255mg linoleic acid (LA). Placebo capsules did not contain EPA or DHA. Both contained 10IU vitamin E and trace riboflavin. **Number of participants in each group** 24 in treatment group, 26 in placebo group	Withdrawals: 2 in treatment group before start of trial - excluded from analysis. 5 in treatment group, 4 in placebo group after 1 month. 1 in placebo group after 2 months. Felt they were not getting better. Adverse events: None stated.

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Physical symptom checklist Fatigue, myalgia, dizziness, poor concentration, depression all scored by the participant from 0-3 (0=absent, 3=severe). Scores combined to give overall severity score. **Baseline values intervention group** 7.0 (range 3-13) **Baseline values control group** 7.5 (range 5-13) **Results in intervention group** 5.5 (range 3-13) change in symptom score -1.0 (range -7 to 3) **Results in control group** 6.0 (range 1-14) change in symptom score -1.5 (range -7 to 9) **Comments** No significant difference at baseline or final assessment. P for difference in change = 0.54.	**Outcome measured** Beck Depression Inventory Self-questionnaire 21 items each scoring 0-3 in severity. **Baseline values intervention group** 15.0 (range 1-26) **Baseline values control group** 15.0 (range 4-26) **Results in intervention group** 12.0 (range 5-23) change -2.5 (-10 to 8) **Results in control group** 11.0 (range 1-46) change -4.0 (-26 to 8) **Comments** p for difference in change = 0.09.	**Outcome measured** Patient assessment of whether they had improved or not **Baseline values intervention group** n/a **Baseline values control group** n/a **Results in intervention group** 29% improved **Results in control group** 46% improved **Comments** p for difference = 0.09.	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

5. Complementary / alternative medicine

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Awdry (1996)[71] **Study design** RCT **Level of evidence** 1-	**Number:** 64 (results presented for only 61) **Adults or children?:** Not stated **Inclusion criteria:** Not suffering from any other chronic medical complaint. Not taking any medication for the 3 months prior to the trial's onset (except vitamin and mineral supplements). Age <65 years, illness duration <10 years **Exclusion criteria:** **Diagnosis/ case definition:** Oxford **Age:** mean 39.9FH, 37.7MH, 42.8FP, 37.5MP **% Female:** H: 8M 22F; P: 10M 21F **Duration of illness:** H 4.8yrs M, 5.0yrs F. P 5.8yrs M, 5.0yrs F. **Baseline functioning:** before trial 10 in the homeopathy group were working, 12 were unemployed, 5 were on sick leave. In the placebo group 10 were working, 12 were unemployed and 7 were on sick leave. **Further details:** none stated all volunteers having read about trial in literature produced by Action for ME and the ME association. Independent verification of their ME diagnosis from their doctor or consultant. In writing from the relevant clinic.	Homeopathy 1. Variety of homeopathic remedies 'as indicated', assessed by homeopath 2. Placebo placebo group - identical but inert powder or tablet. Taken for 1 year. **Number of participants in each group** 32	Withdrawals: 3: 2 in homeopathy group (one due to having myeloid leukaemia and one reason not stated); 1 in placebo group (family circumstances led to taking other homeopathic remedies) Adverse events: none stated

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: daily graphs completed by each patient **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** cumulative results presented graphically for a small part of the scale - not clear on how to extract data or how meaningful this is.	**Outcome measured** end of trial self-assessment charts completed by each patient 5 categories: fatigue, disability, mood disturbance, myalgia, sleep disturbance. **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Homeopathic group: 6 'recovered', 4 were greatly improved, 3 were improved, 6 were slightly better and 11 were largely unchanged. In the placebo group 0 recovered, 1 was greatly improved, 0 were improved, 4 were slightly better and 26 were largely unchanged.	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments: methods presented in 806, results in 805			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Field (1997)[73] **Study design** RCT **Level of evidence** 1-	**Number:** 20 **Adults or children?:** Adults **Inclusion criteria:** Not stated **Exclusion criteria:** **Diagnosis/ case definition:** Not stated **Age:** Mean age = 47 **% Female:** 80% women **Duration of illness:** Not stated **Baseline functioning:** Not stated **Further details:** Not stated Primarily middle SES, 80% white, 20% Hispanic, 55% married, 85% graduates, 30% employed, 56% had never had a massage Subjects with chronic fatigue immunodeficiency syndrome	Massage therapy vs attention control (SHAM TENS) Massage therapy and attention controls (TENS SHAM) participated in treatment in same room for same duration of time at same intervals at the same time of day Therapy given twice a week for 5 weeks and consisted of gentle pressure to arms, torso, legs and head, controls received tactile stimulation from Electro-Acuscope which was not switched on, rolled over same body parts as massage group **Number of participants in each group** 10 in each treatment arm	Withdrawals: Not stated Adverse events: Not stated

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Depression CESD depression score - 20 item self-report scale **Baseline values intervention group** 22.8 **Baseline values control group** 27.6 **Results in intervention group** 14.8 **Results in control group** 26.6 **Comments** p-value for before-after comparison using ANOVA: f(2,17)=12.18, p<0.005	**Outcome measured** Fatigue Profile of fatigue symptoms scores (fatigue and somatic symptoms) **Baseline values intervention group** fatigue: 54.8, emotional distress: 34.6, cognitive distress: 37.7, somatic symptoms: 37.2 **Baseline values control group** fatigue: 53.4, emotional distress: 43.6, cognitive distress:35.8, somatic symptoms: 43.6 **Results in intervention group** fatigue: 47.6, emotional distress: 23.2, cognitive distress:31.4, somatic symptoms: 27.4 **Results in control group** fatigue: 59.6, emotional distress: 25.0, cognitive distress:31.5, somatic symptoms: 40.7 **Comments** p-value for before-after comparison using ANOVA: f(2,17)=4.83, p<0.05	**Outcome measured** Pain Pain in last week **Baseline values intervention group** 4.1 **Baseline values control group** 5.0 **Results in intervention group** 2.8 **Results in control group** 6.6 **Comments** p-value for before-after comparison using ANOVA: f(2,17)=13.65, p<0.005	**Outcome measured** Sleep # hours of sleep **Baseline values intervention group** 6.8 **Baseline values control group** 6.5 **Results in intervention group** 7.5 **Results in control group** 6.2 **Comments** p-value for before-after comparison using ANOVA: f(2,17)=4.72, p<0.05

Outcome 5	Outcome 6	Outcome 7	Outcome 8
Outcome measured Laboratory measures Norepinephrine, epinephrine, dpamine and Cortisol **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** No difference in levels of Norepinephrine or epinephrine. Massage group versus control group experienced significant decreases in Cortisol levels ($F(2, 17)=16.91$, $p<0.001$) and increases in dopamine ($F(2,17)=11.23$, $p<0.01$)	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Perrin (1998)[74] **Study design** Controlled trial **Level of evidence** 2-	**Number:** 58 **Adults or children?:** Adults **Inclusion criteria:** Aged 18-55, able to afford £400 per year for treatment, able to travel to Greater Manchester for treatment, understood the importance of continuing treatment until the end of the year, willing to be part of longer follow up study. People receiving other treatments or any prior physical therapy were excluded form pt group (but not from control group). People receiving physical therapy excluded from both groups. No depression, psychiatric history or any neurological disorder. Excluded if tested positive for any other pathophysiological cause of symptoms. **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1988) **Age:** 18-55 **% Female:** 39 F, 18 M (1 uncertain??) **Duration of illness:** Not stated **Baseline functioning:** Not clear **Further details:** None stated Matched for marital status (more single people in each group). Similar mean educational background in each group. Selected from group of 80 volunteers (ad in ME journal). Diagnosed by physician as suffering from ME, CFS or post-viral fatigue syndrome. Able to travel to the Manchester area for treatment. All control group members of 'Action for ME'. CDC 1988 criteria for CFS; London criteria for ME	Osteopathy 1.Osteopathic manipulation of the thoracic spine. 20 sessions over 1 year. 2. Controls - were allowed to receive any other treatments. 1. Soft tissue massage of paravertebral muscles, trapezii, levator scapulae, rhomboids and muscles of respiration. 2. High and low velocity manipulation of the thoracic and upper lumbar spinal segments using supine and side-lying combined leverage and thrust techniques. 3. Gentle articulation of thoracic and upper lumbar spine plus the ribs, by both long and short lever techniques. 4. Functional techniques to suboccipital region and sacrum. 5. Stimulation of cranio-sacral rhythm by functional-cranial techniques. 6. Efflourage to aid drainage in thoracic and cervical lymphatic vessels. 6. Exercises to improve mobility of thoracic spine and to improve physical co-ordination. **Number of participants in each group** 35 in patient group, 40 in control group.	Withdrawals: Two dropouts in the patient group, 17 dropouts in the control group. Adverse events: None stated

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Fatigue Profile of fatigue related states **Baseline values intervention group** 41.5 **Baseline values control group** 62 **Results in intervention group** 32.5 **Results in control group** 59 **Comments** Interim: control 59.5, patients 56.	**Outcome measured** General health questionnaire developed for this study based on 26 common ME symptoms. High=poor. **Baseline values intervention group** 80% **Baseline values control group** 68% **Results in intervention group** 68% **Results in control group** 67.5% **Comments** Interim: control 65%, patients 70%	**Outcome measured** Back pain questionnaire **Baseline values intervention group** 76.5% **Baseline values control group** 61.5% **Results in intervention group** 68% **Results in control group** 61.5% **Comments** Interim: control 60.5%, patients 67.5%	**Outcome measured** BDI Revised **Baseline values intervention group** 25% **Baseline values control group** 27% **Results in intervention group** 20% **Results in control group** 21.5% **Comments** Interim: control 24%, patients 18%
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome measured Anxiety Beck anxiety inventory **Baseline values intervention group** 32.5% **Baseline values control group** 25.5% **Results in intervention group** 25.5% **Results in control group** 28.5% **Comments** Interim: control 25%, patients 22%	**Outcome measured** Sleep Morgan-Gledhill sleep questionnaire **Baseline values intervention group** 126.5 **Baseline values control group** 133 **Results in intervention group** 113 **Results in control group** 126.5 **Comments** Interim: control 128%, patients 107%	**Outcome measured** Nottingham health questionnaire **Baseline values intervention group** 41.5% **Baseline values control group** 38% **Results in intervention group** 32.5% **Results in control group** 37.5% **Comments** Interim: control 35%, patients 33.5%	**Outcome measured** Cognitive function Broadbent's cognitive function questionnaire **Baseline values intervention group** 58% **Baseline values control group** 57% **Results in intervention group** 54.5% **Results in control group** 61.5% **Comments** Interim: control 58.5%, patients 53.5%
Additional comments: values taken from graphs so not v accurate, 0% = symptom free, 100% = worst symptoms possible. Final measurements at 6 months. Interim at 3 months. Overall mean change in scores patient group 40% (SD 15.8) p<0.0005. Control group -1% (SD 22) p<0.0005.			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Weatherley-Jones (2004)[72] **Study design** RCT **Level of evidence** 1++	**Number:** 103 **Adults or children?:** Adults **Inclusion criteria:** Patients aged over 18 years old reporting severe disabling fatigue that substantially impaired function, requiring use of simple aids for daily living, or limiting moderate activity (such as pushing a vacuum cleaner, walking 100 yards and walking up hill). Patients had to have no clinically significant abnormalities in haematological and biochemical tests. **Exclusion criteria:** Major depression, bipolar disorders, psychosis, eating disorders, substance abuse/ dependence, somatisation disorders. Patients engaged in individual counselling or psychotherapy, in clinical trials for other CFS treatments, and pregnant patients, patients already receiving or having received homeopathic treatment or CBT **Diagnosis/ case definition:** Oxford **Age:** treatment group mean 38.9 yrs, placebo gp mean 38.8 yrs **% Female:** 57% treatment group, 62% placebo group **Duration of illness:** mean 4.8 yrs treatment group, 3.7 yrs placebo group **Baseline functioning:** significant functional impairment (see inclusion criteria) **Further details:** None reported Participants were recruited from two outpatient departments in UK hospitals. Also had physical examination, assessment of functional impairment and psychiatric interview.	Homeopathy Homeopathic consultations over a 6 month period with consultations at monthly periods when individualised prescriptions were made. Dispensing of remedies was double blinded. The control group received a placebo **Number of participants in each group** 53 in treatment arm, 50 in placebo	Withdrawals: 11 withdrew from treatment arm (5 did not complete treatment), 8 from placebo group (6 did not complete treatment) Adverse events: Not reported

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Multidimensional Fatigue Inventory (final scores are changes from baseline) MFI general fatigue; physical fatigue; mental fatigue; reduced activity; reduced motivation **Baseline values intervention group** 18.4 (1.7); 18.0 (2.2); 16.7 (3.7); 16.1 (3.1); 13.0 (3.9) **Baseline values control group** 18.1 (2.2); 17.5 (3.1); 16.5 (3.0); 16.4 (3.8); 13.2 (3.7) **Results in intervention group** 2.70 (3.93); 2.13 (4.00); 2.70 (4.01); 2.72 (4.47); 1.35 (4.15) **Results in control group** 1.35 (2.66); 1.28 (2.74); 2.05 (2.86); 1.81 (2.82); 1.65 (3.02) **Comments** Analysis of covariance showed statistically significant difference between groups for the general fatigue subscale of the MFI (p=0.04). 11 patients (26%) in the homeopathic medicine group showed clinical improvements on all subscales of the MFI compared to 4 (9%) of the placebo group.	**Outcome measured** Fatigue Impact Scale (final scores are changes from baseline) FIS cognitive dimension; physical dimension; social dimension **Baseline values intervention group** 24.1 (9.0); 27.3 (6.8); 44.8 (15.5) **Baseline values control group** 24.2 (8.0); 27.4 (7.1); 44.7 (16.4) **Results in intervention group** 4.88 (9.3); 4.98 (8.5); 7.92 (18.02) **Results in control group** 4.21 (7.18); 5.30 (6.69); 8.20 (14.06) **Comments** no significant differences between groups	**Outcome measured** Functional Limitations Profile (final scores are changes from baseline) FLP physical dimension; psychosocial dimension **Baseline values intervention group** 20.4 (14.1); 35.1 (14.8) **Baseline values control group** 22.1 (14.9); 36.3 (15.0) **Results in intervention group** 5.11 (8.82); 9.81 (14.19) **Results in control group** 2.72 (8.40); 6.76 (10.67) **Comments** significant difference between groups in score changes for physical dimension scale (p=0.04)	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

6. Other

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Goudsmit (1996)[86] **Study design** Controlled trial **Level of evidence** 2-	**Number:** 52 **Adults or children?:** Both **Inclusion criteria:** None stated. **Exclusion criteria:** **Diagnosis/ case definition:** Other **Age:** Intervention group mean 39.6 (13.4) youngest 15. Control group mean 37.7, youngest 14 **% Female:** 35 F, 17 M **Duration of illness:** Intervention gp median 5 (3.69 yrs, range 6 months - 14 yrs. Control gp median 2.1 (3.34) yrs, range 8 months - 15 yrs. p=.06 **Baseline functioning:** Intervention group: 45% still working or studying, 86% changed job or reduced hours due to illness. Control group: 32% still working or studying. 4.5% intervention group and 0 controls were able to do more than half of premorbid activities. **Further details:** Additional illnesses in 23 participnats included asthma, epilepsy, arthritis, ulcers, diverticulitis, hiatus hernia, sinusitis and kidney infections All from waiting list of Dr. Ho-Yen. Intervention group been on list for 1-6 months, control group < 1 month. Control group contained more people in unskilled manual jobs ($p<0.05$). 40% of intervention and 63% of control groups reported sudden onset following infectious condition. 41% of intervention group and 50% control already following Ho-Yen advice (from book). Post-infectious fatigue syndrome diagnosed using Dr Ho-Yen's criteria	Combination Intervention: Ho-Yen programme. Control: Waiting list control. Ho-Yen 5 step management programme: 1. Advice to limit and prevent psychological problems. 2. Information about the illness. 3. Keeping a diary of illness and participant's feelings. 4. Advice about energy and exercise. 5. Advice about food and diet. **Number of participants in each group** 25 in treatment group, 27 in control group (22 in each arm analysed)	Withdrawals: 8 excluded from analysis: 3 from treatment group and 5 from control group. Not stated from which groups the following were excluded. 3 wrongly diagnosed, two wished to discontinue treatment, one lost questionnaire in the post. One improved after stopping oral ocntraceptives, and one was lost to follow up after 3 months. Adverse events: None reported as such: 9% of intervention group and 18% of control group 'felt worse' after treatment duration.

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Symptoms Subscales of profile of fatigue related symptoms: fatigue(F), cognitive difficulty(CD), somatic aymptoms(SS). Mean(sd) **Baseline values intervention group** F 3.5(1.61); CD 2.53(1.33); SS 1.94(1.34) **Baseline values control group** F 4.2(1.14); CD 3.06(1.44); SS 2.29(1.04) **Results in intervention group** F 2.68(1.41); CD 2.28(1.42); SS1.54(1.15) **Results in control group** F 3.84(1.4); CD 2.96(1.51); SS 2.29(1.04) **Comments** Significant differences between groups for fatigue (F(1,40) = 5.13, p=0.03) and somatic symptoms (F(1,40) = 4.66, p=0.04).	**Outcome measured** Mood ? Mishel uncertainty in illness scale-community form: uncertainty(U); self-efficacy(SE) mean(sd) **Baseline values intervention group** U 64.77(7.88); SE 47.05(17.97) **Baseline values control group** U70.19(15.87); SE 62.71(14.05) **Results in intervention group** U 54.3(12.14); SE 62.14(14.55) **Results in control group** U 62.71(14.05); SE 50.20(17.87) **Comments** significant difference between groups: self-efficacy (F(1,38)=6.79, p=0.13). Uncertainty: groups heterogeneous	**Outcome measured** Coping ? Mishel uncertainty in illness scale-community form subscales: maintaining activity(MA), accommodating to the illness(AI), focusing on symptoms(FS), seeking information(SI) **Baseline values intervention group** MA 3.22(0.85); AI 4.00 (0.88); FS 3.6(0.83); SI 3.21(0.91) **Baseline values control group** MA 3.42(0.83); AI 4.17(0.83); FS 3.67(1.08); SI 3.29(1.11) **Results in intervention group** MA 2.59(0.79); AI 4.45(0.86); FS 3.46(1.05); SI 3.46(0.86) **Results in control group** MA 3.13(0.87); AI 4.34(0.91); FS 3.59(1.03); SI 3.22(1.21) **Comments** No significant differences between groups.	**Outcome measured** Anxiety and Depression Hamilton anxiety and depression scale (HAD) **Baseline values intervention group** A 8.77(4.9); D 7.95(3.84); D corrected 5.82(3.26) **Baseline values control group** A 8.81(4); D 9.59(4.04); D corrected 6.86(3.89) **Results in intervention group** A 7.14(3.86); D 6.59(4.12); D corrected 4.91(3.58) **Results in control group** A 8.73(3.93); D 9.05(3.62);D corrected 6.59(3.43) **Comments** As one case had unusually high scores on HAD values were corrected. No significant differences between groups.
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome measured Function Functional impairment scale **Baseline values intervention group** 22.81(4.74) **Baseline values control group** 22.91(4.73) **Results in intervention group** 20.86(6.24) **Results in control group** 22.73(5.71) **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments: Subgroup analysis: no difference in changes in scores between people who had been ill for shorter and longer periods of time. No differences in outcome when participants were defined according to degree of initial functional impairment and emotional distress. Those who reported more initial fatigue showed greater changes in self-efficacy scores (t=2.34, df 10.55, p=0.04). During the intervention period 55% of people in the control group made changes to their diet or began a new treatment, 6% began taking antidepressants. 9 of intervention group began taking antidepressants.			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Hobday (Unpublished data) **Study design** RCT **Level of evidence** 1+	**Number:** 57 **Adults or children?:** Adults **Inclusion criteria:** Had to have CFS diagnosis. **Exclusion criteria:** Excluded if receiving oral contraceptive, HRT or were pregnant; prescribed corticosteroids, immunosuppressive agents, non-steroidal anti-inflammatory agents or antibiotics for one month or less before the study; were already on Candida or other therapeutic diet or had cut out different food groups; were taking vitamins and minerals significantly above current recommendations; had evidence of an eating disorder. **Diagnosis/ case definition:** CDC (1994) **Age:** mean 45.6 yrs LSLY arm, 43.3 yrs HE arm **% Female:** 89% LSLY, 76% HE **Duration of illness:** mean (length of diagnosis) 9.8 yrs LSLY arm, 7.9 yrs HE arm **Baseline functioning:** Two patients in the LSLY group were unable to be weighed due to mobility problems. Not stated how many were severely affected in the HE group. **Further details:** irritable bowel syndrome (IBS): 13 LSLY, 17 HE mean body mass index (BMI) 27.9 LSLY arm, 25.7 HE arm Patients were recruited from the Chronic Fatigue Service at St Bartholomew's Hospital (London, UK).	Low sugar low yeast diet Low sugar low yeast (LSLY) diet based on 'Beat Candida Cook Book' adapted to ensure nutritional requirements were met and provided sufficient diversity to promote adherence. Comparator gorup received a healthy eating (HE) diet based on current Department of Health guidelines. **Number of participants in each group** 28 LSLY arm, 29 HE arm	Withdrawals: 17 (9 HE/ 8 LSLY) lost to follow-up but included in the analysis on an intention to treat basis. Adverse events: not reported.

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Chalder Fatigue Scale **Baseline values intervention group** 23.0 (5.0) **Baseline values control group** 22.5 (6.7) **Results in intervention group** 16.0 (8.2) **Results in control group** 17.7 (10.0) **Comments** no significant difference between groups	**Outcome measured** Medical Outcomes Survey Short Form General health; body pain; role physical; social function; vitality; physical function; role emotion; mental health **Baseline values intervention group** 31.0 (14.8); 40.2 (24.5); 9.0 (15.9); 38.0 (26.4); 21.4 (14.5); 34.6 (26.5); 55.9 (44.9); 64.2 (17.7) **Baseline values control group** 32.6 (19.4); 42.4 (25.1); 11.1 (23.3); 36.1 (25.3); 27.0 (18.7); 38.7 (23.3); 55.1 (46.2); 65.0 (19.2) **Results in intervention group** 34.5 (20.3); 42.3 (29.2); 26.3 (35.8); 63.3 (44.5); 42.0 (29.3); 39.6 (31.2); 29.8 (20.7); 70.7 (21.8) **Results in control group** 40.6 (19.4); 52.2 (24.1); 23.8 (34.9); 61.7 (46.3); 50.6 (29.4); 54.7 (28.7); 36.2 (26.4); 67.8 (18.1) **Comments** no significant differences between groups	**Outcome measured** Hospital Anxiety and Depression Scale Anxiety; Depression **Baseline values intervention group** 9.4 (4.9); 8.1 (3.5) **Baseline values control group** 8.7 (4.4); 7.0 (3.8) **Results in intervention group** 8.5 (5.2); 6.5 (3.6) **Results in control group** 7.3 (4.1); 5.4 (3.7) **Comments** no significant differences between groups	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Marlin (1998)[85] **Study design** Controlled trial **Level of evidence** 2-	**Number:** 71 **Adults or children?:** Adults **Inclusion criteria:** none stated. **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1994) **Age:** mean 40-43 years, range 31-59. **% Female:** 6 M 16 F **Duration of illness:** mean 54-56 months, range 5-117. **Baseline functioning:** All were disabled wrt gainful employment as well as many activities of daily living. None were actively employed and all were receiving disability benefits. Functional ability evaluations confirmed a level of function inconsistent with being gainfully employed. **Further details:** none Results only available for 5 untreated at follow-up and 17 treated. Results available for all 51 treated at end of treatment but not for untreated, therefore no control group therefore comparison is between 17 treated and 5 untreated at F-U. Assessment at privately funded multi-disciplinary clinic. Assessment by general internist, psychiatrist, clinical psychologist and kinesiologist.	Multi treatment (medical treatment of symptoms plus anxiety/ affective disorder, CBT & social) 1. Bringing pt under optimal medical management, 2. Treating any ongoing affective or anxiety disorder pharmacologically and 3. Implementing comp CBT program. Average duration of treatment was 6 months (range 2-12).Patients were seen at home 2-3 x per week by behavioural medicine field researcher. Program tailored to each pt but included: structured physical exercise & activation; sleep mgmt strategies; careful activity mgmt; regulation of stimulant intake and reductions in use of symptomatic medications; cognitive intervention designed to deal with pts beliefs concerning the nature of their disorder; participation of pts family; efforts to establish specific vocational and a vocational goals. Employers were urged to provide employment opportunities and facilitate a gradual return to work. Disability carriers were encouraged to provide interim financial support in the form of disability benefits, support therapeutic intervention and establish clear time-frame access to benefits. **Number of participants in each group** 51 in treatment program, 20 untreated. Assessed: 17 in treatment program, 5 untreated.	Withdrawals: 49/71 were not followed up. 41 were unable to be contacted, 2 refused to give data and in 6 cases follow up was deemed 'professionally inappropriate' Adverse events: None reported

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Employment status Patients either returned to work or work equivalent (education retraining, job searching or other non-paid activity) or remained disabled. **Baseline values intervention group** all 17 disabled **Baseline values control group** all 5 disabled **Results in intervention group** 11 had returned to work , 4 were 'work equivalent', 2 were still disabled **Results in control group** 1 had returned to work, 1 was 'work equivalent', 3 were still disabled. **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Schlaes (1996)[87] **Study design** Controlled trial **Level of evidence** 2-	**Number:** 12 **Adults or children?:** Adults **Inclusion criteria:** Participants were individuals with CFS who felt that they would benefi from information, motional support and help with weekly tasks. **Exclusion criteria:** **Diagnosis/ case definition:** Not stated **Age:** 36-57 **% Female:** 3 male, 9 female **Duration of illness:** Not stated **Baseline functioning:** Not reported **Further details:** None stated 11 caucasian, 1 asican/pacific islander. No difference between experimental and control groups for the demographic variables of race, education, marital status and work status. Patients were recruited through Chicago area CFS specialists, Chicago support groups, 2 Chicaho-area CFS newsletters and a letter sent out through the Chicago CFS Association Participants with CFS	Buddy and mentor programme Half participants given buddies and mentors during study period, other half told they would receive budy at end of the program. Location to intervention was based on geographic location of participants as all of the buddies lived in certain area. Buddies were designed to provide emotional support, social companionship and instrumental support, were individuals in the community who agreed to spend one hour per week conducting home visits to patients with CFS. Mentors were individuals with CFS who were willing and able to engage in 2 hours per month of phone contact with the participants. Role of mentor designed to provide information and emotional support regarding living with CFS. Intervention and follow-up were at 4 months **Number of participants in each group** 6	Withdrawals: 2 participants, one in each group, could not complete post-test measures due to severity of illness. Adverse events: None reported

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Fatigue severity Fatigue self-rating scale (validated) **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Participants in intervention group showed significant decrease in fatigue severity compared to control (p<0.03) - fatigue increased in control group	**Outcome measured** Positive thinking Life Orientation test (revised) **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Participants in intervention group showed increases in positive thinking control group showed decreases, difference approached significance (p=0.08)	**Outcome measured** Depression CES-D scale **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** No significant differences between groups	**Outcome measured** Psychological distress Brief Symptom inventory **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** No significant differences between groups

Outcome 5	Outcome 6	Outcome 7	Outcome 8
Outcome measured Perceived stress Perceived stress scale, short version **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** No significant differences between groups	**Outcome measured** Coping strategies COPE scales **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** No significant differences between groups	**Outcome measured** Perceived social support Interpersonnal support evluation list short form **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** No significant differences between groups	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**
Additional comments: Difference scores were calculated by subtracting pre-test scores from post-test scores. Difference scores from the experimental group were compared to difference scores from the control group. No significant differences between experimental and control groups on measures of depression, psychological distress, perceived stress, coping strategies and perceived social support.			

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Soderberg (2001)[88] **Study design** RCT **Level of evidence** 1-	**Number:** 14 **Adults or children?:** Adults **Inclusion criteria:** Thirty women diagnosed with CFS were invited to join the project. **Exclusion criteria:** People who also had fibromyalgia were excluded. **Diagnosis/ case definition:** CDC (1994) **Age:** median 44.5 years (range 28 to 52 years) **% Female:** 100% **Duration of illness:** median 3.5 years (range 1.5 to 6.5 years) **Baseline functioning:** **Further details:** not reported Nine of the 14 had sudden onset. One was on full time sick leave and 6 had full time temporary disability pensions.	Group therapy not described well: seem to have been quite unstructured discussions, attended by but not led by a psychologist. Ten weekly sessions of 1.5 hours. Controls: received group therapy 5 months after the first group. **Number of participants in each group** 7	Withdrawals: one in control group (not stated why) Adverse events: not reported

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Quality of life Gothenburg Quality-of-Life scale (GQL instrument), visual analogue scale **Baseline values intervention group** GQL 62.3 (17.4), VAS 3.3 (1.8) **Baseline values control group** GQL 67.4 (10.1), VAS 3.3 (2.2) **Results in intervention group** GQL 62.9 (18.0), VAS 4.4 (2.8) **Results in control group** GQL 64.6 (10.8), VAS 3.1 (1.5) **Comments** Comparisons were made within groups (before vs after treatment) and between groups after the contorl group had had the group therapy, but not after therapy in one group versus no therapy in the other group (this would have been the appropriate comparison!)	**Outcome measured** Fatigue symptoms WESS **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments** Results not reported in the paper, due to problems interpreting data categories	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**	**Outcome measured** **Baseline values intervention group** **Baseline values control group** **Results in intervention group** **Results in control group** **Comments**

Study ID	Participants	Interventions/ comparators	Withdrawals and adverse events
Teitelbaum (2001)[90] **Study design** RCT **Level of evidence** 1++	**Number:** 72 **Adults or children?:** Adults **Inclusion criteria:** Patients were excluded if they were overtly hypothyroid or hyperthyroid or if they had creatinine levels >1,9 mg/dl, AST > 60 u/l, glucose >300 mg/dl, hematocrit <0.34 or erythrocyte sedimentation rate > 45 mm/h. Patients were not excluded for depression, anxiety or sleep disorders. **Exclusion criteria:** **Diagnosis/ case definition:** CDC (1994) **Age:** mean 44.6 (sd=8.1), range 23-61. Placebo patients wer an average 4 years older than intervention patients. **% Female:** 92% female **Duration of illness:** mean = 8.3 years (sd=6.5), range 0.5 - 34 years. **Baseline functioning:** Entry visit mean analog total was 176.5 (sd=64.1, range 20-355) and fibromyalgia impact questionnaire score was 53.2 (sd=9.6, range 30.4 - 74.6). **Further details:** All patients had FMS Patients discontinued previous treatments when able that were part of the study protocol. Patients were allowed to continue or begin active treatment upon completing the study and to participate in any other interventions on their own that were not part of the study protocol. All patients were required to meet 1990 American College of Rheumatology criteria for FMS (fibromyalia). Patients were excluded if they had major intercurrent illnessess (e.g. cancer, multiple sclerosis, poorly controlled diabetes, emphysema, or lupus) that could cause their symptoms. All but three also met CFS criteria.	Multi treatment (includes supplements) For sleep all patients received melatonin and valerian and zolpidem, trazadone, cyclobenzaprine, cariprodol, amitriptyline and clonazepan where needed. For nutritional support all patients received multivitamins and magnesium with malic acid. Patients in the intervention group received an individualised treatment programme based on test results or clinical history. Possible treatments were: ferrous fumarate, B12, levothyroxine, cortisol, DHEA, testosterone enanthate, oestrogen replacement, oxytocin, fludrocortisone, sertraline, paroxetine, fluoxetine, nefazadone, nystatin, itraconazole, metronidazole and doxycycline. Patients were treated for: (1) Subclinical thyroid, gonadal or adrenal insufficiency, (2) disordered sleep, (3) suspected neurally mediated hypotension, (4) opportunistic infections, and (5) suspected nutritional deficiencies **Number of participants in each group** 38 in active group, 34 in placebo.	Withdrawals: One patient in each group dropped out because of side effects and one in each group for no reason given. One active patient dropped out because there were "too many pills" and 3 active patients dropped out because they were too busy to be in the study Adverse events: 24 in the active group and 22 in the placebo group reported adverse events, these included dermatological, psychological, gastrointestinal, autonomic dysfunction, sleep changes and miscellaneous.

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome measured: Visual analogue scales How is your energy? How is your sleep? How is your mental clarity? How bad is your achiness? How is your overall sense of well-being? All rated from 0-100, with 100 being best. Gives maximum score of 500. **Baseline values intervention group** 176.1 (70.3) **Baseline values control group** 177.1 (57.6) **Results in intervention group** 310.3 (111.3) **Results in control group** 211.9 (103.7) **Comments** p-value for t-test of difference between values at final readings = 0.0002, The p-value for the treatment main effect in a repeated measures random effects regression model based on data from visit 1 to visit 4, adjusting for entry value and age <0.0001	**Outcome measured** FIQ scale Fibromyalgia Impact Questionnaire (disability index) scored from 0-100, the higher the score the higher the disability. **Baseline values intervention group** 54.8 (10.3) **Baseline values control group** 51.4 (8.4) **Results in intervention group** 33.2 (18.2) **Results in control group** 47.7 (15.5) **Comments** p-value for t-test of difference between values at final readings = 0.0005, The p-value for the treatment main effect in a repeated measures random effects regression model based on data from visit 1 to visit 4, adjusting for entry value and age <0.0001	**Outcome measured** TPI Tender Point Index, calculated by multiplying the number of positive tender points by their degree of tenderness. Maximum score of 72. **Baseline values intervention group** 31.7 (10.5) **Baseline values control group** 35.0 (10.6) **Results in intervention group** 15.5 (9.5) **Results in control group** 32.3 (11.4) **Comments** p-value for t-test of difference between values at final readings <0.0001	**Outcome measured** Patient's overall response **Baseline values intervention group** **Baseline values control group** **Results in intervention group** much better = 16, better = 14, same = 2, worse = 0, much worse = 1 **Results in control group** Much better= 3, better = 9, , same = 11, worse = 6, much worse =4 **Comments** Cochran-Mantel-Haenszel trend test, p<0.0001
Additional comments: For continuous outcomes results presented as mean (sd). Follow up data was available for 41 patients who chose to continue active treatment after the study.			

APPENDIX 3: VALIDITY ASSESSMENT FOR QUESTION 3

a. RCTs

Study details		Randomisation	Concealment of allocation	Participant blinding	Investigator blinding	Baseline comparability of groups	Follow-up	Drop-outs (Intention to treat)	Outcome objectivity	Statistical Analysis	Sample-size calculation	Comparability of treatment of groups	VS
Awdry	1996	Not stated	Not stated	Yes	Yes	Good	Poor	Poor	Good	Poor	Not stated	Not stated	6
Behan	1990	Good	Good	Yes	Yes	Good	Good	Good	Good	Good	Not stated	Adequate	17
Blacker	2004	Good	Adequate	Yes	Yes	Good	Adequate	Adequate	Adequate	Adequate	Good	Good	15
Blockmans	2003	Good	Good	Yes	Yes	Good	Adequate	Poor	Adequate	Good	Not stated	Good	14
Brook	1993	Good	Not stated	Not stated	Not stated	Not stated	Good	Poor	Good	Poor	Not stated	Not stated	6
Brouwers	2002	Adequate	Poor	Yes	Yes	Poor	Adequate	Adequate	Good	Adequate	Good	Poor	10
Cleare	1999	Good	Good	Yes	Yes	Good	Good	Adequate	Good	Good	Good	Adequate	18
Cleare	2002	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated	Adequate	Not stated	Not stated	Not stated	2
Cox	1991	Good	Not stated	Yes	Yes	Good	Good	Poor	Good	Good	Good	Adequate	15
Deale	1997	Good	Good	No	Yes	Good	Good	Good	Good	Good	Good	Adequate	18
De Becker	2001	Not stated	Not stated	Yes	Yes	Not stated	Not stated	Not stated	Adequate	Poor	Not stated	Not stated	3
Diaz-Mitoma	2003	Not stated	Not stated	Yes	No	Not stated	Adequate	Adequate	Good	Adequate	Not stated	Not stated	6
DuBois	1986	Good	Good	Yes	Not stated	Not stated	Good	Poor	Good	Good	Not stated	Not stated	11
Field	1997	Adequate	Not stated	No	Yes	Good	Not stated	Not stated	Good	Good	Not stated	Adequate	9
Forsyth	1999	Not stated	Not stated	Yes	Yes	Good	Good	Adequate	Good	Good	Not stated	Adequate	12
Fulcher	1997	Good	Good	No	Yes	Good	Good	Good	Adequate	Good	Good	Adequate	17
Hickie	1998	Good	Good	Yes	Yes	Good	Good	Good	Good	Good	Good	Adequate	19
Hobday	2005	Good	Adequate	No	No	Adequate	Poor	Adequate	Good	Good	Adequate	Adequate	11
Kakumanu	2001	Adequate	Not stated	Yes	Yes	Not stated	Not stated	Not stated	Poor	Not stated	Not stated	Not stated	3
Kaslow	1989	Not stated	Not stated	Yes	Yes	Adequate	Good	Poor	Good	Adequate	Adequate	Adequate	10
Lloyd	1993	Good	Not stated	Yes	Yes	Good	Good	Poor	Good	Good	Not stated	Adequate	13
Lloyd	1990	Not stated	Not stated	Yes	Yes	Good	Good	Good	Good	Good	Not stated	Adequate	13
McKenzie	1998	Not stated	Not stated	Yes	Yes	Good	Good	Adequate	Good	Good	Good	Adequate	14
Moorkens	1998	Not stated	Not stated	Yes	Yes	Not stated	Poor	Poor	Good	Poor	Not stated	Adequate	5
Morriss	2002	Good	Not stated	Yes	Not stated	Good	Good	Adequate	Good	Poor	Not stated	Good	12
Moss-Morris	2005	Good	Adequate	No	No	Poor	Adequate	Good	Adequate	Adequate	Adequate	Poor	9
Natelson	1996	Not stated	Not stated	Yes	Yes	Poor	Good	Poor	Good	Adequate	Not stated	Adequate	8
Ockerman	2000	Not stated	Good	Yes	Yes	Adequate	Adequate	Adequate	Adequate	Poor	Not stated	Adequate	9
Olson	2003	Poor	Poor	Yes	Yes	Adequate	Good	Not relevant	Adequate	Adequate	Poor	Adequate	8

Peterson	1998	Good	Good	Yes	Yes	Not stated	Good	Poor	Good	Good	Good	Good	16
Peterson	1990	Good	Not stated	Yes	Yes	Adequate	Good	Poor	Good	Good	Good	Good	15
Powell	2000	Good	Good	Not stated	Not stated	Good	Good	Good	Good	Good	Good	Adequate	17
Prins	2001	Good	Good	No	No	Good	Poor	Good	Good	Good	Good	Good	16
Rothschild	2002	Not stated	Not stated	Yes	Yes	Not stated	Adequate	Poor	Not stated	Poor	Not stated	Not stated	3
Rowe	2000	Good	Not stated	Yes	Yes	Good	Good	Good	Good	Good	Good	Good	18
Rowe	1997	Adequate	Not stated	Yes	Yes	Good	Good	Adequate	Good	Good	Good	Good	16
Santaella	2004	Not stated	Not stated	No	No	Adequate	Poor	Poor	Adequate	Poor	Not stated	Adequate	3
See	1996	Not stated	Not stated	Yes	Yes	Good	Good	Adequate	Good	Poor	Not stated	Good	11
Sharpe	1998	Good	Not stated	Not stated	Not stated	Good	Good	Good	Good	Good	Good	Adequate	15
Snorrason	1996	Not stated	Not stated	Yes	Yes	Good	Good	Poor	Good	Poor	Not stated	Adequate	9
Soderberg	2001	Not stated	Not stated	No	Not stated	Poor	Adequate	Not stated	Poor	Poor	Not stated	Poor	1
Steinberg	1996	Not stated	Not stated	Yes	Yes	Good	Adequate	Poor	Good	Adequate	Good	Good	12
Stewart	1987	Adequate	Not stated	Yes	Yes	Good	Poor	Poor	Poor	Poor	Not stated	Adequate	6
Straus	1988	Adequate	Adequate	Yes	Yes	Good	Adequate	Poor	Good	Good	Good	Good	15
Strayer	1994	Adequate	Not stated	Yes	Yes	Good	Good	Poor	Good	Good	Not stated	Adequate	12
Stulemeijer	2004	Good	Good	No	No	Good	Adequate	Good	Good	Adequate	Good	Good	16
Taylor	2004	Adequate	Not stated	No	Yes	Adequate	Good	Not relevant	Adequate	Good	Not stated	Adequate	9
Teitelbaum	2001	Good	Adequate	Yes	Yes	Good	Good	Good	Good	Good	Good	Good	19
Tiev	1999	Not stated	Not stated	Yes	Yes	Good	Adequate	Poor	Good	Good	Not stated	Adequate	10
Vercoulen	1996	Good	Not stated	Yes	Yes	Good	Adequate	Poor	Good	Good	Not stated	Adequate	12
Vermeulen	2004	Adequate	Adequate	No	No	Adequate	Poor	Good	Adequate	Adequate	Good	Adequate	10
Vollmer Conna	1997	Not stated	Not stated	Yes	Yes	Good	Good	Good	Good	Good	Not stated	Adequate	13
Wallman	2004	Adequate	Adequate	No	No	Good	Not stated	Not stated	Good	Poor	Adequate	Good	9
Warren	1999	Adequate	Good	Yes	Yes	Good	Good	Poor	Good	Good	Good	Adequate	16
Wearden	1998	Good	Not stated	Yes	Yes	Good	Good	Good	Good	Good	Good	Adequate	17
Weatherley-Jones	2004	Good	Good	Yes	Yes	Good	Adequate	Good	Adequate	Adequate	Good	Good	17
Whitehead	2002	Not stated	Not stated	No	Not stated	Adequate	Poor	Poor	Adequate	Poor	Not stated	Adequate	3
Williams	2002	Not stated	Not stated	No	No	Good	Poor	Poor	Adequate	Poor	Not stated	Good	5
Zachrisson	2002	Good	Good	Yes	Yes	Adequate	Adequate	Adequate	Good	Adequate	Adequate	Adequate	14

b. Controlled trials

Study details	Participant blinding	Investigator blinding	Baseline comparability of groups	Follow-up	Drop-outs (Intention to treat)	Outcome objectivity	Statistical Analysis	Appropriate-ness of control	Sample-size calculation	Control for confounding	Comparability of treatment of groups	VS
Andersson 1998	Yes	Yes	Good	Poor	Poor	Good	Poor	Good	Not stated	Not relevant	adequate	9
Cox 2002	No	No	No	Adequate	Poor	Poor	Adequate	Adequate	Adequate	Adequate	Adequate	7
Cox 2002	No	No	No	Good	Poor	Poor	Adequate	Adequate	Poor	Good	Good	8
Friedberg 1994	No	No	Poor	Not stated	Not stated	Adequate	Poor	Poor	Poor	Poor	Not stated	1
Goudsmit 1996	No	No	Poor	Poor	Poor	Adequate	Adequate	Poor	Not stated	Poor	Not stated	2
Marlin 1998	No	No	Poor	Poor	Poor	Good	Poor	Poor	Not stated	Poor	Adequate	3
Martin 1994	Yes	Yes	Good	Poor	Poor	Good	Adequate	Good	Poor	Poor	Adequate	10
Natelson 1998	Yes	Not stated	Good	Good	Poor	Good	Adequate	Good	Not stated	Not stated	Adeqaute	11
Perrin 1998	1998	No	No	Not stated	Poor	Poor	Not stated	Poor	Poor	Not stated	Poor	0
Schlaes 1996	1996	No	No	Not stated	Adequate	Poor	Adequate	Good	Adequate	Poor	Poor	4
Viner 2004	No	No	No	No	Poor	Poor	Not stated	Adequate	Adequate	Not stated	Poor	2