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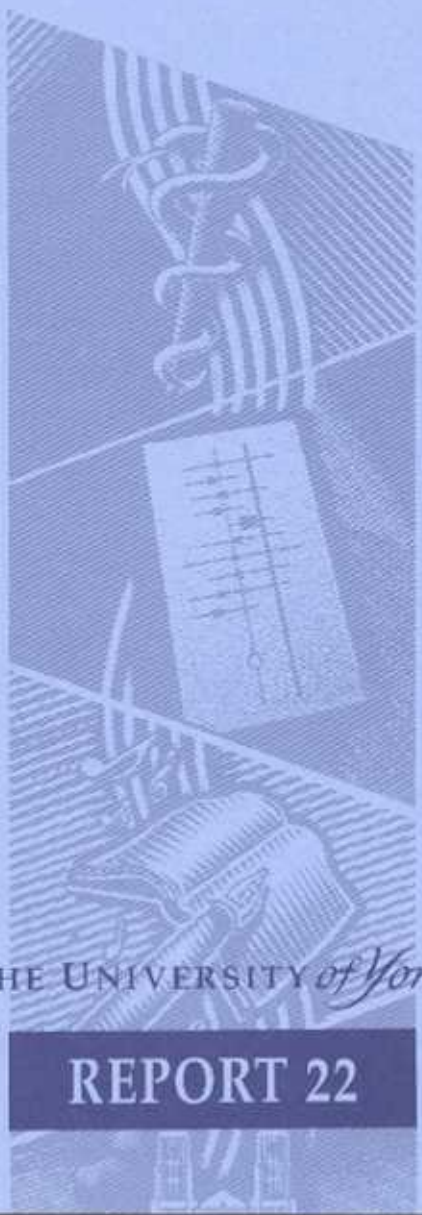
The effectiveness of interventions used in the treatment/management of chronic fatigue syndrome and/or myalgic encephalomyelitis in adults and children



THE UNIVERSITY of York

REPORT 22

The effectiveness of interventions used in the treatment/management of chronic fatigue syndrome and/or myalgic encephalomyelitis in adults and children

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ACKNOWLEDGEMENTS

Preface

This review was commissioned by the Policy Research Programme of the Department of Health. The findings have also been reported in a paper published in the *Journal of the American Medical Association*[1] and in an *Effective Health Care* Bulletin.[2]

We would like to thank Drs S Hickie, Rowe, Powell, Bleijenberg, Speight and Goudsmit, who kindly responded to requests for further information on their studies. We would also like to thank members of our expert panel for providing comments on the original protocol for the review and for clarification on issues relating to outcomes. Additionally, we would like to thank everyone who sent in information in response to the website established for the review.

Advisory panel members

Chris Clark, Action for ME.

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LIST OF ABBREVIATIONS

CBT	Cognitive Behavioural Therapy
CFS	Chronic Fatigue Syndrome
DARE	Database of Abstracts of Reviews of Effectiveness
DLE	Dialyzable Leukocyte Extract
GET	Graded Exercise Therapy
ME	Myalgic Encephalomyelitis
NADH	Nicotinamide Adenine Dinucleotide
NHS	National Health Service
PVFS	Post Viral Fatigue Syndrome
RCT	Randomised Controlled Trial
UK	United Kingdom
US	United States of America

EXECUTIVE SUMMARY

Background

Chronic fatigue syndrome (CFS) consists of a range of symptoms including fatigue, headaches, sleep disturbances, difficulties with concentration and muscle pain. The defining characteristic has been reported to be debilitating fatigue. It is not known what causes CFS although various hypotheses have been suggested, including immunological, viral, psychological and neuroendocrine factors. The uncertainty regarding the cause is reflected in the wide variety of interventions which have been used in the treatment and management of CFS. These interventions have had different objectives including targeting of the underlying disease process, targeting of specific symptoms, focusing on coping strategies, and encouraging rehabilitation. Evaluations of the effectiveness of different approaches suggest a variety of different outcomes and currently a number of interventions are used in the management of CFS.

Myalgic Encephalomyelitis (ME) has sometimes been reported to be a separate syndrome from CFS. However in the research literature CFS is commonly referred to as being the same illness as ME, post viral fatigue syndrome (PVFS) and all similar symptom complexes. The scope of this review was to evaluate interventions for the management of CFS/ME. Therefore, unless specifically named symptom complexes were addressed, CFS/ME is the term used throughout this review.

Objective

To assess the effectiveness of all available interventions which have been evaluated for use in the treatment or management of adults and children with CFS/ME.

Methods

A systematic review of the literature was conducted. Seventeen electronic databases were searched from database inception to February 2002. Additional studies were identified by scanning the bibliographies of retrieved articles, searching the world wide web, through requests to members of the advisory panel and the establishment of a web-site for the review through which additional references could be submitted. To be included in the review studies had to compare an intervention used in the treatment or management of CFS/ME to an untreated control group, or one given placebo or inactive control treatment. Studies in both adults and children with a diagnosis of CFS/ME, based on any criteria, were eligible for inclusion. All outcomes reported by the studies were considered relevant. Two reviewers independently screened titles and abstracts for relevance. Retrieved studies were assessed for inclusion by one reviewer and checked by another. Disagreements were resolved through discussion. Data extraction and validity assessment were performed by one reviewer and checked by a second. Discrepancies were resolved by referral to the original studies. **f** necessary arbitration was by a third reviewer.

A qualitative analysis was undertaken due to the significant heterogeneity between studies in interventions and outcomes. Interventions were categorised into the following seven groupings: behavioural; immunological; antiviral; pharmacological; supplements; complementary/alternative; other. Studies were judged to show some effect of treatment if any of the outcomes measured found a statistically significant difference between the intervention and control groups. Studies were classified as having an overall effect (positive or negative) if they showed a statistically significant effect for more than one clinical (i.e. not a physiological) outcome or, if only one clinical outcome was measured, it was found to show a statistically significant effect. Where no significant differences occurred, a study was classified as showing no effect. The association between study results and treatment duration, validity score, and diagnostic criteria was investigated. Insufficient data were available to assess publication bias using standard methods (e.g. funnel plots), and it was therefore discussed narratively.

Results

Forty six studies met the inclusion criteria: 38 RCTs and eight controlled trials, eleven of the RCTs used a cross-over design. Of the included trials 29 (61%) showed some beneficial effect of the intervention and of these 18 (39%) showed an overall beneficial effect, one study (3%) reported a negative effect of the intervention. In some studies, participants were only eligible if they could physically get to the clinic. In other trials, limited information was given about participants who were ineligible or about the baseline functioning of many of those who were included.

Behavioural

Both cognitive behavioural therapy (CBT) and graded exercise therapy (GET) showed positive results. Three of the four 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 and one controlled trial of modified CBT did not find overall beneficial effects of CBT. These two studies scored lower on the validity assessment, and the controlled trial presented within group differences rather than between group differences. The studies evaluating CBT did not report any adverse effects of the intervention although in one RCT two participants dropped out of the CBT group because they felt a deterioration in their symptoms was due to the intervention. A second RCT reported drop-out rates of around 20-35% in all three intervention groups, with the highest rates in the CBT group, but reasons for drop-outs were not reported. All three RCTs of GET were of high quality and two found an overall beneficial effect of the intervention compared to the control groups. The third, which also investigated Dialyzable Leukocyte Extract (DLE), found a beneficial effect of CBT compared with DLE for one of the outcomes investigated. The studies did not report any adverse effects of GET although two studies did report study withdrawals that may have been related to adverse effects of the intervention.

Immunological

Five RCTs investigated the effects of immunoglobulin G; four found some positive effect, two of which found an overall beneficial effect, and the fifth and largest found no effect of treatment. Some severe adverse effects were found in the studies of immunoglobulin G. Two participants had to withdraw from immunoglobulin G treatment due to severe constitutional symptom reactions and one person withdrew due to mild but transient liver failure. Phlebitis has also been noted with immunoglobulin infusions. It should be noted that immunoglobulins and leukocyte extract are blood products and there are known risks associated with their use, such as the possible transfer of infectious diseases. An overall beneficial effect of ampligen was found in one RCT. One RCT assessed the combined effect of leukocyte extract and cognitive behavioural therapy and although no effect of leukocyte extract on its own was found a beneficial effect on one of the outcomes investigated in the group receiving both leukocyte extract and CBT was reported. One RCT evaluated the antihistamine terfenadine and found no beneficial effects.

Antiviral

Two RCTs evaluated interferon, one of which found an overall beneficial effect. The other presented only within group differences and so no conclusion regarding the effects of treatment can be drawn. No significant effects were found in a small RCT of ganciclovir, or in a controlled trial of vaccination with staphylococcus toxoid. The trial of gancilovir was ended prematurely due to adverse events in the intervention group. The effect of aciclovir was assessed in one small RCT and a negative effect was reported for some of the outcomes investigated. Three people had to withdraw from aciclovir treatment due to reversible renal failure.

Pharmacological

Very few of the RCTs showed an overall beneficial effect.

Antidepressants

Two poor quality RCTs of phenelzine and fluoxetine, and a good quality RCT of moclobemide reported no effects of treatment either on symptoms of depression or on any of the other outcome measures reported. A good quality RCT of fluoxetine combined with graded exercise therapy also showed no effect on depression or other measured outcomes. One controlled trial of selegiline reported some positive effects of treatment but found no overall effect.

Corticosteroids
Four reasonable quality RCTs assessed the effects of steroid treatment. Two RCTs of fludrocortisone reported no effect of treatment, two of hydrocortisone found some beneficial effect of treatment.

Anticholinergic agents
A poor quality RCT of sulbutiamine reported no effect of treatment. One trial which assessed galanthamine hydrobromide, presented results as within group differences and no conclusion regarding the effect of treatment can be drawn from this trial.

Other pharmacological agents
One trial which assessed the growth hormone Genotropin presented results as within group differences and no conclusion regarding the effect of treatment can be drawn from this trial. One poor quality RCT showed an overall beneficial effect of oral nicotinamide adenine dinucleotide (NADH).

Adverse events serious enough to cause people to withdraw from the study occurred with fludrocortisone, moclobemide, sulbutiamine, galanthamine hydrobromide, phenelzine and fluoxetine.

Supplements
Two good quality RCTs of essential fatty acids reported some beneficial effects of the intervention and one also found an overall beneficial effect. Magnesium supplements were found to have an overall beneficial effect in one good quality, but small RCT. One poor quality RCT and one controlled trial evaluated general supplements. The controlled trial reported no significant effect of treatment, but the RCT reported an overall beneficial effect. One poor quality RCT of liver extract reported no beneficial effects. The RCT of magnesium supplements reported that two participants left the intervention group after experiencing a generalised rash and the other studies did not report adverse effects.

Complementary/alternative
Alternative therapies were evaluated in three poor quality RCTs and one controlled trial. An overall beneficial effect of massage therapy was found in one small RCT. Two RCTs assessed the effectiveness of homeopathy; one found a positive effect and the second reported overall beneficial effects. A very poor controlled trial of osteopathy found overall beneficial effects. There were no reports of adverse events from the interventions in any of these studies.

Other
A good quality RCT reported overall beneficial effects of treatment with a combination of drugs depending on the specific symptoms of each patient. An overall beneficial effect was found in two controlled trials of two different multi-treatment approaches, one of which included CBT and one of which was based on providing information and advice. 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.

Conclusions
Overall the interventions demonstrated mixed results in terms of effectiveness. All conclusions about effectiveness should be considered together with any methodological inadequacies of the studies. Interventions for which there is evidence of effectiveness from RCTs include CBT and GET. In some of the included studies, bed or wheelchair restricted patients have been excluded and only one study included young people under 18 years of age, which raises questions about the applicability of findings to all people with CFS/ME. Further research is needed into (i) how subgroups of patients may respond differently to treatments and (ii) the potential additive or combined effects of treatments where more than one therapy is used. The large number of outcome measures used makes standardisation of outcomes a priority for future research. Future research needs to combine scientific rigour with patient acceptability and good quality research is needed to evaluate the effectiveness of a range of interventions including pacing, ideally in comparison with CBT and GET.

1. BACKGROUND

Chronic fatigue syndrome (CFS) consists of a range of symptoms including fatigue, headaches, sleep disturbances, difficulties with concentration and muscle pain. The defining characteristic has been reported to be debilitating fatigue.[3-5] Children and adults present with similar symptoms.[6] Myalgic encephalomyelitis (ME) is sometimes reported to be a separate syndrome from CFS, characterised by muscle weakness, pain and neurological disturbance.[7] It has been suggested that CFS and ME are part of a group of similar symptom complexes such as postviral fatigue syndrome and neurasthenia.[4] ME is sometimes diagnosed among people with these symptom complexes in the UK but is not commonly diagnosed in other countries, such as the USA.[8] However in the research literature CFS is commonly referred to as being the same illness as ME, post viral fatigue syndrome (PVFS) and all similar symptom complexes.

Whilst the review authors are aware of the controversy over the separation or otherwise of CFS, ME and other symptom complexes, it is not within the scope of this systematic review to determine whether CFS, ME and all other similarly named symptom complexes represent the same condition. The scope of this review was to evaluate interventions for the management of CFS/ME. Therefore, unless specifically named symptom complexes were addressed, CFS/ME is the term used throughout this review, in keeping with the brief given by the Department of Health.

The cause of CFS/ME remains unknown although various hypotheses have been suggested that include one or more of the follpwing factors: immunological, viral, psychological and neuroendocrine. Diagnosis is based entirely on symptoms reported by the patient. Definitions commonly used tend to be research criteria, and there are several available (see DEC Report No 50 for a list[9]). Two frequently used definitions for CFS are the UK (Oxford) criteria[3] and the US Centers for Disease Control and Prevention criteria.[4] Both state that debilitating fatigue must be present for at least six months, that there is some functional impairment, and that these have not been caused by any other identifiable clinical condition. The definitions differ however in the number and severity of other symptoms which must be present (see Table 1.1). A different set of criteria are sometimes used to diagnose ME, for example, the Dowsett criteria[7] or the London criteria (unpublished)[10] which are more stringent than the CFS criteria. In practice a clinical assessment is used which aims to increase the probability of a correct diagnosis of CFS/ME and to rule out other conditions.[11] This involves taking a full clinical history, a mental health evaluation, sleep evaluation and a physical evaluation. It is recommended that a series of basic screening tests be undertaken to exclude other conditions that can present as fatigue.[11]

Estimates of prevalence vary, and may be attributed to the diversity in diagnostic criteria (more stringent criteria result in a lower prevalence estimate) and to variations in the extent to which alternative medical and psychiatric diagnoses are excluded. One small study in the UK reported that the point prevalence of CFS was 0.6% (95% confidence interval 0.2 - 1.5%), using the Oxford Criteria for diagnosis.[12] A larger UK study reported a prevalence ranging from 0.5%, when comorbid psychological disorders were excluded, to 2.6% when they were not.[13] Most commonly, onset is reported to be early twenties to mid-forties.[11] It is reported to be approximately twice as common in women as in men, affects all social classes to a similar extent and affects all ethnic groups.[11] Based on an estimate of adult population prevalence of 0.4%, the CFS/ME Working Group reported that a general practice with a population of 10,000 patients is likely to have 30-40 patients with CFS/ME, about half of whom may need input from specialist services.[11]

It is generally recognised that prognosis is variable. Many patients improve quite quickly. However, in those who do not improve quickly, the illness can persist for a long time. The prognosis tends to be worse for severely ill patients than for less severely ill patients.[11] The findings from prospective natural history studies are varied.[14] At 12 to 18 months, rates of self-reported global improvement in symptoms range from 11-64% and rates of self reported worsening of symptoms ranged from 15-20%. Epidemiological studies of the natural history of CFS/ME show high rates of spontaneous improvement. In one study[15] 123/226 no longer met symptom criteria for CFS after 1.5 years and in another[16] 65/103 had improved, but not made a full recovery, after 3.2 years.

The recent CFS/ME Working Group Report[11] stated that the provision of services specifically designed for patients with CFS/ME is limited in some areas and non-existent in others. While patients have access to the normal range of primary, secondary and tertiary care services, few are tailored to this patient group. Specialist services for children and young people, including inpatient facilities, are limited to a few nationwide.[11] Referrals from primary care are to one or more specialists such as

Table 1.1 Criteria for case definitions of CFS/ME

Criteria	
US Centers for Disease Control and Prevention (CDC) 1988 (CFS)[5]	6 months duration of fatigue Functional activity – 50% decrease in activity 6 or 8 symptoms required. Physical signs sometimes required Neuropsychiatric symptoms – may be present New onset required *Exclusions:* Extensive list of known physical causes, psychosis, bipolar disorder, substance abuse
US Centers for Disease Control and Prevention (CDC) 1994 (CFS)[4]	6 months duration of fatigue Substantial functional impairment 4 symptoms required Cognitive or neuropsychiatric symptoms may be present New onset required *Exclusions:* Clinically important medical conditions, melancholic depression, substance abuse, bipolar disorder, psychosis, eating disorders
Australia 1990 (CFS)	6 months duration of fatigue Substantial functional impairment – disruption of daily activities Post exertion fatigue No symptoms specified Cognitive or neuropsychiatric symptoms required New onset not required *Exclusions:* Known physical causes, psychosis, bipolar disorder, substance abuse, eating disorders
United Kingdom 1991 'Oxford criteria' (CFS)[3]	6 months duration of fatigue Disabling functional impairment – affects physical and mental functioning No symptoms specified Cognitive or neuropsychiatric symptoms – may be present Definite onset required *Exclusions:* Known physical causes, psychosis, bipolar disorder, eating disorder, organic brain disease, substance abuse Other psychiatric disorders (depressive illness, anxiety disorders) are not reasons for exclusion
Dowsett (ME) 1990[7]	Complaint of general or local muscular fatigue following minimal exertion with prolonged recovery time Neurological disturbance, especially of cognitive, autonomic and sensory functions Variable involvement of cardiac and other systems, a prolonged relapsing course Syndrome commonly initiated by respiratory and/or gastro-intestinal infection but an insidious or more dramatic onset following neurological , cardiac or endocrine disability
London Criteria, 1994[10]	All of the following three criteria must be present: 1. Exercise-induced fatigue precipitated by trivially small exertion (physical or mental) relative to the patient's previous exercise tolerance 2. Impairment of short-term memory and loss of powers of concentration, usually coupled with other neurological and psychological disturbances such as emotional disability, nominal dysphasia, disturbed sleep patterns, disequilibrium or tinnitus 3. Fluctuation of symptoms, usually precipitated by either physical or mental exercise These symptoms should have been present for at least 6 months and should be ongoing

general physicians, immunologists, neurologists, haematologists and psychiatrists. The CFS/ME Working Group Report suggests that the lack of locally-based specialist services may be a problem for patients, who need access to services yet are unable to reach them, and for commissioners who wish to reduce the cost of out-of-area treatments.[11]

A variety of interventions have been used in the treatment and management of CFS/ME. Evaluations of the effectiveness of different approaches suggest a variety of different outcomes and currently a number of interventions are used in the management of CFS/ME. Whilst there is some lack of agreement about management strategies, there is also considerable agreement on elements of these, even if terminology may convey otherwise (personal communication). The CFS/ME Working Group Report[11] identified three therapeutic strategies as potentially beneficial: cognitive behavioural therapy (CBT), graded exercise therapy (GET), and pacing. The evidence for CBT and GET comes from randomised controlled trials (RCTs) whilst that for pacing comes from patient reports and clinical experience. The report called for more research, particularly into pacing.

The variable course of CFS/ME suggests that any investigation of treatment or management of the condition should include an untreated control group.[17] The subjective nature of many of the *outcomes*

used suggests a high risk of measurement bias, and good quality studies will have taken measures to avoid such bias by adopting practices such as blinding. It has been suggested that within CFS/ME subgroups may exist and that the illness takes a different course in those with CFS/ME of sudden onset than in those whose illness developed gradually, in children than in adults, and in those with certain 'bio-markers'. Other sub-groups may include those with severe and seemingly unremitting disease and disability.

2. OBJECTIVES

The aim of this systematic review is to assess the effectiveness of all available interventions which have been evaluated for use in the treatment or management of adults and children with CFS/ME.

In particular, the following questions were addressed:

- What evidence is there for the effectiveness of available interventions for CFS/ME among adults and children?
- What is the evidence that sub-groups of patients respond differently to treatments?
- What is the evidence for additive or combined effects of treatments where more than one therapy is used?

3. METHODS

3.1 Advisory panel

A panel of relevant experts, including topic experts, practitioners and potential users of the review were identified and recruited. They were asked for input at various stages of the review process and in particular for comment on the review protocol, and draft report. (See Appendix G for a list of the panel members).

3.2 Search strategy

Individual search strategies were developed for each electronic database searched. The following databases were searched: MEDLINE (1966 to July 2001), EMBASE (1980 to July 2001), PsycINFO (1887 to August 2001), ERIC (1966 to August 2001), CCCTR (2002 issue 2), Social Science Citation index (1981-August 2001), Science Citation Index (1981-August 2001), Index to Scientific and Technical Proceedings (1982-1999), PASCAL (1973 – August 2001), MANTIS (1880 – April 2000), JICST (1985 – July 2001), Conference Proceedings Index (1973 – July 2001), AMED (1984 – September 2001), NTIS (1964 – August 2001), Inside Conferences (1993 - August 2001), Life Sciences (1982 - May 2001), CAB Health (1983 - July 2001), BIOSIS (1969 - August 2001), TGG Health & Wellness (1976 - June 2000). Search terms included the following: chronic fatigue syndrome, myalgic, encephalomyelitis, akureyri disease, chronic epstein barr virus, cfids, chronic fatigue and immune dysfunction syndrome, chronic mononucleosis, effort syndrome, iceland* disease, low natural killer cell syndrome, neuromyasthenia, post viral fatigue syndrome, post-infectious fatigue, chronic postviral fatigue syndrome, raggedy ann* syndrome, royal free disease/epidemic/hospital disease, tapanui disease*, yuppie flu, yuppy flu and fibromyalgia (see Appendix A for an example of the search strategy used in Medline (Silverplatter)). Update searches of all the above databases, from the date on which they had previously been searched, were carried out in Feburary 2002.

The bibliographies of retrieved articles were scanned for any additional references. In addition, web searching was carried out using Copernic 2000, which is a meta-search engine used to scan a number of individual search engines all at the same time (e.g. Lycos, alta vista, etc). A dedicated web-site was set up for the review (http://www.york.ac.uk/inst/crd/cfs.htm) through which additional references could be submitted. The advisory panel was contacted and asked to submit any references which they thought might meet inclusion criteria for the review.

3.3 Inclusion criteria

All papers which met the inclusion criteria (see below) were included in the review, regardless of language of publication.

The following inclusion criteria were used to select studies:

Interventions

Any intervention used in the treatment or management of CFS/ME, compared to placebo, inactive control, or no treatment.

Participants

Adults and children with a diagnosis of CFS/ME based on any criteria. The symptoms of CFS/ME show considerable overlap with those of clinical depression, fibromyalgia, neuromuscular diseases and chronic pain. For inclusion in this review however, individuals must have a diagnosis of CFS/ME, or other syndrome which has similar criteria for diagnosis such as chronic fatigue immune deficiency syndrome or chronic epstein barr virus infection.

Outcomes

All outcomes reported in the studies were considered relevant to reflect the wide range of medical and psychosocial outcomes used as markers of treatment response (*e.g.* fatigue, pain, mood, physical functioning, quality of life, acceptability of the treatment, possible side effects, employment/return to employment, consumption of health service resources). This was in response to the recommendations made by several members of the expert panel.

Type of studies

Study designs eligible for inclusion were randomised controlled trials (RCTs), controlled trials or systematic reviews of RCTs or controlled trials.

Two reviewers independently assessed all titles and abstracts identified from the literature searches for relevance. All retrieved studies were independently assessed by two reviewers for possible inclusion. If the two reviewers could not agree, a third reviewer was consulted to resolve the differences.

3.4 Validity assessment

Validity assessment was carried out, using an existing validity assessment tool,[18] by one reviewer and checked by a second, using the following predefined criteria:

Method of randomisation (randomised studies only)
Aadequate concealment of allocation (randomised studies only)
Baseline comparability of groups
Degree of adjustment for confounding factors (controlled studies only)
Appropriateness of the control group i.e. whether the control group was taken from the same population as the intervention group (controlled studies only)
Blinding of participants and/ or investigators
Completeness of follow-up
Handling of drop-outs and missing data (intention-to-treat analysis)
Objectivity and blinding of outcome assessment
Appropriateness of the statistical analysis
Whether the groups were treated identically other than the named interventions
Sample size/ statistical power

Discrepancies were resolved by discussion or, when agreement could not be reached, by consultation with a third reviewer.

3.5 Data extraction

Study details were extracted by one reviewer and checked by a second reviewer onto a Microsoft Access database. Discrepancies were resolved by referral to the original studies. If necessary arbitration was by a third reviewer. Data from systematic reviews were extracted onto the form used to abstract systematic reviews included on the DARE database (http://agatha.york.ac.uk/darehp.htm).

Data extracted included:
Author, year
Study design
Intervention details (including drug dose or intensity of intervention, frequency, duration, content, information about person/s delivering the intervention including any relevant training they were given, setting, whether group or individual intervention, co-interventions, details of control and study duration and length of follow-up).
Stated purpose of intervention
Duration of follow-up
Number of participants in each intervention arm
Participant details:
Diagnostic criteria and any additional details
Inclusion criteria
Baseline functioning
Whether the study was conducted with adults or children
Sub-groups investigated
Concurrent diagnoses
Duration of illness
Total number of participants
Age
Sex
Other reported details
Drop-outs in each group including reasons for withdrawal
Results, including the outcome measures used, the baseline and final levels of each outcome in control and treatment groups, if stated, adverse effects, and any other details of results, such as whether significant differences were detected between the groups (including p-values if stated).
Additional comments

3.6 Data synthesis

A narrative synthesis was undertaken due to the significant heterogeneity between studies in interventions and outcomes. Results of RCTs and controlled trials were reported separately, and a distinction was made between those studies which focused on CFS and those which focused specifically on ME or other named syndromes. All of the outcomes reported in the included studies were described. Outcomes were grouped together (in tables) into the following five categories to make results easier to interpret:

- Resource use (e.g health service resource use)
- Physical (e.g fatigue, disability, exercise, activity)
- Physiological (e.g. immune outcomes, laboratory measurements)
- Psychological (e.g anxiety, cognitive function, depression, mood)
- General health and quality of life (e.g. employment, quality of life, symptom measures)

A distinction was made between clinical (resource use, physical, psychological, general health and quality of life) and physiological outcome measures. Physiological measures included measures of fatty acid concentration, immune outcomes, and laboratory measures (for a full list of physiological outcome measures reported by the included studies see section 4.3.4). The distinction was made because physiological changes may occur as a result of the intervention, e.g. changes in immunological cell counts, but have no clinical benefit to the patient.

The interventions were categorised into the following seven groupings:

- Behavioural
- Immunological
- Antiviral
- Pharmacological
- Supplements
- Complementary/Alternative Medicine
- Other

The rationale for evaluating each intervention was briefly described, and study results in the text were reported as individual studies grouped by intervention category.

A further table was produced summarising the results for each intervention type by each outcome group. To provide an overall estimate of whether each study found a positive, negative or no effect of the intervention each study was classified according to two separate methods: whether the study showed **any effect** of treatment, and whether it showed **any overall effect.** Studies were judged to show some effect of treatment if any of the outcomes measured showed a statistically significant difference between the intervention and control groups. Studies were classified as having an overall effect (positive or negative) if they showed a statistically significant effect for more than one clinical (i.e. not a physiological) outcome or, if only one clinical outcome was measured, it was found to show a statistically significant effect. The effect was considered to be positive if the intervention group showed a greater improvement than the control group, and negative if the control group showed the greater improvement. Where no statistically significant differences occurred, this was classified as showing no effect. Where studies presented their findings as within group differences rather than as differences between the intervention and control group, these results are presented but are not included in the synthesis of results and should be treated with caution.

Results from trials which included subgroups, or which assessed potential additive effects of interventions, were presented in a separate section in the text, but not presented separately in associated tables.

The inclusion criteria and baseline functioning of participants in each study were used as an indicator of the severity of illness. These were discussed narratively as insufficient data were available for further analysis. Bar charts were produced to investigate any association between duration of treatment/follow-up and diagnostic criteria, and the effect (positive, negative or no effect) of the intervention on outcomes, as classified above (any effect and overall effect). Study drop-outs, and reasons for withdrawing from studies were discussed separately for each intervention type. Pie charts showing the distribution of outcomes, interventions and diagnostic criteria were produced.

The validity of the included studies was assessed as described in section 3.4. For each criterion studies scored 0 for ‘not stated’ or ‘poor’, 1 for ‘adequate’ and 2 for ‘good’ (or, alternatively, 0 for ‘not stated’, 0 for ‘no’ and 1 for ‘yes’, for the measures of participant and investigator blinding). The

maximum potential score for each study was 20 points (RCTs were not assessed for 'controlling for confounding' or 'appropriateness of control group', and controlled studies were not assessed for 'method of randomisation' or 'concealment of treatment allocation'). The validity score was included in all results tables to allow the results to be considered alongside the quality of the study. The proportion of possible points scored for each validity criterion was calculated by adding the points across each variable (e.g. total points scored by all studies for method of randomisation), dividing by the total possible number of points (e.g. for randomisation – number of studies multiplied by 2 – total number of points available for that category), and multiplying by 100 to make a percentage. A bar chart was produced showing the distribution of scores for each validity criterion, separately for RCTs and controlled trials. This allows a visual assessment of the validity criteria which were most frequently fulfilled and which were not. The association of validity score with study outcome was assessed. RCTs were divided according to study outcome as described above (any effect and overall effect). Study validity score was plotted against the proportion of RCTs which scored at least that score. This was not done for controlled trials due to the small number included.

3.7 Publication bias

Every effort was made to negate the effects of publication bias (the tendency for studies which show certain results, usually beneficial effects, to be published). Unpublished studies were searched for. Duplicate publications were actively screened for and, where found, the latest or most complete report was included. The review reports all duplicate publications found to enable future reviewers in this area to spot duplicate reports easily (see Appendix F). Insufficient data were available to assess publication bias using standard methods (e.g. funnel plots), and it was therefore discussed narratively.

4. RESULTS

4.1 General results

A total of 368 studies meeting relevance criteria were identified through the literature searches. Of these 46 met the inclusion criteria: 38 RCTs and eight controlled trials, eleven of the RCTs used a cross-over design, although for one of these results are only available for the first section of the study and so this study is treated as a non-crossover RCT.[19] Of these studies, 36 included participants diagnosed with CFS only, one included patients who fulfilled criteria for both CFS and ME,[20] one included patients diagnosed with ME,[21] and one included participants diagnosed with fibromyalgia, all but three of whom also had CFS.[22] The remaining seven included participants with syndromes that had similar symptoms to CFS and ME, including post-infectious fatigue syndrome. A systematic review of Cognitive Behavioural Therapy (CBT)[23] also met the inclusion criteria. The trials included in this review[24-26] are included individually in the results below. The results of the systematic review are presented in Appendix C and are not discussed further.

Within the 46 included studies, a total of 32 different interventions have been evaluated using 38 different outcomes, with a total of 132 outcomes evaluated. In addition to the differences in interventions and in outcomes there was also heterogeneity between studies in terms of quality. Formal pooling of results and investigation of heterogeneity was not possible and a narrative synthesis is presented below.

This review had 3 objectives:

1. What evidence is there for the effectiveness of available interventions for CFS/ME among adults and children?
2. What is the evidence that sub-groups of patients respond differently to treatments?
3. What is the evidence for additive or combined effects of treatments where more than one therapy is used?

Objective 1 is addressed in the results section below, objective 2 is discussed in section 4.4.9 and objective 3 in section 4.4.8.

4.2 Study participants

Of the 46 included primary studies, 34 were carried out with adults, one with children, two with both adults and children and the remaining nine did not give this information. Nineteen studies gave the age range of participants which ranged from 11 to 87 years. In 32 studies the participants' mean age was reported and was from 15.3 to 47 years. Four studies did not state the age of the participants included in the review. All except one of the studies that reported on the sex of study participants (n=33) included both men and women, and one study was conducted with women only.[27] Overall, the percentage of women was generally higher than men with a range of 19 to 100% and a mean of 71%. The number of participants included in each trial ranged from 11 to 326, with a total of 2943 participants included in the 46 trials combined.

Thirty-seven of the 46 studies included some information about duration of illness. In 22 studies the range was presented, which was from 27 days to 34 years. Thirty four studies gave the mean duration of illness which was from 27 months to 13 years. Seven studies gave information about concurrent diagnoses. One study reported that nine participants had a history of psychiatric illness,[28] in another 75% of participants had major depression,[26] in another 64%[29] had a current psychiatric condition, and in a fourth, all participants had neurally mediated hypotension.[30] The fifth study stated that of 60 participants five had a diagnosis of dysthymia, nine had major depression, three had anxiety disorders and six had both depression and anxiety disorders.[24] In the sixth study, 23 of 52 participants had illnesses which included asthma, epilepsy, arthritis, ulcers, diverticulitis, hiatus hernia, sinusitis and kidney infections. The seventh study included participants who met diagnostic criteria for fibromyalgia; all but three patients also met criteria for CFS and so this study has been included. Fourteen studies reported that illness onset followed an 'acute infectious disease-like episode' in the majority of participants. One study stated explicitly that participants were permitted to take other medication, including anti-depressants, in addition to those medications under investigation in the trial.[31] It did not state what medications were taken concomitantly and whether there were differences in medication use between the two groups, thus other medication use could have confounded the results of this study. One study stated that all participants were prescribed certain nutritional supplements and medications to aid sleep, where necessary.[22] Three studies denied participants all

medication other than those under investigation.[28,32,33] In 15 other trials specific medications were permitted or excluded while other studies do not report on concomitant medication usage.

Details of participants' baseline functioning were reported in 30 trials, although the amount of information provided varied widely and so it is difficult to draw any conclusions regarding overall baseline functioning across studies. None of the studies stated whether the participants were in relapse or remission. Inclusion criteria applied by several of the studies limited the participants to those able to travel to the study centre for treatment (n=8), those who scored above or between certain levels on some measure of CFS symptoms (n=4), and those who did not have psychiatric illnesses (n=15), such as depression.

4.3 Outcomes reported in included studies

A wide variety of outcomes were assessed in the 46 studies included in the review. Even where the same outcome was used to assess the same intervention, almost invariably a different scale or type of measurement was used, making it difficult to synthesise results across studies. Some studies assessed many outcomes making it possible that any statistically significant differences between groups were due to chance, rather than to the effectiveness of the intervention over control conditions.

Some results were presented as actual values, some as percentages and some as changes from pre-treatment status. Four studies presented the results of statistical tests not as between-group differences, as appropriate, but as within-group differences i.e. difference in before- and after-treatment values.[29,34-36] These results are presented but are not included in the synthesis of results and should be treated with caution.

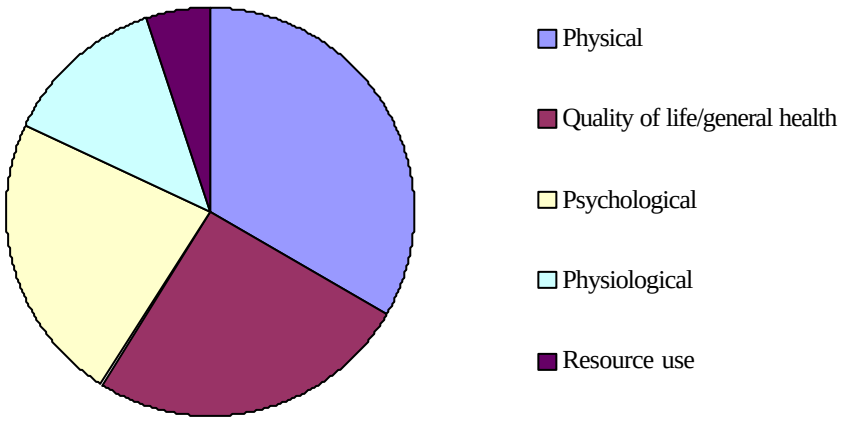
Members of the expert panel were consulted about the outcomes they considered to be the most important. It was decided that all outcomes were equally important and thus the results of all outcomes have been reported. The outcomes presented were grouped into five broad categories, which are outlined in table 4.1.

Table 4.1 Outcome categories

Outcome (number of outcomes)	Number of different measurements used
Psychological (9)	25
Physical (13)	52
Quality of life/ General health (10)	43
Physiological (5)	10
Resource use (1)	2

Figure 4.1 shows the relative distribution of the outcomes used grouped into the five categories outlined above.

Figure 4.1 Distribution of outcomes



4.3.1 Psychological outcomes

a. Anxiety

i. Beck anxiety inventory (n=1).
ii. Hospital anxiety and depression score (n=2), range 0-21.

b. Cognitive function

i. Memory, measured on a visual analogue scale (n=1).
ii. Broadbent's cognitive function questionnaire (n=1).
iii. Perceived cognitive deficit using SCL-90-R questionnaire (n=1).
iv. Speed of cognitive function assessed using Hick paradigm reaction time (n=1).
v. Fatigue related cognition, 14 item self-report scale developed by authors (n=1).

c. Depression

i. Beck Depression Inventory (BDI) self-questionnaire 21 items each scoring 0-3 in severity (n=4).
ii. SCL-90-R, with anxiety (n=1).
iii. Zung's self-rating depression scale – 20 items measuring both somatic and affective components on a 4 point scale (1=normal, 4=maximum severity) (n=2).
iv. Hamilton Depression Rating Scale (HDR-S) administered by psychiatrists (n=2).
Centers for Epidemiological Studies of Depression (CES-D) 20 item self-report scale pencil and paper test for depression (n=5).
v. Hospital anxiety and depression scales (HAD) (n=3), measured from 0-21, >10=clinical depression.

d. Mood

i. Profile of Mood States questionnaire (POMS) self-assessment – 6 variables assessed including fatigue, vigour, depression, anger, anxiety and confusion (n=8).
ii. Positive and negative affect scale (n=1).
iii. Positive thinking measured using Life Orientation Test (n=1)

e. Psychological assessment

i. Mental health subscale of Karnofsky score (n=1).
ii. General Health Questionnaire (GHQ) (n=1).
iii. Comprehensive psychopathological rating scale (CPRS), 15 reported and observed items on 7 scale steps from 0 (normal) to 6 (maximum severity) (n=1).
iv. Psychological distress measured on brief symptom inventory (n=1)
v. Psychological well-being measured on SCL90 (n=1)

f. Illness beliefs

i. Strength of illness beliefs (n=1)
ii. Mishel uncertainty in illness scale (n=1)

g. Stress

i. Perceived stress scale (short version) (n=1)

h. Coping strategies

i. COPE scales (n=1)

i. Social support

i. Interpersonal support evaluation short form (n=1)

4.3.2 Physical outcomes

a. Activity

i. Karnofsky functional status questionnaire (n=2), daily activity and performance scores. Scored out of 100.
ii. Baecke's measure of activity (n=1), divided into: work, sport and leisure activity.
iii. ECOG scale (n=1), scored 0-IV:
0: able to carry out normal activity without restrictions
I: restricted in physically strenuous 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.
iv. Barthel's activities of daily living index (n=1)

v. Activity scale developed by authors (n=1): 10 point scale.
vi. Percentage interference with activities (n=1)
vii. Duke activity status index (n=1)

b. Disability

i. Work and social adjustment scale (WSAS) (n=1)
ii. Medical outcomes short form 36 (n=1) – physical function and role limitation subscales.

c. Exercise and work

i. Treadmill test (n=4), duration of exercise at 1mph (minutes) to exhaustion.

d. Fatigue

i. Fatigue severity scale (n=7)
ii. Chalder's fatigue scale (n=1) – self-rated questionnaire, 14 item scale. Change in score and % below 'case level' presented.
iii. MFI score (n=1), divided into general fatigue, physical fatigue, activity, motivation, and psychological fatigue.
iv. Visual analogue scales (n=1), scored out of 10
v. Profile of fatigue symptom scores (fatigue and somatic symptoms) (n=1).
vi. Profile of fatigue related states (n=1)
vii. Degree of tiredness on first arising, severity of tiredness during day, work output and general feeling of wellness etc (n=1).
viii. Self-administered fatigue score – scored according to Likert 0, 1, 2, 3 system to be sensitive to change (n=1), scored out of 11.
ix. Subjective fatigue score (n=1) – fatigue measured 4 times a day on 4 point scale (scored out of 4).
x. Fatigue scores on scale from 0-11, 11 is most severe (n=1)
xi. Fatigue problem rating (n=1)
xii. Wood mental fatigue index (n=1)
xiii. Profile of fatigue related symptoms (n=1)
xiv. CIS fatigue score (n=1)
xv. Fatigue self-rating scale (n=1)

e. Functional measure

i. Karnofsky performance score (n=5), scored out of 100.
ii. Functional status questionnaire (n=2), 9-11 items
iii. Medical outcome short form-36 (n=7), scored from 0 (worst) to 100 (best).
iv. Improved/not improved (n=1) – 25% improvement in mean functional score at 6 months
v. Functional score (n=1).
vi. Physical functioning scale of General Health Survey (n=1)
vii. Functional impairment scale (n=1)
viii. Sickness Impact profile (n=1)

f. Myalgia

i. Measured on 2 visual analogue scales (n=1).

g. *Pain*

i. Back pain questionnaire (n=1), no further details
ii. Momentarily perceived pain (n=1) – measured using visual analogue scale, varied from no pain to worst pain imaginable.
iii. Pain in last week (n=2) – measured using visual analogue scale, varied from no pain to worst pain imaginable.
iv. Pressure pain threshold (n=1) – measured using hand-held electronic pressure algometer.

h. Energy

i. Energy levels measured using Likert scale, scored 1-10 (n=1)

i. Bowel movements

i. Frequency, other (n=1)

j. Physical

i. Physical questionnaire devised by authors (n=1).
ii. Physical measures of weight, fat mass ***etc***. (n=1).

iii. Number of non-sedentary hours by standardised diary (n=1).
iv. Functional work capacity (ml of oxygen consumed) (n=1)
v. Physical symptom list (n=1)

k. Rest

i. Hours per day (n=1).
ii. Number of days per week in bed (n=1).

l. Sleep

i. Hours per day (n=1).
ii. Sleep disturbance, measured on 3 visual analogue scales (n=1).
iii. Morgan-Gledhill sleep questionnaire (n=1).
iv. Sleep disturbance measured on scale of Jenkins, range 0-20, 20 indicates maximum problems (n=1).

m. Dizziness

i. Measured using 2 visual analogue scales (n=1)

4.3.3 Quality of life and health status outcomes

a. Clinical assessment

i. Method not stated (n=1).
ii. Clinical global impression – improvement scale (CGI-I) some clinician rated and some self-rated (n=3).

b. Graphs

i. Daily graphs completed by each participant (n=1).

c. *Employment*

i. Either returned to work or work equivalent (eg. education retraining, job searching or other non-paid activity) or remained disabled (n=3).
ii. Work capacity/ satisfaction, measured on visual analogue scale (n=1).
iii. Improvement in work status (n=1).
iv. Work and social adjustment scale (n=1).
v. Proportion employed (n=1).
vi. Number of hours at work (n=1)

d. General health

i. Whether or not improvement had occurred (n=9).
ii. Nottingham health questionnaire (energy, pain, emotional reactions, sleep, social isolation, physical mobility) (n=2).
iii. Overall condition evaluated (whether felt worse, unchanged or better compared to baseline) made by doctor in consultation with participant (n=1).
iv. MOS short form scales: physical function, role/ occupation function, social function, pain, health perceptions, mental health (n=2).
v. Wellness score – single item global health score ranging from 0 (worst ever felt) to 100 (best ever felt), self-rated (n=3).
vi. General health questionnaire (GHQ), self-rated, 4 point scale (n=3).
vii. General health questionnaire (GHQ), developed for study based on 26 common CFS/ME symptoms (n=1).
viii. Personal well-being. Wellness scores self-assessment from 0 (dying) to 100 (being as well as could be imagined) (n=1).
ix. Global well-being measured using 10 item visual analogue scales from which a cumulative score was calculated (n=2).
x. Overall energy and activity level assessed using five item scale – self-rated (n=1).

e. Illness severity

i. Ferreri's score of incapacity (n=1).
ii. Illness severity scale (modification of Karnofsky, expanding areas of mild to moderate disability (n=2).

f. Quality of life

i. QOL visual analogue scale modified to include 10 aspects of physical or neuropsychological symptomatology typical of CFS/ME, self-rated (n=2).

ii. Scored 0 – 60 (60 = worst score) (n=1).
iii. Nottingham Health Profile (NHP) and specifically designed questionnaire for quality of life assessment in GH-deficient adults (QOL-AGHDA) (n=1).
iv. EuroQOL scale (n=1)

g. Recovery
i. Change in status (n=3)

h. Symptom measures
i. 16 question symptom severity checklist used scale from 0-4 (n=2).
iii. Self-assessment form – symptom checklist 90 or 90-R (n=2).
iv. Following symptoms scored from 0 to 3 (0=absent, 3=severe): fatigue, myalgia, dizziness, poor concentration and depression, symptom scores combined to give index of disease severity (n=1).
v. Symptom scoring system developed by authors 50 item questionnaire assessing symptoms of CFS/ME each scored on scale of 1 to 4, where 1 represented minimum severity and 4 maximum (n=1).
vi. Sickness impact profile (n=1).
vii. Various symptomatic and functional measures (n=1).
viii. Self-reported somatic symptoms (n=1).
ix. Self-assessment 4 point scale (none to severe) (n=1).
x. 10cm visual analogue scale with 0= no problem to 10 = worst it could be (n=1).
xi. Symptoms and disability assessed by physician (n=1).
xii. Symptoms measured using Likert scales from 1 to 10 (n=1).
xiii. Brief symptom inventory, measures symptoms on 53 item self-report scale (n=1)
xiv. End of trial self-assessment charts completed by each participant, categories: fatigue, disability, mood disturbance, myalgia, sleep disturbance (n=1).
xv. Course of symptoms over time (n=1)

i. Patient satisfaction
i. Patient satisfaction with treatment outcome (n=1).
ii. Patient assessment of usefulness of treatment (n=1).

j. Relapses
i. Number of relapses suffered (n=1).

4.3.4 Physiological outcomes

a. Fatty acid concentration
i. Measured in red cell membranes (n=1)

b. Immune outcomes
i. NK function, %NLP, CD4 count, CD8 count (n=1)
ii. CD4 lymphocyte, PHA and DTH response (n=1)
iii. CD4, CD8 cell counts, DTH skin response (n=2)
iv. IgG1 and IgG3 levels (n=1)

c. Laboratory measures
i. Blood levels of norepinephrine, epinephrine, dopamine and cortisol (n=1).
ii. Serum levels of IGF-1, thyrotrophin, free tri-iodothyronine, free thyroxine, prolactin, cortisol, FSH, LH, testosterone, sex-hormone-binding globulin, Lp(a), amino acids (n=1).
iii. Changes in magnesium concentration in plasma, whole blood and red blood cells (mmol/L) (n=1).

d. Temperature
i. Oral temperature, self-measured (n=1).

e. Measure of neurally medicated hypertension
i. Tilt test (n=1)

4.3.5 Resource use
i. Health service resource use (n=1)
ii. Medication use (n=1).

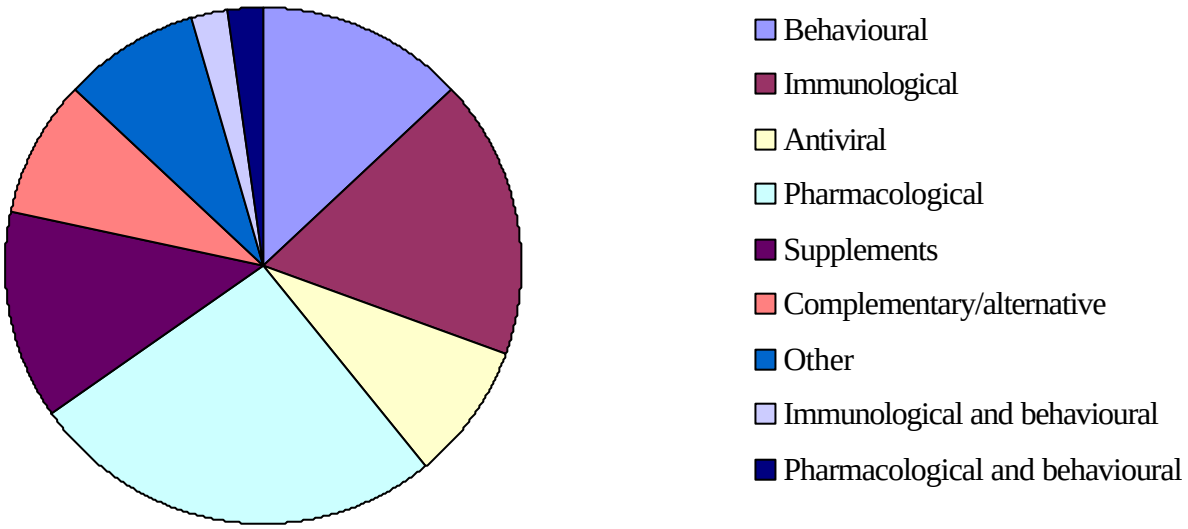
4.4 Interventions

Thirty one different interventions were investigated in the 46 included studies. Interventions were grouped into seven broad categories as outlined in table 4.2. The relative distribution of the interventions, grouped as outlined below, is shown in figure 4.2.

Table 4.2 Intervention categories

Intervention	Number of studies
Behavioural	6
Immunological	8
Antiviral	4
Pharmacological	12
Supplements	6
Complementary/alternative	4
Other	4
Immunological and behavioural	1
Pharmacological and behavioural	1

Figure 4.2 Distribution of interventions



Due to the heterogeneity between interventions and outcomes it was not possible to pool data from individual studies, instead studies are grouped together by intervention type. Within each broad intervention category a brief description of the various interventions, the rationale given for their use (taken mainly from the included studies), together with a summary of the effects are presented. Results of all studies grouped by intervention are presented in tables 4.3-4.9, and more detailed descriptions and results for each study are presented in Appendix B. All study results should be considered in relation to the methodological quality assessment.

4.4.1 Behavioural interventions

a. Cognitive Behavioural Therapy (CBT) - rationale

CBT is a collaborative approach which aims to reduce levels of disability and symptoms associated with CFS/ME. Treatment components which should be tailored may include:

- Record keeping in order to monitor the condition and understand it better
- Gradually resuming activitites which were previously too difficult
- Establishing a sleep routine
- Treating any associated anxiety or depression
- Making lifestyle changes which may have contributed to the development of the condition
- Monitoring throughts and changing any unhelpful ideas which may be hampering progress with treatment.[37]

b. Graded exercise therapy (GET) - rationale

GET is a form of structured and supervised activity management that aims for gradual but progessive increases in aerobic activities such as walking or swimming.[11] The initial programme is deigned in collaboration with the patient, based on current capability. The duration/intensity of exercise is gradually increased under the supervision of a trained professional. Small, usually weekly incremental increases are jointly agreed, depending on progress. The aim of GET is to increase fitness, strength, stamina and the gradual uptake of previously avoided activites.

Main results of behavioural intervention trials (Table 4.3)

Recommendations about the use of behavioural interventions such as CBT can be misinterpreted when the perceived suggestion is that CFS/ME is a psychological condition. However, conclusions about the cause of the condition should not be drawn from the fact that certain therapies may be effective. Behavioural interventions, and CBT in particular, have been used effectively in other physical illnesses, such as heart disease[38] and chronic low back pain.[39]

Four RCTs evaluated weekly or biweekly sessions of CBT. A controlled trial of 'modified CBT' used a different form of treatment without graded activity, which is normally considered an integral part of CBT. 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.[29] All studies included people with CFS. CBT was compared to routine medical care in one RCT,[25] to relaxation in a second RCT,[24] to natural course (control) in a third RCT,[40] and to guided support in the controlled trial of 'modified CBT'.[29] A fourth RCT compared four groups: CBT plus placebo injections; CBT plus leukocyte extract (a fraction of blood containing white blood cells); a control clinic plus leukocyte extract; and a control clinic plus placebo injections.[26]

Participants who received combined leukocyte extract and CBT showed a significantly greater improvement in general health than the other three groups. No significant differences were found between groups (including CBT alone) for the other outcomes investigated.[26] The controlled trial of modified CBT reported within group rather than between group differences.[29] This study scored very poorly on the validity assessment, scoring only 1 out of a possible 20.

The remaining three RCTs reported an overall beneficial effect of CBT when compared to control groups.[24,25,40] All three RCTs found a significant short-term improvement in physical functioning, general health and fatigue. Neither of the two studies that assessed depression found any significant differences between groups.[24,25] One of these RCTs also followed patients for five years after the intervention.[24,41] At five year follow-up global improvement was significantly greater in the intervention group, as was the mean number of hours worked per week and the proportion of participants who completely recovered (the definition of 'completely recovered' was based on fatigue and physical functioning scores as well as UK (Oxford) CFS criteria).[41] However, no significant differences were reported between the groups for physical functioning, fatigue, general health, symptoms, relapses or the proportion of participants that no longer met the UK (Oxford) criteria for CFS.

Two RCTs of CBT in primary care are reported to be ongoing.[42,43]

The effects of GET were investigated in three fairly large RCTs of patients with CFS, two of which found overall beneficial effects.[44,45] One found some beneficial effects.[46] Significant improvements in measures of physical function were found in all three RCTs.[44-46] Two also showed a significant improvement in general health and fatigue[44,45] and one in physiological measurements and symptoms.[44] When exercise was combined with fluoxetine there was no additional effect.[46] One RCT assessed different interventions to encourage graded exercise and found significant benefits of GET compared to standardised medical care for all outcomes investigated. However, there were no significant differences between the different intervention groups for any of the outcomes investigated.[45]

In one RCT two participants dropped out of the CBT group as they felt a deterioration in their symptoms was due to the intervention.[25] A second reported drop-out rates of around 20 - 35% in all three intervention groups.[40] 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. In one of the RCTs evaluating GET, one participant dropped out from each group due to worsening of symptoms.[44] 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.[46]

Table 4.3 Results of behavioural intervention trials

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	Deale (1997)[24] 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[41] 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)[26] n=90		*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	13
	Prins (2001)[40] 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
Modified CBT	Friedberg (1994)[29] n=44		*Fatigue:* Significant reduction in treatment group (p<0.03) but not in control group – within group differences	*Depression:* no significant differences in either treatment group – within group differences		*Stress symptom score:* no significant differences in either treatment group – within group differences	2 patients who did not want CBT refused to participate in control group	1 (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
GET	Fulcher (1997)[44] n=66		***Fatigue & function:*** **Chalder fatigue score (p=0.004), total fatigue score (p=0.04), physical fatigue score (p=0.006), physical function score (p=0.01)were significantly better in treatment group** *Mental fatigue and sleep*: no significant difference between groups	*Depression and anxiety:* no significant difference between groups	***Physiological:*** **treatment group showed significant increase in peak oxygen consumption (p=0.03) and maximum ventilation** (p=0.04) but not other measures compared to controls (p-value not reported)	***General health:*** **greater improvement in treatment group (p=0.04)** ***Symptom score:*** **symptom score (p=0.05) and general health score (p=0.03) significantly greater in treatment group**	7 participants dropped out, 4 in exercise group and 3 in control, 1 from each group dropped out due to worsening of symptoms	17
	Powell (2000)[45] n=148		***Physical functioning, fatigue:*** **greater improvement in all intervention groups than control (p<0.001),** no significant difference between intervention groups ***Sleep problems:*** **greater improvement in all intervention groups than control (no measure of significance),** no significant difference between intervention groups	***Depression and anxiety:*** **greater improvement in all intervention groups than control (no measure of significance),** no significant difference between intervention groups		*Improvement, and patients report of improvement:* **greater improvement in all intervention groups than control (p<0.01),** no significant difference between 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
	Wearden (1998)[46] 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 dropped out 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

Results in **bold type** indicate significant differences between intervention and control groups

4.4.2 Immunological

Immune therapies which aim to correct immune dysfunction have been proposed for CFS on the assumption that it is a disease of the immune system.[47] Although the cause of CFS is unknown it has been suggested that a persistent viral infection may be of aetiologic importance and the finding of a high number of immunologic abnormalities in participants with CFS have suggested that an immunoregulatory defect may be involved.[27,48-50]

a. Immunoglobulin G - rationale

Immunomodulatory therapy with high dose intravenous immunoglobulin G (an antibody fraction of blood) has been suggested to be of use in a number of diseases featuring disordered immunoregulation.[51] It has been argued that intravenous immunoglobulin G could provide potential benefit to participants with CFS in two possible ways: either by providing neutralising antibodies against persistent viral antigens or by analogy with its efficacy in autoimmune disorders by correcting immunoregulatory disturbances.[48,52] Immunoglobulins are blood products and there are known risks associated with the use of these, such as the possible transfer of infectious diseases.

b. RNA drug (ampligen) - rationale

Bistranded RNAs are bifunctional molecules with both antiviral and immunomodulatory activities. Poly(I).poly(C12U) (ampligen), a specifically configured RNA drug has generally been well tolerated clinically and thus is thought to be safe to administer on a long-term basis.[53]

c. Leukocyte extract- rationale

Dialysable leukocyte extract is a component of leukocytes that is capable of transferring delayed-type hypersensitivity in humans. This agent has been used therapeutically in participants with disorders in which a defect in cell-mediated immunity has been established, such as leprosy and chronic mucocutaneous candidiasis. In contrast to intravenous immunoglobulin, dialysable leukocyte extract is relatively inexpensive, can be administered by intramusuclar injection and is reported to have minimal adverse effects.[26]

d. Staphylococcus toxoid vaccine - rationale

Staphylococcus toxoid vaccine may have the potential to stimulate the immune system.[27]

e. Antihistamine (Oral terfenadine) - rationale

An association between allergy and CFS has been suggested, and there are anecdotal reports of the symptoms of CFS improving in participants using antihistamine to treat their concomitant allergies.[50] Terfenadine was selected as the antihistamine of choice because of its reported absence of central nervous system side effects.

Main results of immunological treatment trials (Table 4.4)

Five RCTs investigated the effects of immunoglobulin G, four in people diagnosed with CFS and one in people diagnosed with chronic mononucleosis syndrome.[54] Four found some positive effect, two of which found an overall positive effect, and the fifth found no effect of treatment. One RCT found significantly greater improvements in the intervention group on symptom scores and functional capacity but not in depression, immune outcomes or quality of life.[51] A second smaller RCT found significantly improved immune measurements (physiological outcome) but not functional or symptom measures.[48] A larger RCT reported significantly improved functional capacity, which was the only outcome investigated.[55] A fourth RCT, which was the largest of the immunoglobulin G trials, found no significant improvement in any of the outcomes investigated (functional status, mood, immune outcomes and quality of life).[52] The fifth small RCT was found to significantly improve general health (the only outcome investigated).[54]

The effects of ampligen were investigated in one relatively large (n=92) RCT, which reported significant improvements in functional ability, activity, exercise, cognitive function and work measures but not in depression scores.[53] In the same RCT, elective use of other medications by participants increased significantly in the placebo group compared to the intervention group. One RCT assessed the combined effect of leukocyte extract and CBT using a factorial design.[26] 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. A third RCT evaluated the antihistamine terfenadine and found no significant effects of the intervention compared to control.[50]The effects of vaccination with staphylococcus toxoid were investigated in one small controlled trial of patients with CFS. No significant differences were reported in depression, pain or psychological outcomes between the

intervention and control group. However, a significantly greater improvement in the clinical global impression in the treatment group was found.[27]

Some severe adverse effects were noted in participants in the immunological intervention groups. Two people withdrew from immunoglobulin G treatment due to severe constitutional symptom reactions.[52] One recipient of immunoglobulin G therapy also withdrew due to mild but transient liver failure[51] and phlebitis has also been noted with immunoglobulin G infusions.[51] 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.

4.4.3 Anti-viral

a. Interferon - rationale

Alpha interferon has potent immunomodulatory and antiviral effects and has been used in the treatment of several tumour and viral infections, including hepatitis B and C.[36,49]

b. Antiviral (aciclovir and ganciclovir) - rationale

Aciclovir is reported to inhibit the replication of Epstein-Barr virus in vitro and in vivo. As there is a reported link between Epstein-Barr virus infection and CFS, it was thought possible that aciclovir or ganciclovir may be effective in the treatment of CFS, where prior Epstein Barr virus or human cytomegalovirus infection has been established.[56]

Main results of antiviral treatment trials (Table 4.5)

Two RCTs evaluated interferon, one of which found an overall beneficial effect, the other reported only within group differences rather than between group differences and so no conclusions can be drawn from this study.[36] The RCT which reported an overall beneficial effect was very small and found that treatment led to significantly increased physical activity and recovery which remained after 8 months follow-up.[49]

The effect of aciclovir was investigated in one small RCT in those who fulfilled criteria for CFS and additionally had prior infection with Epstein Barr virus confirmed.[56] 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 second very small poor quality RCT of only 11 participants investigated the effects of ganciclovir. There was a slight improvement in energy index and symptom scores for the treatment group compared to the control group but the statistical significance of these differences was not reported.[19]

Some severe adverse effects were noted in participants in these trials. Three people had to withdraw from aciclovir treatment due to reversible renal failure.[56] Two participants who were undergoing right ventricular endomyocardial biopsies experienced serious pericardial bleeding in the study of ganciclovir and so the study was ended prematurely.[19]

Table 4.4 Results of immunological treatment trials

Intervention		Author (year), number of participants	Results						
			Resource use	Physical	Psychological	Physiological	Quality of life and general health	Drop-outs/adverse effects	Validity score
Immunmodulators	Immuno-globulin G	DuBois (1986)[54] n=19					***General health*: greater improvement in treatment group compared to control (p<0.001)**	No participants dropped out due to adverse effects	11
	Immuno-globulin G	Lloyd (1990)[51] 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
	Immuno-globulin G	Peterson (1990)[48] 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. (No p-values were reported)**	*Symptom measure*: no significant differences between groups	2 participants dropped out due to adverse effects, 1 from each treatment group	15
	Immuno-globulin G	Rowe (1997)[55] 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
	Immuno-globulin G	Vollmer Conna (1997)[52] 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
	Leukocyte extract	Lloyd (1993)[26] n=90		*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 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)[53] 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
Antihistamine	Terfenadine	Steinberg (1996)[50] 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
Vaccine	Staphylococcus toxoid	Andersson (1998)[27] 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)

Results in **bold type** indicate significant differences between intervention and control groups

Table 4.5 Results of antiviral treatment trials

Intervention	Author (year), number of participants	Results						
		Resource use	Physical	Psychological	Physiological	Quality of life and general health	Drop-outs/adverse effects	Validity score
Aciclovir	Straus (1988)[56] 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 aciclovir infusions and were withdrawn from the study	15
Ganciclovir	Lerner (2001)[19] n=11					***Symptoms and energy:* slightly greater improvement in treatment compared to control, significance not reported**	2 participants developed serious pericardial bleeding whilst undergoing right ventricular endomyocardial biopsies, the study was ended prematurely	4
Interferon	Brook (1993)[49] 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 (p<0.05)**				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)[36] n=30				*Immune outcomes*: NK function increased significantly (p<0.05) in treatment group but not in control.- within group differences No differences in %NLP, CD4 or CD8 counts	*QOL*: no significant differences in either treatment group – within group differences	4 participants on interferon treatment withdrew: 2 had neutropenia, one palpitations and one worsened fatigue	11

Results in **bold type** indicate significant differences between intervention and control groups

4.4.4 Pharmacological

a. Antidepressants (non monoamine oxidase inhibitors)- rationale

Participants with CFS may be comorbidly depressed and so part of the rationale for the use of anti-depressants is to treat the depression associated with CFS.[47] Antidepressants have also been suggested to be of benefit in treating some of the other common symptoms of CFS such as pain and sleep disorders.[47] A third possible reason for treatment of CFS with antidepressants relate to their action on central monoaminergic transmission suggesting that they might have a direct effect on the core features of CFS.[47] There is some support for the notion that abnormalities of central neurotransmitters such as serotonin are seen in CFS.[47,57]

The reason for the choice of specific anti-depressant was stated in one trial.[58] CFS patients may tolerate first generation tricyclic antidepressants poorly because side effects include sedation and exacerbation of fatigue, thus fluoxetine was selected as it has fewer sedative and autonomic nervous system side-effects. The rationale for the choice of treatment in one of the studies differed from that of the others.[59] The authors state that the symptoms of CFS are very similar to the symptoms produced by treatment with reserpine. The authors suggested that CFS was the clinical manifestation of a state of reduced central sympathetic drive via increased firing of the locus coeruleus, a state also produced by reserpine. Phenelzine decreases locus coeruleus firing and increases central sympathetic neurotransmission to sensitised receptors. Thus, if the authors' hypothesis is correct, treatment with phenelzine at doses well below those used to treat depression should relieve the symptoms of CFS.

b. Monoamine oxidase inhibitors - rationale

Selegiline is reported to have an experimental ability to improve cognitive performance in Alzheimer's patients and to retard age-related memory decline in animals. It was suggested that selegiline may be effective in treating the mild cognitive impairment that exists in some patients with CFS.[60] Another study used a monoamine oxidase inhibitor as the authors stated that patients with CFS closely resemble patients with atypical depression, a syndrome characterised by a preferential response to monoamine oxidase inhibitors.[61]

c. Corticosteroids - rationale

It has been suggested that CFS may be associated with a down-regulated hypothalmic-pituitary-adrenocortical axis.[32,47] Given the overlap between the symptoms of Addison's disease and CFS it has been postulated that hypocortisolism may be important in the mediation of central fatigue.[28] There have been suggestions that the underactivity of the HPA axis could result from factors that are secondary to the primary aetiology of CFS, such as sleep disturbance. One possibility is that low circulating cortisol could act as a biological factor that contributes to fatigue chronicity and interacts adversely with perpetuating cognitive and behavioural processes. Thus a rise in cortisol concentrations, by treatment with hydrocortisone or fludrocortisone, might improve fatigue in patients with CFS.[32,62]

d. Anticholinergic - rationale

It has been suggested that a dysfunction of components of the cholinergic systems is at the heart of the pathogenesis of chronic post infectious fatigue (CPIF). Sulbutiamine crosses the blood-brain barrier and plays a part in the regulation of the cholinergic, serotonin and noradrenergic systems and enhances the metabolism of cerebral glycogen.[35]

e. Hormones - rationale

It has been suggested that patients with CFS and adults with growth hormone deficiency show clinical similarities and there is some evidence of attenuated growth hormone responses in patients with CFS.[34]

f. Oral NADH - rationale

It has been suggested that there may be a dysfunction of the neurocrine-endocrinologic-immunologic (NEI) network in CFS. NADH, the co-enzyme, is known to trigger energy production through ATP generation. It has been suggested that the coenzyme may replenish depleted cellular stores of ATP, thus improving fatigue and cognitive dysfunction.[31]

Main results of pharmacological treatment trials (Table 4.6)

Antidepressants and monoamine oxidase inhibitors

The effects of antidepressants and monoamine oxidase inhibitors were investigated in four RCTs and one controlled trial.[58-61] RCTs of fluoxetine,[58], fluoxetine with and without GET, [46] moclobemide,[61] and phenelzine[59] found no beneficial effects of treatment on depression or any other of the outcome

measures reported. The RCT of fluoxetine also reported no difference in effect between depressed and non-depressed individuals. A small controlled trial of selegiline was associated with significantly 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.[60]

Corticosteroids

The effects of steroid treatment were investigated in four RCTs of participants with CFS.[28,30,32,62] Two of these RCTs evaluated hydrocortisone and both reported some beneficial effect.[28,32] One found a significant improvement in general health but not in activity, depression, mood or symptom measures.[32] The second smaller RCT found significant improvements in fatigue, and suggested improvements in symptoms and disability, although the improvement in disability was not significant and only within group differences were reported for symptoms.[28] The other two RCTs assessed fludrocortisone and did not find any statistically significant association between treatment and the outcomes investigated.[30,62]

Anticholinergic agents

Two RCTs evaluated anticholinergic agents. One very large RCT (n=326) which included participants diagnosed with chronic post-infectious fatigue (CPIF), evaluated the anticholinergic drug sulbutiamine.[63] No significant differences between groups were reported for fatigue, activity, clinical global impression and illness severity. The second investigated galanthamine hydrobromide and also found no significant effects of treatment.[35]

Other pharmacological agents

Oral nicotinamide adenine dinucleotide (NADH) led to a significantly greater improvement in symptoms (the only outcome investigated) in the intervention group compared to the control group in one small RCT.[31] One small study assessed the growth hormone Genotropin and found no significant effect of the intervention.[34]

Adverse events serious enough to cause people to withdraw from the study occurred with fludrococrtison,[30] moclobemide,[61] sulbutiamine,[63] galanthamine hydrobromide,[35] phenelzine[59] and fluoxetine.[58]

One of the expert panel has mentioned a large RCT of galanthamine hydrobromide which has not been published. We have been unable to find any results of this trial.

4.4.5 Supplements

a. Essential fatty acids - rationale

It has been suggested that people with CFS may have lowered erythrocyte membrane essential fatty acids and elevated levels of saturated fatty acids compared to healthy controls.[64] Serum fatty acids have been shown to fall in several acute and chronic viral infections, including AIDS and may remain persistently low, correlating with the physical malaise, after, for example, acute Epstein-Barr virus infection. These acids also play important roles in immunity. A study in those with post viral fatigue syndrome (PVFS) states that both unsaturated and saturated fatty acids may inactivate certain viruses in vitro and inhibit their replication in vivo.[65]

b. Liver extract-folic acid-cyanocobalamin (LEFAC) - rationale

The rationale for the use of this intervention was not stated clearly in the paper. In the discussion section of the paper the authors say that extracts of liver seem to have an in vitro effect on mono-nuclear cell function.[66]

c. Magnesium - rationale

Many of the symptoms of CFS are reported to be similar to those of magnesium deficiency (anorexia, nausea, learning disability, personality change, weakness, tiredness, and myalgia) and it has been suggested that patients with CFS have subnormal red blood cell magnesium concentrations.[67]

d. General supplements - rationale

There have been reports of beneficial effects from vitamin and mineral supplementation on patients diagnosed with CFS in general practice.[68] Patients with CFS may have lower vitamin levels than people who do not have CFS. Candida yeast infection is often reported to be present and accordingly the normal population of colon bacteria will be reduced. A powerful supplementation programme aimed at facilitating immune system function, helping fat metabolism, improving digestion and alleviating fatigue was suggested as a possible treatment for many of the symptoms of ME.[21]

Table 4.6 Results of pharmacological treatment trials

Intervention		Author (year), number of participants	Results						
			Resource use	Physical	Psychological	Physiological	Quality of life and general health	Drop-outs/adverse effects	Validity score
Antidepressant and monoamine oxidase inhibitors	Phenelzine	Natelson (1996)[59] 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)[58] 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 & Flueoxetine	Wearden (1998)[46] n=136		*Fatigue and functional work capacity:* no significant difference between groups with and without fluoxetine.	*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
	Moclobemide	Hickie (2000)[61] 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)[60] 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)
Corticosteroids	Hydrocortisone	McKenzie (1998)[32] 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

Intervention		Author (year), number of participants	Results						
			Resource use	Physical	Psychological	Physiological	Quality of life and general health	Drop-outs/adverse effects	Validity score
	Hydrocortisone	Cleare (1999)[28] 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 (p-value not reported) *Symptom measure:* significant improvement on treatment (p=0.04) not on placebo (p=0.21), do not report on significance of difference in improvement	3 participants dropped out before treatment started	18
	Fludrocortisone	Peterson (1998)[62] 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)[30] 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
Anticholinergic	Galanthamine hydrobromide	Snorrason (1996)[35] n=49		*Sleep disturbance, fatigue, myalgia:* no significant differences in either treatment group – within group differences	*Cognitive function:* no significant differences in either treatment group – within group differences		*Work capacity/satisfaction:* no significant differences in either treatment group – within group differences	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
	Sulbutiamine	Tiev (1999)[63] 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
Growth hormone	Growth hormone	Moorkens (1998)[34] n=20		*Physical examination*: no significant differences in either treatment group – within group differences				3 participants withdrew, however no participants dropped out due to adverse effects	5
NADH	Oral NADH	Forsyth (1999)[31] 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

Results in **bold type** indicate significant differences between intervention and control groups

Main results of supplement treatment trials (Table 4.7)
Two studies investigated the effect of essential fatty acid supplements. One RCT in patients with CFS found a significant improvement as perceived by the participants but not in general symptoms or depression.[64] A slightly larger RCT trial investigated the effect of essential fatty acid supplements in those diagnosed with post viral fatigue syndrome (PVFS).[65] Significant 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 significant 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.[67] One very small RCT assessed the effects of liver extract in patients with CFS but found no significant difference in outcomes between the intervention and control groups.[66] General supplements had an ovverall beneficial effect in a very small (n=12) RCT[21] but no significant effect in a small controlled trial (n=42) of patients with CFS.[68]

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.[67]

4.4.6 Complementary/alternative medicine

a. Homeopathy - rationale
Homeopathy has been used to treat all the symptoms of CFS combined as a holistic system of treatment.[33]

b. Massage therapy - rationale
Massage therapy has been shown to reduce depression, anxiety and stress hormones in groups of depressed individuals and it was suggested that it may have similar effects in patients with chronic fatigue immunodeficiency disorder.[69]

c. Osteopathy - rationale
It has been suggested that ME may be caused by a mechanical dysfunction affecting the upper back which leads to a chronic disturbance of the sympathetic nervous system.[20] Such a dysfunction could be managed by biomechanical treatment, which involves manipulation of the inter-vertebral apophyseal joints of the thoracic spine and massage of the surrounding soft tissues to increase blood supply and stimulate lymphatic drainage.[20]

Main results of complementary/alternative medicine treatment (Table 4.8)
Massage therapy significantly 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).[69] Osteopathy improved measures of fatigue, back pain and sleep, anxiety and cognitive function and general health in a controlled trial of patients diagnosed with ME. The values were reported on a graph and no indication of the significance of the difference was reported. A combined treatment measure showed significant improvements ($p<0.005$). However the quality of this study was poor (score = 0 out of 20).[20] Two RCTs assessed the effectiveness of homeopathy.[33,70] One study, for which only preliminary results were available, found a significant improvement for one of the six outcomes investigated (general fatigue). The second study reported that a significantly greater proportion of the intervention group recovered compared to the control group. The authors of the second study state that participants were suffering from ME, however the Oxford criteria for CFS were used to make the diagnosis.

4.4.7 Other

a. Multi-treatment – rationale
It has been suggested that CFS may be heterogeneous in nature and reflects a complex interaction between a variety of physiologic, behavioural, emotional and cognitive factors. Multi-disciplinary interventions, including appropriate medical investigations and intervention, treatment for depression and any other comorbid psychiatric disorder, nutritional supplements and various forms of behavioural and cognitive-behavioural intervention have been proposed for managing CFS.[71]

b. Buddy and mentor programme – rationale
It has been suggested that individuals with CFS often experience significant reductions in social and occupational functioning and in the ability to complete necessary daily tasks.[72] The buddy/mentor

programme was established to try to fill the significant need of patients with CFS for social support, as a means of reducing stress which may inhibit recovery.[72]

Main results of multidimensional treatment trials (Table 4.9)

One RCT investigated a multi-treatment programme in people with fibromyalgia and CFS which involved treating specific patient symptoms with a variety of different medications. All patients, in both control and intervention groups, also received nutritional supplements. The study found significant improvements in the intervention compared to the control group for all of the outcomes investigated. Patients in the treatment arm were found to have greater improvements in energy, sleep, mental clarity, achiness, well-being, fibromyalgia impact questionnaire, tender points and overall response to treatment compared to those in the control group.[22] The study was good quality.

One controlled trial of combination treatment (including CBT) in patients with CFS was included.[71] A significantly 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 scored very poorly on the validity assessment 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.[73] Again, a low score on the validity assessment 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.[72]

Table 4.7 Results of supplement treatment trials

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)[64] 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)[65] n=63				***Fatty acid concentration:* greater shift towards normal levels in treatment groups (most were s tatistically 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)[67] n=34		***Energy and pain:* significant improvement in treatment group compared to control (p-value not reported)** *Sleep and physical mobility:* no significant differences between groups	***Emotional reactions:* significant improvement in treatment group compared to control (p-value not reported)** *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)[66] 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
General supplements	Martin (1994)[68] 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)
General supplements	Stewart (1987)[21] n=12		***Fatigue:* suggestion of greater improvement in treatment group *Bowel movements and digestion:* increased and improved in treatment groups, no measure of significance presented**				2 participants dropped out, adverse effects not discussed	6

Table 4.8 Results of complementary/alternative medicine treatment trials

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								
Any homeopathic remedy	Awdry (1996)[33] n=64					**Greater improvement with treatment than in control group (p<0.01)**	3 participants dropped out, 2 in homeopathy group, however, no participants dropped out due to adverse effects	6
	Weatherley-Jones (2001)[70] n=104		***General fatigue:* significant improvement in treatment compared to control group (p = 0.041)** *Physical and mental fatigue and activity*: no significant difference between groups	***Motivation:*** no significant difference between groups			11 withdrew from the treatment arm, 8 withdrew from the placebo group. Reasons for drop-outs are not reported.	8
Massage therapy	Field (1997)[69] 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 significant difference in levels of norepinephrine or epinephrine, **significant decrease in cortisol levels in treatment group (p<0.01)**		Not stated	9
Osteopathy	Perrin (1998)[20] n=58		***Fatigue, back pain, sleep:* greater improvement in intervention group compared to control (significance level not reported)**	*Depression*: no difference between groups ***Anxiety and cognitive function:* greater improvement in treatment group compared to control (significance level not reported)**		***General health and Nottingham health questionnaire*: greater improvement in treatment group compared to control (significance level not reported)**	2 drop-outs in treatment group, 17 in control, reasons for drop-outs not stated	0 (NB controlled trial)

Results in **bold type** indicate significant differences between intervention and control groups

Table 4.9 Results of multidimensional treatment trials

Intervention	Author (year), number of participants	Results						
		Resource Use	Physical	Psychological	Physiological	Quality of life and general health	Drop-outs/adverse effects	Validity score
Multi-treatment with various different medications	Teitelbaum (2001)[22] n=72		***Tender point pain*** **greater improvement in treatment group compared to control (p<0.001)**			***Fibromyalgia impact, overal response and various visual analogue scales:*** **greater improvement in treatment group compared to control (p<0.001)**	One patient in each group dropped out because of side effects, and one in each group for which no reason was given. One active patient withdrew because there were too many pills and 3 active patients because they were too busy. 24 in the active group and 22 in the placebo group reported adverse events	19
Combination multitreatment	Marlin (1998)[71] n=71					***Employment status*****: Greater number of participants returned to work in treatment group (p<0.05)**	49/71 were not followed up. The authors do not report adverse effects	3 (NB controlled trial)
Broad-based management	Goudsmit (1996)[73] n=52		*Functional impairment:* No significant differences between groups *Coping:* No significant differences between groups **Significant improvement in intervention groups compared to control group in fatigue (p=0.03)**	*Uncertainty, self-efficacy:* No significant differences between groups *Anxiety and depression:* No significant differences between groups. *Cognitive difficulty:* No significant differences between groups		***Symptoms:*** **Significant improvement in intervention groups compared to control group in somatic symptoms (p=0.04)**	Eight excluded from analysis: 3 in intervention group and 5 controls. Two wished 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)[72] 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)

Results in **bold type** indicate significant differences between intervention and control groups

4.4.8 Combination treatments

Two trials investigated the combined effects of more than one intervention. One RCT which evaluated fluoxetine and GET found no significant effect of fluoxetine either as the sole treatment or in combination with GET, although a significant beneficial effect of GET was reported for one of the outcomes investigated when used in isolation.[46] The results of this RCT are presented in tables 4.3 (behavioural) and 4.6 (pharmacological). Full details are presented in Appendix B.

The second RCT evaluated the combined effects of leukocyte extract and CBT.[26] The results of this RCT are presented in tables 4.3 (behavioural) and 4.4 (immunological). Full details are presented in Appendix B. There were no significant differences between the groups receiving either: i) leukocyte extract and clinic treatment, ii) CBT and placebo or clinic treatment and iii) placebo, for any of the outcomes investigated. However, the group receiving both CBT and leukocyte extract showed a significantly greater improvement in general health than the other intervention groups but did not differ significantly for any of the other outcomes assessed.

4.4.9 Subgroups

Two RCTs[58,61] and one controlled trial[29] assessed participants with depression or psychological distress as subgroups. One RCT of fluoxetine[58] found no significant difference in response between depressed and non-depressed groups and one RCT of moclobemide[61] found no significant difference between those with major depression or general psychological distress and those without. One controlled trial of CBT found that those participants who were depressed (as defined by a high score on CES-D scale, using a median split of all trial participants) had greater improvements on several outcomes including depression, stress, fatigue and fatigue-related thinking than those who were not.[29]

The RCT of moclobemide[61] also assessed participants with reduced immune responses. This subgroup showed a significantly greater improvement with moclobemide on the Karnofsky Performance Index than those in the intervention group who did not have reduced immune responsiveness. Another RCT[26] also mentioned those with reduced immune response as a subgroup but no results were presented for this subgroup.

One RCT of fludrocortisone assessed separately participants who had been ill for three years or more, versus those who had been ill for less than three years and found no significant differences in response to treatment.[30]

One RCT of ampligen grouped participants according to whether they had evidence of human herpes virus 6 (HHV-6) infection. No significant differences were found between groups in response to treatment as measured by change in Karnofsky Performance Index.[53]

Results for subgroups are given in individual study details in Appendix B, in the 'general comments' section under 'outcomes'

4.4.10 Children

One RCT of immunoglobulin G included only young people aged less than 18.[55] 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 young people in the intervention group had an improvement in score of 25% or more. A second RCT of immunoglobulin G included both adults and children according to standard definitions, although no participants under the age of 16 were included.[51] 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. Immunoglobulin is a blood product and there are known risks associated with the use of these, so the use of this treatment should be carefully considered. No trials of other interventions investigated in children were identified. However, a pilot study of CBT in children has been completed[74] and a randomised controlled trial is currently in progress.[75]

4.5 Validity of included studies

The results for individual studies and intervention categories presented above need to be considered alongside the methodological assessment. The quality of the 38 RCTs included in this review was variable, with 29 of them (76%) scoring 10 points or more (out of 20) on the validity criteria. Overall, the controlled trials were of much poorer quality, the highest score achieved was 11 out of 20, and only two of the eight trials (25%) scored 10 points or more.

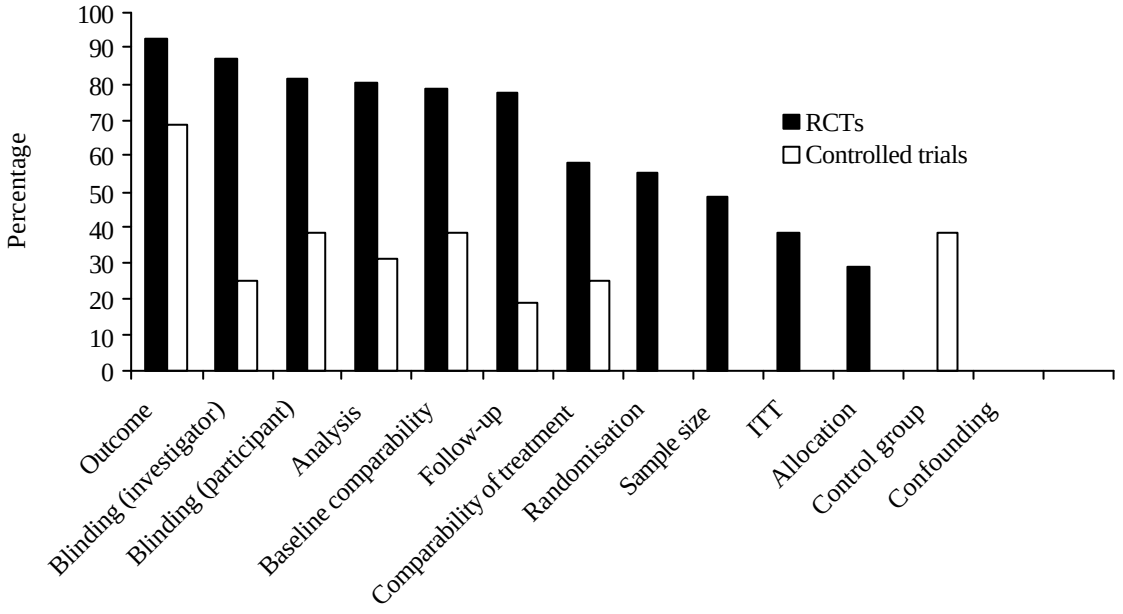
The results of the validity assessment for each study (separately for RCTs and controlled studies) are shown in Table 4.10 (the validity grading of studies is shown in Appendix D).

The percentage of the total available points scored by the studies for each validity criterion is presented below, separately for RCTs and controlled trials, and is illustrated in figure 4.3.

Validity criterion	**RCTs**	**Controlled trials**
Objectivity and validity of outcome	92	69
Blinding (investigator)	87	25
Blinding (participant)	82	38
Appropriate analysis	80	31
Baseline comparability of treatment groups	79	38
Completeness of follow-up	78	19
Comparability of treatment of groups other than named interventions	58	25
Method of randomisation	55	Not assessed
Sample size or power calculation	49	0
Handling of drop-outs (Intention-to-treat)	38	0
Concealment of treatment allocation	29	Not assessed
Appropriate control group	Not assessed	38
Adjustment for confounding factors/ baseline differences where found	Not assessed	0

Most RCTs scored well on objectivity and validity of outcomes, blinding of investigators and participants, baseline comparability of groups, completeness of follow-up and appropriate statistical analysis. RCTs generally scored poorly on concealment of treatment allocation and failed to use an intention-to-treat analysis. Controlled trials also scored well on objectivity and validity of outcomes but scored less than 40% for all other validity criteria. None of the controlled trials in which groups were not comparable at baseline adjusted for baseline differences or confounding factors. None of the controlled trials used a sample size calculation or an intention-to-treat analysis.

Figure 4.3 Percentage of the total available points scored for each validity criterion (separately for RCTs and controlled trials)



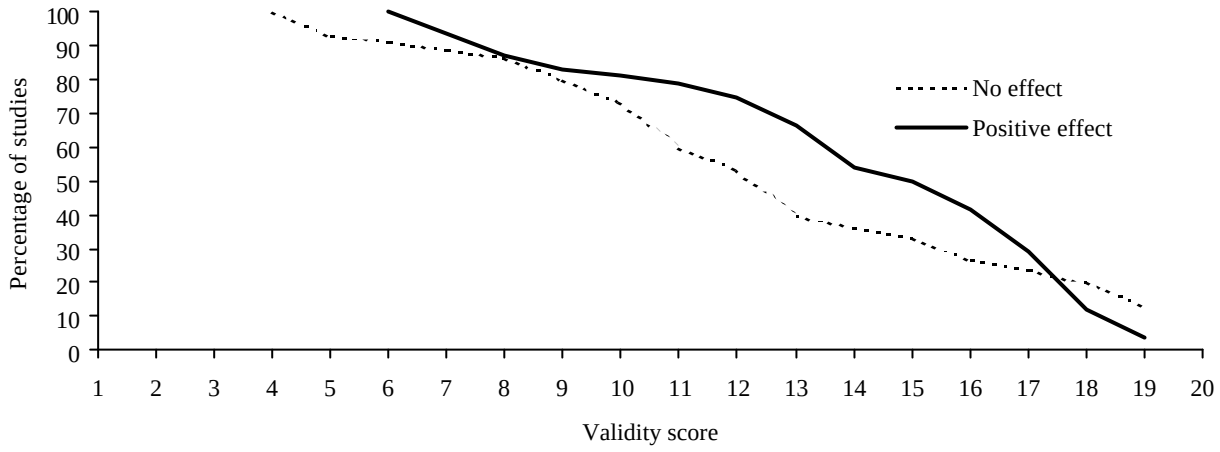
No one intervention type scored more highly on the validity criteria than any other, although trials of GET and of essential fatty acid supplements all scored 16 points or more.

It has been suggested that studies of lower quality are more likely to show a positive result. [76] To investigate this theory, the validity score for each RCT was plotted against the percentage of RCTs

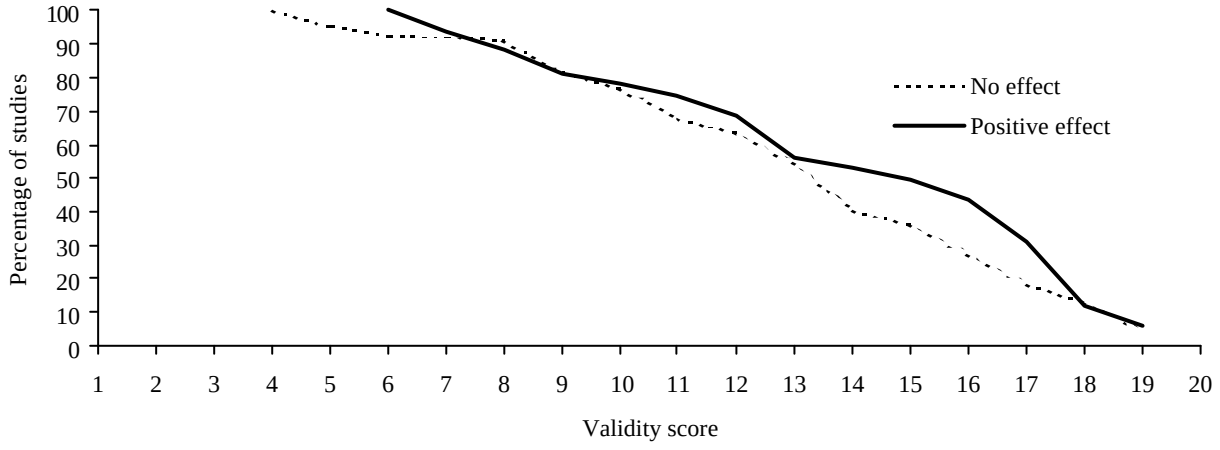
showing at least that score. This was done separately for studies that showed any effect of treatment, and for the overall treatment effect (see section 3.6 for description of methods used to classify effect of treatment).(Figure 4.4) If study quality made no difference to whether a positive result was reported it would be expected that the two lines (representing no effect and positive effect) would be close together. If the studies which scored poorly on validity assessment were more likely to show a positive result it would be expected that the line representing no effect would be above that indicating positive effects. Instead the graph indicates that the line representing studies which found a positive effect (any and overall effects) is above the line for studies showing no effect. This finding suggests that a positive effect was more likely to be reported by the studies of better quality.

Figure 4.4 Validity score plotted against the percentage of RCTs showing at least that score

a. Studies classified according to whether they show any effect of treatment



b. Studies classified according to whether they show an overall effect of treatment



Note: The y-axis represents the percentage of RCTs which scored at least n points on validity assessment (n being the corresponding number on the x-axis). A higher percentage of RCTs scored at least five points on validity assessment than scored at least 18 points (for example), hence the direction of the lines.

Table 4.10 Validity assessment

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[33]	1996	0	0	1	1	2	0	0	2	0	0	0	6
Behan[65]	1990	2	2	1	1	2	2	2	2	2	0	1	17
Brook[49]	1993	2	0	0	0	0	2	0	2	0	0	0	6
Cleare[28]	1999	2	2	1	1	2	2	1	2	2	2	1	18
Cox[67]	1991	2	0	1	1	2	2	0	2	2	2	1	15
Deale[24]	1997	2	2	0	1	2	2	2	2	2	2	1	18
DuBois[54]	1986	2	2	1	0	0	2	0	2	2	0	0	11
Field[69]	1997	1	0	0	1	2	0	0	2	2	0	1	9
Forsyth[31]	1999	0	0	1	1	2	2	1	2	2	0	1	12
Fulcher[44]	1997	2	2	0	1	2	2	2	1	2	2	1	17
Hickie[61]	1998	2	2	1	1	2	2	2	2	2	2	1	19
Kaslow[66]	1989	0	0	1	1	1	2	0	2	1	1	1	10
Lerner[19]	2001	0	0	1	1	0	0	0	0	2	0	0	4
Lloyd[26]	1993	2	0	1	1	2	2	0	2	2	0	1	13
Lloyd[51]	1990	0	0	1	1	2	2	2	2	2	0	1	13
McKenzie[32]	1998	0	0	1	1	2	2	1	2	2	2	1	14
Moorkens[34]	1998	0	0	1	1	0	0	0	2	0	0	1	5
Natelson[59]	1996	0	0	1	1	0	2	0	2	1	0	1	8
Peterson[48]	1990	2	0	1	1	1	2	0	2	2	2	2	15
Peterson[62]	1998	2	2	1	1	0	2	0	2	2	2	2	16
Powell[45]	2000	2	2	0	0	2	2	2	2	2	2	1	17
Prins[40]	2001	2	2	0	0	2	0	2	2	2	2	2	16
Rowe[30]	2001	2	0	1	1	2	2	2	2	2	2	2	18
Rowe[55]	1997	1	0	1	1	2	2	1	2	2	2	2	16
See[36]	1996	0	0	1	1	2	2	1	2	0	0	2	11
Sharpe[17]	1998	2	0	0	0	0	2	2	2	2	2	1	13
Snorrason[35]	1996	0	0	1	1	2	2	0	2	0	0	1	9
Steinberg[50]	1996	0	0	1	1	2	1	0	2	1	2	2	12
Stewart[21]	1987	1	0	1	1	2	0	0	0	0	0	1	6
Straus[56]	1988	1	1	1	1	2	1	0	2	2	2	2	15
Strayer[53]	1994	1	0	1	1	2	2	0	2	2	0	1	12
Teitelbaum[22]	2001	2	1	1	1	2	2	2	2	2	2	2	19
Tiev[63]	1999	0	0	1	1	2	1	0	2	2	0	1	10
Vercoulen[58]	1996	2	0	1	1	2	1	0	2	2	0	1	12
Vollmer Conna[52]	1997	0	0	1	1	2	2	2	2	2	0	1	13
Warren[64]	1999	1	2	1	1	2	2	0	2	2	2	1	16
Wearden[46]	1998	2	0	1	1	2	2	2	2	2	2	1	17
Weatherley-Jones[70]	2001	0	0	1	1	0	1	0	1	2	0	2	8
Maximum score available		**2**	**2**	**1**	**1**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**20**

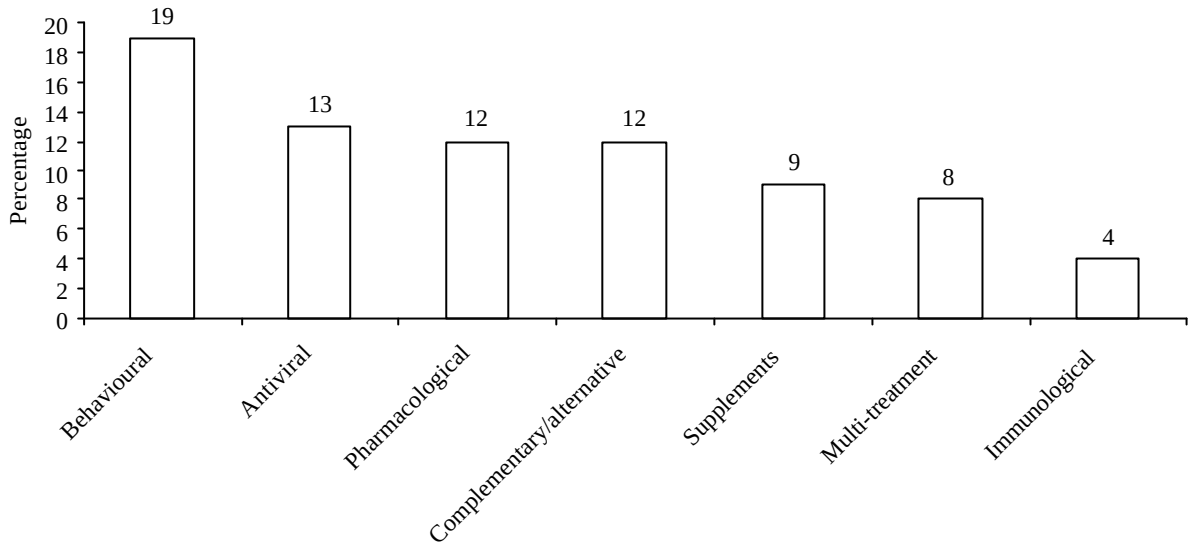
b. Controlled trials

Study details		Participant blinding	Investigator blinding	Baseline comparability of groups	Follow-up	Drop-outs (Intention-to-treat)	Outcome objectivity	Statistical Analysis	Appropriateness of control	Sample-size calculation	Control for confounding/ baseline differences	Comparability of treatment of groups	VS
Andersson[27]	1998	1	1	2	0	0	2	0	2	0	0	1	9
Friedberg[29]	1994	0	0	0	0	0	1	0	0	0	0	0	1
Goudsmit[73]	1996	0	0	0	0	0	1	1	0	0	0	0	2
Marlin[71]	1998	0	0	0	0	0	2	0	0	0	0	1	3
Martin[68]	1994	1	1	2	0	0	2	1	2	0	0	1	10
Natelson[60]	1998	1	0	2	2	0	2	1	2	0	0	1	11
Perrin[20]	1998	0	0	0	0	0	0	0	0	0	0	0	0
Shlaes[72]	1996	0	0	0	1	0	1	2	0	0	0	0	6
Maximum score available		**1**	**1**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**20**

4.6 Drop-outs

The overall drop-out rate from all the included studies was 15% (444/2943 participants): 13% (333/2611) in the RCTs and 33% (111/332) in the controlled trials. Drop-out rates by intervention group for the RCTs are shown in Figure 4.5.

Figure 4.5 Percentage of drop-outs by intervention for the RCTs



The highest drop-out rates for the RCTs was in the behavioural trials, where 19% (162/838) of participants dropped out. The high drop-out rate in these trials was due largely to the high drop-out rates in one of the RCTs of CBT,[40] and one of GET.[46] The CBT study had a drop-out rate of 40% (37/92) in the CBT group, 32% (29/90) in the support group and 20% (18/88) in the control group. There was a significant difference in the proportion of drop-outs between the groups ($Chi^2 = 8.27$ $p = 0.016$). The GET trial had a drop-out rate of 29%, 37% in the exercise groups and 22% in the non-exercise groups.[46] The other RCTs of CBT had lower drop-out rates which ranged from 2-12% and none of the studies reported significant differences in withdrawals between intervention and control groups. The remaining two trials of GET also had lower drop-out rates. In one trial[44] 11% of participants dropped out, a percentage which was equal across the groups. In the second the intervention groups had higher drop-out rates than the control group with an overall drop-out rate of 14%. It is possible that that the higher drop-out rates in the exercise groups are the result of the unacceptability of treatment and so it is important that the results of these studies are analysed using an intention-to-treat analysis. The one controlled trial of CBT did not report any drop-outs.[29]

Trials of antiviral treatments also reported relatively high drop-out rates of 13% (11/88). All of these trials were small with samples size of 30 or less and between 2 and 4 participants withdrew from the studies. Almost all of the withdrawals occurred in the intervention groups suggesting that these types of intervention may not be acceptable to patients.

The pharmacological therapy RCTs had a drop-out rate of 12% (102/869), with four of the twelve trials reporting more withdrawals from the intervention groups. The one controlled trial of a pharmacological therapy showed a higher drop-out rate with 24% (6/25) of participants leaving the study.[60]

Studies in the grouping of complementary/alternative treatments also had a drop-out rate of 12%. This relatively high drop-out rate was largely due to the drop-out rate in one of the trials of homeopathy which reported a drop-out rate of 18% (19/104 participants).[70] The other RCT of homeopathy reported a drop-out rate of 5% (3/64 participants) and the RCT of massage therapy[69] did not report on trial withdrawals. The controlled trial of osteopathy recorded a significantly higher drop-out rate in the control group compared with the intervention group (17 versus 2 respectively), although the reasons for this are unclear.[20]

RCTs of supplements had a drop-out rate 9% (15/174). One of the trials of essential fatty acids had a high drop-out rate of 20% (10/50), however, there were equal numbers of withdrawals in the treatment and control groups. The other four studies had lower drop-out rates ranging from 5-8%; none of these reported higher drop-out rates in the intervention compared to control groups. The controlled trial of general supplements had a very high drop-out rate of 55% (23/42).[68]

In the grouping of 'other' interventions there was only one RCT, the other three studies were controlled trials. This RCT reported a drop-out rate of 8% (6/72), with more participants withdrawing from the intervention group compared to the placebo group, although the reasons for this do not appear to have been related to adverse effects but rather to the large number of pills to be taken.[22] The controlled trial of a multidimensional intervention had the highest withdrawal rate reported by any of the trials, with 69% (49/71) of participants unavailable at the end of the 52 week intervention.[71] The other controlled trial, of broad based management, had a lower drop-out rate of 15% (8/52).[73] The controlled trial of social support was very small with only 12 participants, of which 4 (33%) dropped out.

RCTs of the remaining intervention category, immunological, showed relatively low drop-out rates of 4%. In the RCTs of immunological therapy only 22 of the total of 480 participants dropped out. Drop-out rates were only higher in the intervention than the control group for one of the 8 studies.[51] The controlled trial of immunological therapy reported a higher drop-out rate of 14% (4/28), with a greater number of drop-outs in the control group.

4.7 Duration of intervention and follow-up

The duration of intervention and follow-up varied between studies and within intervention types. In most trials the duration of intervention and follow-up was the same. Twelve of the 46 trials followed up participants for several weeks or months after the intervention had ceased. (Table 4.11) Seven of these trials assessed immunological or antiviral treatments, of which one also included CBT, three evaluated behavioural interventions, and two assessed pharmacological treatments. One RCT of CBT followed up participants five years post intervention; in the other eleven trials follow-up ranged from two weeks to nine months. These trials showed a mixture of no effect, some positive effects, some negative effect, and an overall positive effect. There are insufficient trials with longer follow-up to investigate whether there is any association between study outcome and a longer follow-up period.

Table 4.11 Results of studies where follow-up was longer than the duration of the intervention

Study	Treatment	Any effect	Overall effect	Duration of follow-up (intervention) (weeks)
Rowe (2001)[30]	Fludrocortisone	<>	<>	11(9)
Andersson (1998)[27]	Staphylococcus toxoid	+	<>	12 (2)
Vercoulen (1996)[58]	Fluoxetine	<>	<>	12 (8)
Straus (1988)[56]	Aciclovir	-	<>	18 (13)
Rowe (1997)[55]	Immunoglobulin G	+	+	26 (13)
Vollmer Conna (1997)[52]	Immunoglobulin G	<>	<>	26 (13)
Lloyd (1990)[51]	Immunoglobulin G	+	<>	26 (13)
Deale (1997)[24,41]	CBT	+	+	26 (and 5 years)(26)
Lloyd (1993)[26]	Immunologic + CBT	+	<>	30 (16)
Brook (1993)[49]	Interferon	+	+	52 (12)
Powell (2000)[45]	GET	+	+	52 (26)
Prins (2001)[40]	CBT	+	+	61 (35)

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

Intervention duration ranged from two weeks to one year, with an average duration of 17 weeks. Duration of intervention was longest in one RCT of alternative treatments (52 weeks), and the average duration of the intervention was longest for the complementary/alternative therapy trials (34 weeks) and the trials of 'other' interventions (27 weeks). Behavioural interventions also had a relatively long average intervention duration of 25 weeks. The average duration of the intervention was relatively short in the immunologic and antiviral (15 weeks), supplements (11 weeks) and pharmacologic (9 weeks) treatment trials. The distribution of treatment duration by intervention grouping is shown in Figure 4.6.

To investigate whether there was any association between treatment duration and study outcome, treatment duration (grouped as <1 month, 1-<3 months, 3-<6 months and 6-12 months) was plotted against trial results (no effect and positive effect) (Figure 4.7).

These figures suggest that studies with a longer treatment duration (>3 months) are more likely to report any positive effect and an overall positive effect of the intervention. However, the association between treatment duration and trial outcome was not significant for any effect of treatment (Chi^2 (3df) = 6.64, p = 0.084) or for the overall treatment effect (Chi^2 (3df) = 7.56, p = 0.056).

Figure 4.6 Distribution of treatment duration by intervention grouping

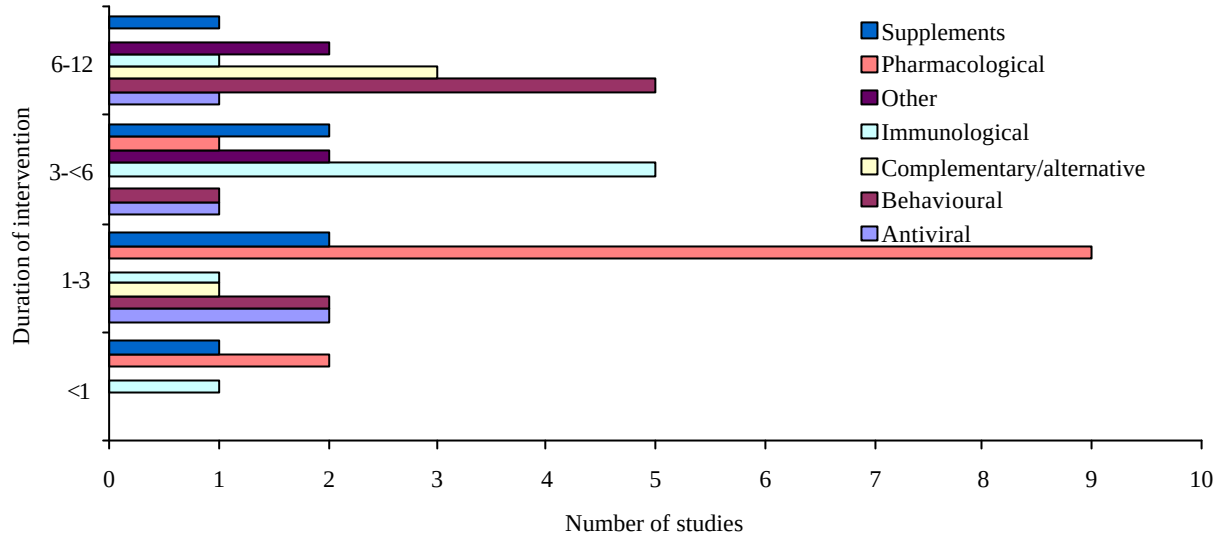
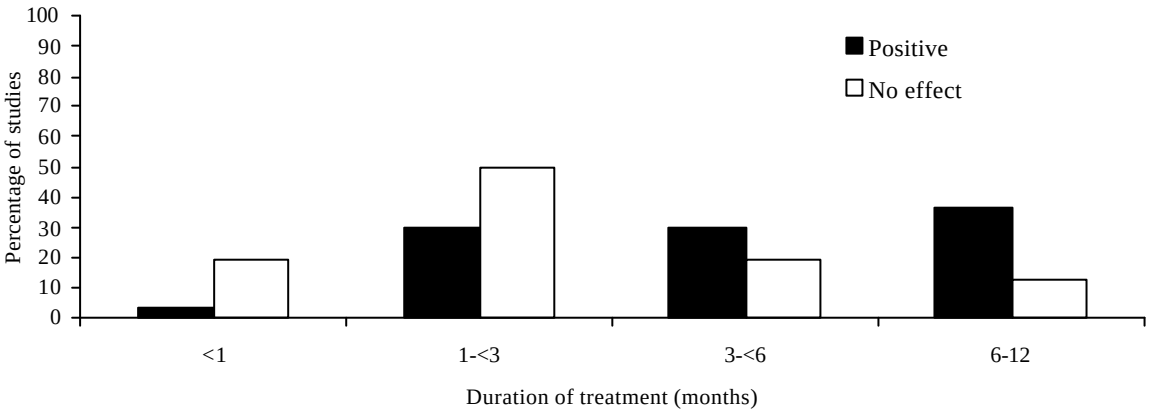
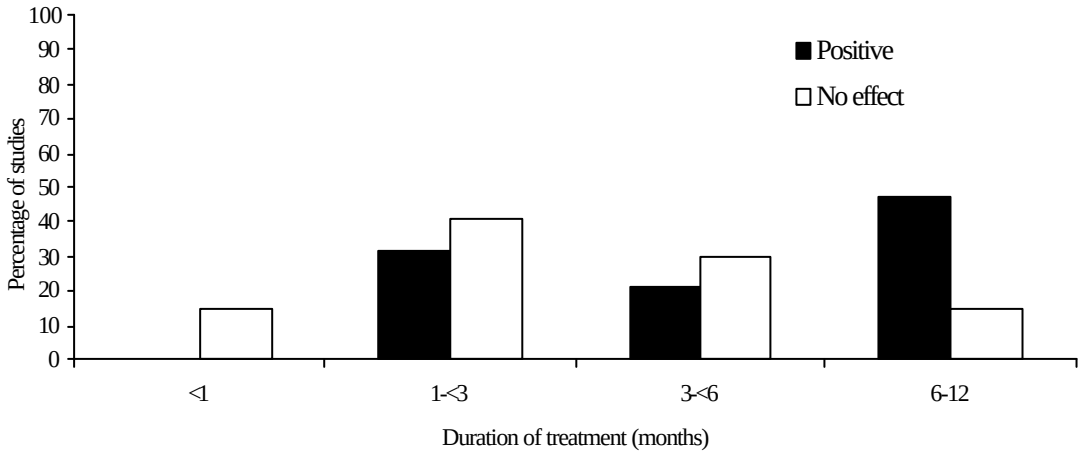


Figure 4.7 Effect of treatment by treatment duration

a. Studies classified according to whether they show any effect of treatment



b. Studies classified according to whether they show an overall effect of treatment



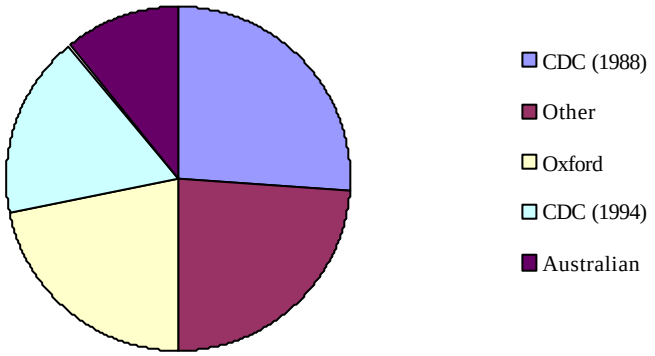
4.8 Diagnostic criteria

Diagnostic criteria used to identify people with CFS/ME were as follows (see Table 1.1 for a description of each criterion):

Oxford criteria (CFS)	10 studies
CDC 1988 criteria (CFS)	12 studies
CDC 1994 criteria (CFS)	8 studies
Australian criteria (CFS)	5 studies
Other criteria (ME, PVFS, CFIDS, PIFS etc)	11 studies

These results are shown in figure 4.8. One study used both the CDC (1988) and (1994) criteria to diagnose participants, and was classified as using CDC (1988) criteria as these are stricter than the later criteria. Eight studies used other diagnostic criteria to diagnose people with post-viral fatigue syndrome,[65] chronic fatigue immunodeficiency syndrome,[69] ME,[21] chronic mononucleosis syndrome,[54] chronic post-infectious fatigue[63], post-infectious fatigue syndrome,[73] chronic fatigue syndrome (diagnostic criteria not described further)[72] and a main complaint of fatigue.[35] In one study the author's own criteria was used, in which two of the following three criteria had to be present for at least three months: muscle pain, mental/physical fatigue at rest or on minimal exercise, persisting/relapsing course of illness. In addition the following two criteria had to be fulfilled: patient was well before illness, exclusion of other cause of symptoms.[68] One study that diagnosed patients using CDC (1994) criteria stated that participants did not have to meet the CDC criteria of 4/8 additional symptoms, however, participants did have to score above certain levels on fatigue severity and sickness impact scales.[40] One study included patients with a diagnosis of CFS based on the CDC (1988) criteria and who also met the London Criteria for ME.[20] One study stated that patients had CFS but gave no information on the criteria used to diagnose patients.[19] One study included only patients who fulfilled the 1990 American College of Rheumatology criteria for fibromyalgia,[78] however, all but three of these patients also met the CDC (1994) criteria for CFS.

Figure 4.8 Distribution of diagnostic criteria



Summary effects (no effect and positive effect, for any effect and overall effect) are presented in a bar chart for each set of diagnostic criteria (Figure 4.9).

4.9 Publication bias

Due to heterogeneity of outcomes and interventions it was not possible to assess the extent of publication bias using funnel plots. However every effort was made to trace unpublished studies (see 'Methods'). No trials found an overall negative effect of the intervention compared to control conditions, suggesting that there may be bias towards publication of trials showing a positive effect.

4.10 Summary of results

The results of each trial grouped by intervention category, ranked according to validity score, are presented in Table 4.12. Trials were classified as having a positive, negative or no effect, under the classifications of overall effect and any effect (section 3.5). The findings from each study should be considered alongside the methodological quality.

Of the 46 included trials 31 (67%) showed some beneficial effect of the intervention and of these 19 (41%) showed an overall beneficial effect, one study (3%) reported a negative effect of the intervention. Overall, of those studies that found some beneficial effect of the intervention, one study (of an immunological intervention) 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. The results from four studies (evaluating alpha interferon,[36] growth hormone,[34] galanthamine hydrobromide[35] and cognitive behavioural therapy[29]) were not included in this summary of findings as they were based on within group comparisons rather than comparisons between groups.

4.10.1 Behavioural

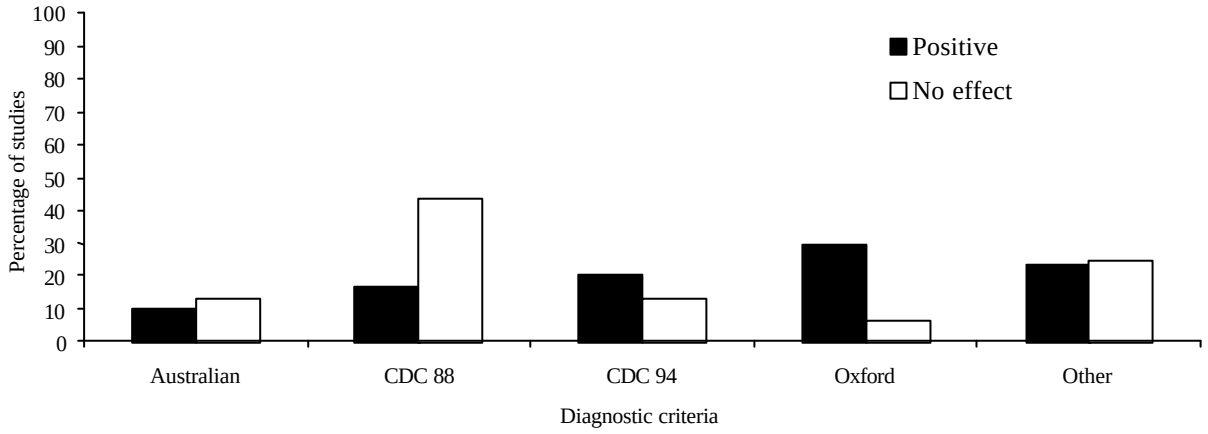
Both CBT and GET showed positive results. Three[24,25,40] of the four RCTs evaluating CBT found a positive overall effect of the intervention and these studies also scored highly on validity assessment. One RCT which also included immunologic therapy[26] did not find overall beneficial effects of CBT. The controlled trial of CBT reported within group rather than between group differences and so conclusions cannot be drawn from the results.[29] These two studies scored lower on the validity assessment, especially the controlled trial which scored 1 out of a possible 20. Two of the three RCTs of GET found an overall beneficial effect of the intervention compared to the control groups, the third found some beneficial effect of treatment. These RCTs all scored highly in the validity assessment, scoring 17 or more out of a possible 20.[44-46]

4.10.2 Immunological

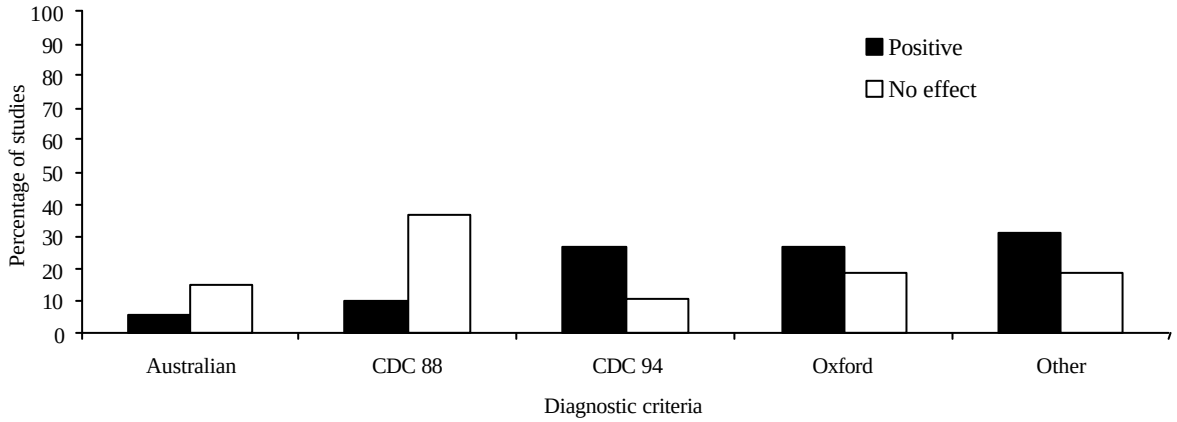
Five RCTs assessed the effects of immunoglobulin G in patients with CFS, of these two showed an overall beneficial effect,[54,55] (however in both these trials only one outcome was investigated), two showed some positive effects[48,51] (however, in one trial this effect was seen in physiological outcomes only,[48]) and one found no effect.[52] Immunoglobulins are blood products so possible transfer of, for example, infectious diseases must be considered. One RCT of ampligen found an overall beneficial effect,[53] and a positive effect was found in a small controlled trial of staphyloccoccus toxoid.[27] A small RCT of the antihistamine oral terfenadine reported no beneficial effects.[50] These three studies scored between 9 and 12 on the validity assessment.

Figure 4.9 Effect of treatment by diagnostic criteria

a. Studies classified according to whether they show any effect of treatment



b. Studies classified according to whether they show an overall effect of treatment



The bar chart for any effect suggests that more participants with a positive response to the intervention were diagnosed using the Oxford criteria. The bar chart for overall effect is less clear. The association between method of diagnosis and study outcome was not significant for any effect of treatment (Chi^2 (4df) = 6.05, p = 0.195) or for the overall treatment effect (Chi^2 (4df) = 6.53, p = 0.163).

4.10.3 Antiviral

Two small RCTs evaluated interferon, one of these found an overall beneficial effect[49] and the other reported within group differences and so conclusions cannot be drawn from this study.[36] The methodological quality of both these studies was fairly poor; scoring 6 and 11 respectively (out of a possible 20) on the validity assessment. A small RCT of aciclovir, 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.[56] This study scored 15 out of 20 on the validity assessment. A very small poor quality RCT of ganciclovir reported some beneficial effects of treatment but the significance of the results was not reported. This study was ended prematurely due to adverse events in the intervention group.[19]

4.10.4 Pharmacological

Two poor quality RCTs of anti-depressants,[58,59] and a good quality RCT of moclobemide[61] reported no effects of treatment either on symptoms of depression or on any of the other outcome measures reported. One controlled trial of selegiline reported some positive effects of treatment but found no overall effect.[60] Two RCTs of fludrocortisone reported no effect of treatment, these studies were of reasonable quality.[30,62] Two RCTs of hydrocortisone reported some beneficial effects of treatment.[28,32] One of these was of good quality scoring 18 out of 20,[28] the other was of average quality with a score of 14 out of 20.[32] A poor quality RCT of sulbutiamine[63] also reported no effect of treatment. One poor quality RCT showed an overall beneficial effect of oral NADH.[31] Two studies, one of growth hormone[34] and the other of galanthamine hydrobromide,[35] reported within group rather than between group differences.

4.10.5 Supplements

In the supplements category two good quality RCTs of essential fatty acids reported some beneficial effects of the intervention[64,65] and one also found an overall beneficial effect.[65] Magnesium supplements were found to have an overall beneficial effect in the one good quality RCT where these were evaluated.[67] One poor quality RCT and one controlled trial evaluated general supplements, the controlled trial reported no significant effect of treatment[68] but the RCT reported an overall beneficial effect.[21]

4.10.6 Complementary/alternative medicine

Alternative therapies were evaluated in three poor quality RCTs and one controlled trial.[33] Two RCTs looked at homeopathic treatment, one of these found an overall beneficial effect of treatment, the second found some beneficial effect of the intervention. The other small RCT looked at massage therapy and found an overall beneficial effect. All three RCTs scored poorly on the validity assessment scoring less than 10 out of a possible 20. A controlled trial of osteopathy found some improvements in the intervention group, but the values were estimated from graphs and so the results may not be entirely accurate.[20] This study scored very poorly on the validity assessment, scoring 0.

4.10.7 Other

A good quality RCT found overall beneficial effects of treatment with a combination of drugs depending on the specific symptoms of each patient.[22] An overall beneficial effect was found in two controlled trials of two different multi-treatment approaches, one of which included CBT[71] and one of which was based on providing information and advice.[73] However, both of these studies scored poorly on the validity assessment. 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.[72]

4.10.8 Children

One RCT of immunoglobulin G which included only young people aged under 18 found an overall beneficial effect on two measures of functional ability.[55] This study is also presented in the overall summary of results (above). No controlled studies conducted in children were identified for any other intervention categories.

4.10.9 Subgroups

Two RCTs[58,61] and one controlled trial[29] assessed participants with depression or psychological distress as subgroups of the main diagnostic criteria. One RCT of fluoxetine[58] reported no differences in response between depressed and non-depressed participants and one RCT of moclobemide found no differences between those with major depression or general psychological distress and those without.[61] One controlled trial of CBT reported that participants who were depressed improved more than those who were not on outcomes including depression, stress, fatigue severity and fatigue related thinking.[29]

In addition to depression, one study also assessed participants with reduced immune responses.[61] This group were found to have a greater improvement on the Karnofsky Performance Index with moclobemide than those in the same group who did not have reduced immune responsiveness.

In another study participants were grouped according to whether they had evidence of human herpes virus 6 (HHV-6) infection. No differences were found between the two groups in response to ampligen, as measured by changes on the Karnofsky Performance Index.[53]

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.[30] 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.[73] 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.[73]

The categories of potential subgroups investigated in the trials was limited. For example, no studies were found which 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.

4.10.10 Combination therapies

Two trials investigated the combined effects of more than one intervention.[26,46] One RCT evaluated fluoxetine and GET and found no significant effect of fluoxetine either as the sole treatment or in combination with GET, although a beneficial effect of GET on its own was reported.[46] The other RCT evaluated the combined effects of leukocyte extract and CBT and found no significant difference between the groups receiving either: i) leukocyte extract and clinic treatment, ii) CBT and placebo or clinic treatment and iii) placebo for any of the outcomes investigated.[26] The group receiving both CBT and leukocyte extract showed a significantly greater improvement in general health than the other intervention groups but did not show any significant differences for any of the other outcomes investigated.

4.10.11 Additional or alternative criteria to CFS

Two trials, one RCT of massage therapy[69] and one controlled trial of osteopathy,[20] both found overall benefits of the intervention in those diagnosed with CFIDS (massage) and ME (osteopathy). It should be noted however that both studies were methodologically poor, and in particular the trial of massage therapy reported within-group comparisons, rather than between group differences. One very small RCT of immunoglobulin G found an overall benefit in those diagnosed with chronic mononucleosis syndrome.[54] In another RCT some positive effects of aciclovir were reported, but there was no overall positive effect in those diagnosed with CFS who had had previous Epstein Barr virus infection.[56] Essential fatty acids produced an overall beneficial effect in people diagnosed with post viral fatigue syndrome in one RCT[65] and general supplements had a positive (but not an overall) effect in one RCT where participants were diagnosed with ME.[21] A controlled trial of broad-based management found an overall beneficial effect in those diagnosed with post-infectious fatigue syndrome.[73] A trial of many different medications based on symptomatology and laboratory tests found on overall benefit for people with fibromyalgia and CFS.[22]

It must be noted for some 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. 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. In many of the trials very limited information was given about participants who were ineligible or about the baseline functioning of many of those who were included. Therefore, it is difficult to extrapolate how the findings might transfer to other people with CFS/ME.

Table 4.12 Summary of study results

Treatment	Diagnostic criteria	Duration of follow-up† (weeks)	Number of participants	Outcomes investigated	Any effect	Overall effect	Validity score (maximum 20)
BEHAVIOURAL							
GET[44]	Oxford	12	66	**PH**; PS; **LAB; QOL**	+	+	17
GET[45]	Oxford	52 (26)	148	**PH; PS; QOL**	+	+	17
GET & Fluoxetine[46]	Oxford	26	136	**PH**; PS; QOL	+	<>	17
CBT[24,41]	Oxford	26 (and 5 years)	60	**PH**; PS; **QOL**	+	+	18
CBT[40]	CDC 94	61(35)	270	**PH; PS; QOL**	+	+	16
CBT[25]	Oxford	52	60	**PH**; PS; **QOL**	+	+	13
CBT + DLE[26]	Australian	30 (16)	90	PH; PS; LAB; **QOL**	+	<>	13
CBT[29]	CDC 88	9	44	PH; PS; QOL	<>	<>	1
IMMUNOLOGICAL							
Immunoglobulin G[55]	CDC 94	26 (13)	71	**PH**	+	+	16
Immunoglobulin G[48]	CDC 88	21	30	PH; **LAB**; QOL	+	<>	15
Immunoglobulin G[51]	Australian	26 (13)	49	PS; **QOL**	+	<>	13
Immunoglobulin G[52]	Australian	26 (13)	99	PH; PS; LAB; QOL	<>	<>	13
Gamma globulin[54]	Other	17	19	**QOL**	+	+	11
Ampligen[53]	CDC 88	26	92	**RU; PH; PS**	+	+	12
Terfenadine[50]	CDC 88	9	30	PH; QOL	<>	<>	12
Staphylococcus toxoid[27]	CDC 94	12 (2)	28	PS; **QOL**	+	<>	9
ANTIVIRAL							
Alpha interferon[36]	CDC 88	12	30	**LAB**; QOL	+	<>	11
Interferon[49]	CDC 88	52 (12)	20	**PH**	+	+	6
Aciclovir[56]	CDC 88	18 (13)	27	PH; **PS**; LAB; QOL	–	<>	15
Ganciclovir[19]	Not stated	26	11	QOL	<>	<>	4
PHARMACOLOGICAL							
Moclobemide[61]	Australian	6	90	PH; PS; LAB; QOL	<>	<>	19
Fluoxetine[58]	Oxford	12 (8)	107	PH; PS; QOL	<>	<>	12
Phenelzine[59]	CDC 88	6	24	PH; PS; QOL	<>	<>	8
Selegiline[60]	CDC 88	6	25	PH; **PS**; QOL	+	<>	11
Hydrocortisone[28]	Oxford/CDC 94	9	32	**PH**; QOL	+	<>	18
Hydrocortisone[32]	CDC 88	12	70	PH; PS; **QOL**	+	<>	14
Fludrocortisone[30]	CDC 94	11 (9)	100	PH; PS; LAB; QOL	<>	<>	18
Fludrocortisone[62]	CDC 88 & 94	18	25	PH; PS; QOL	<>	<>	16
Sulbutiamine[63]	Other	4	326	PH; QOL	<>	<>	10
Galanthamine hydrobromide[35]	Other	2	49	PH; PS; QOL	<>	<>	9
Oral NADH[31]	CDC 94	12	26	**QOL**	+	+	12
Growth hormone[34]	CDC 94	12	20	PH	<>	<>	5
SUPPLEMENTS							
Essential fatty acids*[65]	Other	13	63	**LAB; QOL**	+	+	17
Essential fatty acids*[64]	Oxford	13	50	PS; **QOL**	+	<>	16
Magnesium[67]	Australian	6	34	**PH; PS; LAB; QOL**	+	+	15
Liver extract[66]	CDC 88	2	15	PH; PS; QOL	<>	<>	10
General supplements[21]	Other	7	12	**PH**	+	+	6
General supplements[68]	Other	26	42	PH; QOL	<>	<>	10
COMPLEMENTARY/ALTERNATIVE							
Any homeopathic remedy[70]	Oxford	26	104	**PH**; PS	+	<>	8
Any homeopathic remedy[33]	Oxford	52	64	**QOL**	+	+	6
Massage therapy[69]	Other	5	20	**PH; PS; LAB**	+	+	9
Osteopathy[20]	CDC 88 + London (ME)	52	58	**PH; PS; QOL**	+	+	0
OTHER							
Multi-treatment[22]	CDC 94	13	72	**PH; QOL**	+	+	19
Buddy/ mentor[72]	Other	17	12	**PH**; PS; QOL	+	<>	4
Combination[71]	CDC 94	52	71	QOL	+	+	3
Broad based management[73]	Other	26	52	**PS; QOL; PH**	+	+	2

+ 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.

5. DISCUSSION

5.1 Methodological quality of included studies

The overall methodological quality of the included studies was variable. More than half of the studies scored 10 points or more on the validity scale (out of a maximum of 20 points). RCTs scored well on blinding of both participants and investigators, objectivity of outcome assessments and baseline comparability of groups. Controlled trials scored well on objectivity and validity of outcomes.

Many of the outcomes were based on participants' self-assessment, which is subjective rather than objective, but for the outcomes being measured (level of fatigue, mood, etc) an objective assessment would not be possible or appropriate. Studies were classified as 'good' for objectivity of outcome assessment if they used a validated questionnaire to assess outcomes or used other methods considered to be appropriate. For laboratory measurements, such as immunological functioning, and physical outcomes (e.g. treadmill tests) objective measurements using blind assessors had to be used for studies to be classified as 'good'.

Ten of the RCTs used a crossover design. Cross-over studies benefit from the fact that participants in both groups are identical, and so fewer participants are needed in each trial. However it can be difficult to maintain blinding in a crossover trial and validity can also be limited by the effects of one intervention persisting while the other intervention is being evaluated. Two of the controlled trials recruited participants for the intervention group from a different population to the control group, i.e. the intervention group was constructed from people attending specialist CFS clinics and the control group from patient support organisations, or the intervention group was taken from people who had been on a waiting list for considerably longer than the control group. This is not appropriate as the groups are drawn from different populations and may not be comparable in terms of disease severity, and other factors which may affect prognosis and the apparent effect of the intervention.

In some of the RCTs, both the method of randomisation and concealment of allocation were poorly reported. Intention-to-treat analysis was rarely performed, which limits the validity of the findings. This is a particular problem for CFS/ME as some interventions may be poorly tolerated by participants and can lead to withdrawals related to the intervention; the effect of which needs to be considered when assessing whether an intervention is beneficial.

A major flaw in many of the included studies was in the reporting of outcomes. There was significant heterogeneity in the outcome measures used (see next section), and outcomes were often not reported fully. Mean scores on measurement scales were sometimes reported without any measures of variance such as standard deviations or standard errors of the mean. Sometimes mean scores were only reported if the difference between groups was significant. Some studies only reported mean scores for groups where the difference was significant for measurements made at the start of the trial compared to measurements made at the end of the trial. Where authors have reported only within-group differences rather than between-group differences, these have been reported in the results section and in all associated tables.[34,35,69] They were not however considered in the summary results section as it is inappropriate to draw conclusions from data analysed in this way, because the event rate in the control group has not been taken into account.

5.2 Outcomes

Many different outcomes, measured using a variety of different scales were reported in the studies included in this review. It was therefore not appropriate to pool data for interventions investigated in more than one trial. It also makes it difficult to compare the results of the trials in a non-quantitative analysis. Trial authors rarely included detailed information about the scales and measurements used to assess outcomes. Consequently, it is not clear whether a positive result based on one scale to measure (for example) disability is as good as, better, or worse than, a positive result on a different scale. It is also unclear what is represented in clinical terms by the divisions on each of the scales and whether these are similar and how many of these scales or measures have been validated.

Some studies reported on physiological measures including measures of fatty acid concentration, immune outcomes, and other laboratory measures. These outcome measures are difficult to interpret as their relevance to disease status and clinical measures of patient symptoms has not been established. For this reason less emphasis was placed on the results of these outcomes than on the clinical outcomes. In order for a study to be classified as having an overall beneficial effect it had to report a significant improvement in two or more clinical outcome measures compared to the control group, or if only one clinical outcome was reported then they had to show a significant benefit for this outcome.

A few studies measured employment status at baseline, but this was often not reported at the end of the intervention. It could be argued that such an outcome is more relevant to those suffering from CFS/ME than outcomes such as CD4 cell counts, and should be reported more frequently. Outcomes such as 'improvement' where participants were asked to rate themselves as better or worse than they were before the intervention began were frequently reported. However, the person may feel better able to cope with daily activities because they have reduced their expectations of what they should achieve, rather than because they have made any recovery as a result of the intervention. A more objective measure of the effect of any intervention would be whether participants have increased their working hours, returned to work or increased their physical activities.

Across the studies different outcomes have been favoured, possibly as a result of views about the aetiology of the syndrome. Those holding the view that CFS is a different syndrome to ME might prefer outcomes that measure muscle fatigue, time to recovery and pain. Whereas those who hold the view that the term CFS covers all similar syndromes - including ME - might argue that measurements of fatigue or functioning are the most important outcomes. Use of adult oriented scales, such as the Karnofsky Performance Scale, to measure activity in children may not be appropriate. There is a need for standard outcome measures to be used in trials evaluating interventions for CFS/ME so that results can be meaningfully compared across studies. A mix of validated tools for different dimensions or domains is needed to take into consideration the wide and pervasive impact of this illness on many domains. A comprehensive review of outcome measures currently used would be the first step in this process. The outcomes measures identified via the intervention studies included in this review could form the basis of such a review.

5.3 Interventions

The number of different interventions assessed is almost as large as the number of studies included in this review, possibly reflecting the uncertainty in the field over the aetiology of CFS/ME. This is also reflected in the rationale given by the studies for their selection of a specific intervention. Immunological and antiviral, and pharmacological and behavioural interventions were the most frequently investigated.

Detailed information on interventions was not provided in the majority of studies. Studies of pharmacological, immunologic, and antiviral interventions gave the most detailed information. For studies of behavioural therapies information was rarely given about the level of training of those administering the intervention, something which may have more effect on the outcome of these interventions than on the outcomes of pharmacological interventions.

5.4 Nature of participants in included studies and diagnostic criteria

The American CDC criteria (1988) were most frequently used to diagnose people with CFS, followed by the Oxford criteria. Most of the studies included people diagnosed with chronic fatigue syndrome. One study[20] included only participants diagnosed with ME according to the London criteria, and one[21] included only participants diagnosed with ME according to their GPs. Other diagnoses included post viral fatigue syndrome,[65] chronic mononucleosis syndrome,[54] chronic post-infectious fatigue[63], post infectious fatigue syndrome[73] and chronic fatigue immunodeficiency syndrome.[69] One study used a subset of participants diagnosed with CFS who had previously had Epstein Barr virus infection.[56] Another study stated that participants had ME but used the Oxford criteria for diagnosis, which ME support groups claim are the least likely set of diagnostic criteria with which to identify those with ME.[8]

It has been suggested that CFS and ME are two separate conditions. If this is the case then the results of the studies presented in this review may be mostly applicable to patients diagnosed using CFS criteria, as CFS was the most common diagnosis. Although the different sets of criteria for diagnosing CFS vary in stringency, they all include debilitating fatigue as the major symptom, and it is likely that the findings from studies which have used one set of criteria to diagnose CFS can be applied to people diagnosed using other criteria.

5.5 Baseline functioning

Details of baseline functioning were reported by the majority of trials but the information provided varied widely between studies. Nine studies excluded people who were unable to get to the trial centre[20,24,26,28,45,59,60,79] and the results of these studies may not be applicable to people with severe CFS/ME who cannot walk unaided. In those trials which did report baseline functioning, the majority of participants were unable to take part in full time employment. Trials that examined immunological function found reduced function at baseline. It would have been very helpful as regards the generalisability of the trial results if more details had been given of participants' baseline functioning in a standardised way. Some form of classification system which assesses the severity of the illness would be helpful for future trials.

5.6 Drop-outs

Drop-out rates may be important indicators of the acceptability of an intervention. Alternatively, high drop-out rates may indicate that the trial protocol is too rigid to accommodate any but a very specific group of participants, which will again limit the generalisability of the findings. As a way of dealing with drop-outs an intention-to-treat analysis should be conducted. It cannot be assumed that the participants who remain in the trial are representative of participants who have dropped out, for example participants with more severe symptoms may be more likely to leave the trial than those with milder symptoms. An intention-to-treat analysis takes into account participants that have dropped out of the trial, so that the overall effect of the intervention can be evaluated.

An intervention may be effective in treating a disease or condition but may not be acceptable, for example the side effects may be severe or the intervention itself may not be acceptable. Findings based on an analysis which only includes participants that completed the trial may conclude a beneficial effect when in reality very few people would be happy receiving the intervention. This would be better reflected in the results of an intention-to-treat analysis.

Intention-to-treat analyses were conducted in 12 of the studies and so the results of these trials are more likely to be valid.[22,24,25,30,40,44-46,51,52,61,65] The studies of CBT[40] and GET[45,46] with the highest drop-out rates all used an intention-to-treat analysis. However, all the included studies in this review used the 'last observation carried forward' method of intention-to-treat analysis which may give an over-optimistic picture of the effects of the intervention. It is probable that those who drop-out of a trial - rather than remaining the same as when they were last observed in the trial - will either deteriorate or improve. A more robust approach would incorporate a sensitivity analysis which could make two assumptions about drop-outs: the worst case scenario, and the best case scenario. Two separate analyses could be carried out using these substitute values for drop-outs (worst and best) and the true values for the intervention effect are then likely to lie between the results of the two analyses. Such an approach was not used in any of the trials included in this review.

Where drop-out rates are higher in the intervention group than in the control group it may be the case that there is something about the intervention which trial participants find unacceptable. It may be the method or frequency of administration, or adverse effects arising from the intervention may be sufficiently great for participants to discontinue with the intervention. In this review more participants from the intervention than control groups dropped out in studies of the following interventions: CBT, aciclovir, immunoglobulin G, alpha interferon, phenelzine and fluoxetine (both antidepressants), GET plus fluoxetine. For GET and CBT the difference was only seen in one trial and not the others so it is not clear whether it was the GET or the antidepressant fluoxetine which was unacceptable to participants. Fluoxetine was unacceptable to participants in the only other trial in which it was used, as was phenelzine. Some of the immunologic treatments also seem to have been unacceptable to trial participants.

5.7 Duration of follow-up

There is little evidence from the literature as to the appropriate duration and follow-up of interventions used in the management of CFS/ME. However, as chronic fatigue syndrome is, by definition, long term it would seem sensible for trials of interventions for CFS/ME to follow up participants for at least 6-12 months, if not longer. The relapsing nature of the illness suggests that follow-up should continue for an additional 6-12 months (at least) after the intervention period has ended, to confirm whether any improvement persisits for a relevant period of time.

Ten trials treated participants for more than six months[20,24,25,33,40,45,46,53,68,71] and four trials followed up participants for six months or more after the intervention had ended.[24,40,45,49] Three trials[40,45,80] fulfilled both criteria. One trial of CBT followed up participants five years later.[24,41] All the other trials are limited in terms of generalisability about the long term outcome in people with chronic relapsing illness.

5.8 Subgroups

The most commonly investigated subgroup was depressed versus non-depressed participants (3 trials). Other subgroups investigated were HHV-6 infected participants, participants with reduced immune response and participants who had been ill for three years or more. Other important potential subgroups, such as those who are bed or wheelchair bound, have not been studied. Future studies should consider these and other possible subgroups.

In one controlled trial of CBT those who scored higher on the CES-D scale for depression were more likely to respond to the intervention than those with low scores.[29] It is worth noting that this trial was not randomised and that the two other RCTs of this intervention showed no differential response of depressed versus non-

depressed participants.[24,25] In an RCT, of moclobemide, those in the intervention group with reduced immune responses scored the most impressive improvement on the Karnofsky Performance Index.[61]

5.9 Combination therapy

As CFS/ME affects so many different aspects of functioning and symptoms, combined therapies will necessarily be part of clinical interventions, even though they may initially have to be studied individually. Only three trials investigated the combined effects of more than one intervention. One RCT evaluated fluoxetine and graded exercise and found no significant effect of fluoxetine either as the sole treatment or in combination with GET, although a beneficial effect of GET was reported.[46] Fluoxetine showed no beneficial effect in the only other trial in which it was investigated.[58]

The other RCT evaluated the combined effects of leukocyte extract and CBT[26] and found the group receiving both CBT and leukocyte extract showed a significantly greater improvement in general health than the other intervention groups. No significant differences were found for any of the other outcomes investigated. Given that most people with CFS/ME have tried a variety of interventions, more RCTs of combined therapy would be helpful.

The third RCT investigated the effects of treating specific symptoms of CFS. This study found a beneficial effect of treatment in those in the intervention group compared to the control group.[22]

5.10 Children

One RCT of immunoglobulin G including only young people aged less than 18[55] reported an overall beneficial effect on two measures of function. A second RCT of immunoglobulin G including both adults and children (although no-one under the age of 16 was included[51]) reported an overall beneficial effect on measures of symptoms and function. When considering immunoglobulin G as a possible treatment for CFS/ME the fact that it is a blood product with the known risks attached to this should be taken into consideration.

No other evaluations of interventions conducted in children were identified. Other interventions in children with CFS/ME need to be evaluated and should be a priority for future research.

6. CONCLUSIONS

- A total of 46 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 cognitive behavioural therapy 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.
- Immunoglobulin G is the only intervention which has 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.
- Future research needs to combine scientific rigour with patient acceptability and good quality research is needed to evaluate the effectiveness of pacing, ideally in comparison to CBT and GET. The large number of outcome measures used makes standardisation of outcomes a priority for future research.

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APPENDIX A: SUMMARY OF LITERATURE SEARCHING FOR CFS/ME

Original MEDLINE search strategy as below:
SilverPlatterASCII 3.0WINNSelected Databases
"Fatigue-Syndrome-Chronic"/ all subheadings
chronic fatigue syndrome in ti,ab
myalgic encephalomyelitis in ti,ab
#1 or #2 or #3
exact{BIOGRAPHY} in PT
exact{DUPLICATE-PUBLICATION} in PT
exact{HISTORICAL-ARTICLE} in PT
exact{INTERVIEW} in PT
exact{RETRACTION-OF-PUBLICATION} in PT
exact{CASES} in PT
#5 or #6 or #7 or #8 or #9 or #10
#4 not #11

This strategy was run on the following databases:

MEDLINE	1966- Jul 1999
EMBASE	1980- Jun 1999
PsycLIT	1887-Jun 1999
CCCTR	2002/2

In the next phase of searching these databases were searched:

Social Science Citation Index	1981-Aug 2001
Science Citation Index	1981-Aug 2001
ASSIA	1987-1999
Index to Scientific & Technical Proceedings	1982-1999
PASCAL	1973-Aug 2001
MANTIS	1880-Apr 2001
JICST	1985-Jul 2001
Conference Proceedings Index	1973-Jul 2001
AMED	1984-Sep 2001

to retrieve additional records.

The strategy was then revised to include additional terms suggested by the expert panel:
SilverPlatterASCII 3.0WINNSelected Databases
"Fatigue-Syndrome-Chronic"/ all subheadings
chronic fatigue syndrome in ti,ab
myalgic encephalomyelitis in ti,ab
#1 or #2 or #3
exact{BIOGRAPHY} in PT
exact{DUPLICATE-PUBLICATION} in PT
exact{HISTORICAL-ARTICLE} in PT
exact{INTERVIEW} in PT
exact{RETRACTION-OF-PUBLICATION} in PT
exact{CASES} in PT
#5 or #6 or #7 or #8 or #9 or #10
#4 not #11
akureyri disease
chronic epstein barr virus
cfids
chronic fatigue and immune dysfunction syndrome
chronic mononucleosis
chronic mononucleosis syndrome
chronic mononucleosis like syndrome
chronic mononucleosis-like syndrome
effort syndrome
iceland* disease
low natural killer cell syndrome

neuromyasthenia
post viral fatigue syndrome
postviral fatigue syndrome
post-viral fatigue syndrome
post viral syndrome
postviral syndrome
post-viral syndrome
post infectious fatigue
postinfectious fatigue
post-infectious fatigue
chronic postviral fatigue syndrome
chronic post viral fatigue syndrome
chronic post-viral fatigue syndrome
raggedy ann* sysndrome*
raggedy anne
royal free disease*
royal free epidemic*
royal free hospital disease*
tapanui disease*
yuppie flu
yuppy flu
chronic infectious mononucleosis like syndrome
chronic infectious mononucleosis-like syndrome
"Fibromyalgia"/ all subheadings
#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35
#36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47
#48 or #49 or #50
#51 not #12

This strategy was run on :

MEDLINE	1966-Jul 2001
EMBASE	1980-Jul 2001
PsycINFO	1887-Aug 2001

to retrieve additional records.

The revised strategy was also run on these additional databases:

ERIC	1966-Aug 2001
NTIS	1964-Aug 2001
Inside Conferences	1993- Aug 2001
Life Sciences	1982- May 2001
CAB Health	1983- Jul 2001
BIOSIS	1969- Aug 2001
TGG Health & Wellness	1976- Jun 2001

Update searches of all the above databases, from the date on which they had previously been searched, were carried out in February 2002.

1. Behavioural

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Deale (1997)[24,41] **Study design:** RCT	**Intervention:** CBT **Number of participants in each arm:** 30 in each group **Study duration:** 26 weeks **Length of follow-up**: 26 weeks **Purpose of intervention:** To compare CBT for CFS with relaxation. **Intervention details:** **Intervention**: 13 sessions over 4-6 months of CBT (graded activity and cognitive restructuring). **Control:** 13 sessions over 4-6 months of relaxation. Patients were seen individually.	**Sub-groups:** None stated **Number:** 60 **Age:** Mean 31 (sd=9) in CBT group, mean 38 (sd=11) in relaxation group **Sex:** 70% female in CBT group, 67% in relaxation group **Concurrent diagnoses:** 5 patients had additional diagnoses of dysthymia, 9 had major depression, 3 had anxiety disorders, and 6 had both depression and anxiety disorders **Duration of fatigue:** Mean 3.4 (sd=2.1) years in CBT group, mean 4.6 (sd=3.3) years in relxation group **Further details:** 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 **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.	**Diagnostic criteria:** Oxford **Details:** Also met CDC 94 criteria **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 attend all treatment sessions	**Drop-outs:** 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 reason & 2 found relaxation exercises overly tiring. **Adverse effects:** None reported

Results: at 6 month follow up.[24] Results presented as mean (sd)

Outcome 1	Outcome 2:	Outcome 3:	Outcome 4:
Outcome: Improvement in physical functioning. Increase of 50 or more from pre-treatment to 6 months follow-up or end score of 83+ on physical functioning scale of General Health survey **Final treatment group**: 70% excluding drop-outs, 63% including drop-outs **Final 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:** Physical functioning scale of Medical Outcomes Study Short-Form General Health Survey **Baseline treatment group**: 25.5 (18.9) **Baseline control group**: 27.8 (27.1) **Final treatment group**: 71.6 (28.0) **Final control group**: 38.4 (26.9) **Comments**: p >0.50	**Outcome:** Work and Social adjustment scale **Baseline treatment group**: 6.0 (1.2) **Baseline control group**: 6.1 (1.3) **Final treatment group**: 3.3 (2.2) **Final control group:** 5.4 (1.8) **Comments:** p <0.001	**Outcome:** Long-term goals rating (mean of two) **Baseline treatment group**: 7.0 (0.7) **Baseline control group**: 6.8 (1.0) **Final treatment group**: 2.9 (1.9) **Final control group**: 5.9 (1.8) **Comments:** p <0.001

Outcome 5:	Outcome 6:	Outcome 7:	Outcome 8:	Outcome 9:
Outcome: Fatigue problem rating **Baseline treatment group:** 7.0 (0.9) **Baseline control group**: 6.3 (1.2) **Final treatment group:** 3.4 (2.2) **Final control group**: 5.5 (1.9) **Comments**: p <0.001	**Outcome:** Fatigue questionnaire **Baseline treatment group**: 10.2 (1.3) **Baseline control group**: 9.5 (2.6) **Final treatment group**: 4.1 (4.0) **Final control group**: 7.2 (4.0) **Comments**: p <0.01	**Outcome:** Depression: BDI score **Baseline treatment group:** 14.5 (7.2) **Baseline control group**: 14.2 (6.1) **Final treatment group**: 10.1 (6.9) **Final control group:** 12.3 (8.5) **Comments**: p >0.30	**Outcome:** General health questionnaire **Baseline treatment group:** 6.2 (3.6) **Baseline control group**: 6.0 (4.2) **Final treatment group**: 3.4 (3.7) **Final control group:** 4.3 (3.9) **Comments:** p>0.70	**Outcome:** Global improvement self rating, proportion better or much better **Final treatment group:** 70% **Final control group**: 31% **Comments**: p <0.01

Outcome 10:	Outcome 11:	Outcome 12:	Outcome 13:	Outcome 14:
Outcome: Patient assessment of usefulness of treatment **Final treatment group:** 96% useful or very useful **Final control group:** 85% useful or very useful **Comments:** p >0.10	**Outcome:** Functioning: Blinded assessor rating of physical functioning at 3 month follow-up **Final treatment group:** 80% better or much better **Final control group:** 26% better or much better **Comments:** p <0.001	**Outcome:** Fatigue: Blinded assessor rating of fatigue at 3 month follow-up **Final treatment group:** 72% better or much better **Final control group:** 17% better or much better **Comments:** p <0.001	**Outcome:** Patient satisfaction with treatment outcome **Final treatment group**: 78% satisfied or very satisfied **Final control group:** 50% satisfied or very satisfied **Comments:** p <0.05	**Outcome:** Proportion employed **Final treatment group:** 56% **Final control group**: 39% **Comments:** p=0.05 Mean hours worked per week **Final treatment group:** 19.9 (sd=15.8) **Final control group:** 9.9 (sd=15.8) **Comments**: p<0.05

Outcome 15
Logistic regression analysis of predictors of global improvement indicated 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.

Follow up at 5 years: 25 CBT patients and 28 relaxation patients [41]			
Outcome 1	**Outcome 2:**	**Outcome 3:**	**Outcome 4:**
Outcome: Global improvement: Proportion much or very much better **Final treatment group**: 64% **Final control group**: 36% **Comments**: p<0.05	**Outcome:** MOS physical functioning scale, proportion with score>83 **Final treatment group**: 48% **Final control group**: 32% **Comments**: p=0.272	**Outcome:** Fatigue questionnaire, proportion with score <4 **Baseline treatment group**: 0% **Baseline control group**: 7% **Final treatment group:** 32% **Final control group**: 25% **Comments**: p=0.571	**Outcome:** General health: GHQ score < 4 **Baseline treatment group**: 30% **Baseline control group**: 33% **Final treatment group**: 48% **Final control group:** 54% **Comments**: p=0.579
Outcome 5:	**Outcome 6:**	**Outcome 7:**	**Outcome 8:**
Outcome: Symptoms: Course of symptoms over time **Final treatment group**: absent: 68%, fluctuated markedly 28%, worsened or consistently severe 4% **Final control group:** Steadily improved or absent: 43%, fluctuated markedly 36%, worsened or consistently severe 21% **Comments:** p=0.05	**Outcome:** Relapses **Final treatment group:** None:36%, 1/2:12%, 3/4 20%, 5+: 32% **Final control group:** None:7%, 1/2:11%, 3/4: 21%, 5+: 61% **Comments**: p=0.05	**Outcome:** Proportion that no longer meet UK CFS criteria **Final treatment group**: 52% **Final control group**: 39% **Comments**: p=0.415	**Outcome** Proportion completely recovered **Final treatment group:** 24% **Final control group**: 5% **Comments**: p=0.05

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (Year) Friedberg (1994)[29] **Study design:** Controlled trial	**Intervention:** Modified CBT **Number of subjects in each arm:** 22 **Study duration:** 9 weeks **Length of follow-up**: 9 weeks **Purpose of intervention:** To determine if treatment related changes differ from naturally occurring symptom fluctuations. **Intervention details:** **Intervention:** 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 prescription. **Control:** No treatment.	**Sub-groups:** High and low depression **Number:** 44 **Age:** mean 35.7 in treatment group, 39.7 in control **Sex:** 95.5% women in treatment group, 67.2 in control (p<0.02) **Concurrent diagnoses:** 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. **Duration of fatigue:** 32.5 months in treatment group, 74 in control **Further details:** 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 **Baseline functioning:** Both groups had significantly elevated fatigue severity scores compared to depression control group (p<0.002)	**Diagnostic criteria** CDC (1988) **Details:** Not stated **Inclusion criteria:** Not stated	**Drop-outs:** 2 patients who did not want CBT refused to participate in control group. **Adverse effe cts:** Not stated

Results				
General comments: Subgroup (depression): 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)	**Outcome 1** **Outcome** Depression symptom score. CES-D scale, 20 item self-report scale scored from 0-60 **Final treatment group:** lower than pre-treatment score, p=0.058 **Final control group**: No significant difference **Depression subgroup:** Significant reduction (t=4.60, df=10, p<0.001)	**Outcome 2:** **Outcome** Stress symptom score: Brief symptom inventory, 53 item self-report scale **Final treatment group:** No significant difference **Final control group:** No significant difference **Depression subgroup:** Significant reduction (t=3.20, df=10, p<0.01)	**Outcome 3:** **Outcome** Fatigue severity score, 9 items on 7 point Likert scale **Final treatment group:** No significant difference **Final control group:** No significant difference **Depression subgroup:** Significant reduction (t=2.70, df=10, p<0.05)	Outcome 4: **Outcome** Fatigue related cognition scale, 14 item self-report scale developed by one of trial authors **Final treatment group:** Significant reduction, p<0.023 **Final control group:** No significant difference **Depression subgroup:** Significant reduction (t=2.40, df=10, p<0.04)

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (Year) Fulcher (1997)[44] **Study design:** RCT	**Intervention:** GET **Number of participants in each arm:** 33 in each group **Study duration:** 12 weeks. **Length of follow-up:** 12 weeks. **Purpose of intervention:** To test the efficacy of graded aerobic exercise programme in chronic fatigue syndrome and to assess physiological, functional and symptomatic changes. **Intervention details:** **Intervention:** Graded aerobic exercise. Participants attended for supervised treatment and given next week's exercise prescription, home exercise was prescribed for 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, participants 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 participants complained of increased fatigue were advised to continue with same level of exercise for extra week and increase when fatigue had lessened. **Control:** Flexibility training. Participants were taught stretching routine and relaxation techniques building up to longer sessions like exercise group, specifically told to avoid doing any extra physical activities.	**Sub-groups:** None stated **Number:** 66 **Age:** mean = 37.2 (sd=10.7) **Sex:** 74% women **Concurrent diagnoses:** Not stated **Duration of fatigue:** Median duration = 2.7 years (range 0.6 - 19 years) **Further details:** Mean BMI= 23.8 (sd=4.6). Twenty participants were taking full dose anti-depressants, 10 were taking low dose tricyclic antidepressants as hypnotics, 44 participants blamed viruses for their illnesses **Baseline functioning:** not stated	**Diagnostic criteria:** Oxford **Details:** Physical screening investigations were carried out or, when appropriate, full recent records were obtained from referring doctors to ensure other disorders had been discounted. **Exclusion criteria**: Participants 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)	**Drop-outs** 7 participants dropped out: 4 in exercise group and 3 in control, 1 from each group dropped out as said treatment made them worse

Results

Outcome 1	Outcome 2:	Outcome 3:
Outcome General health: CGHI 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) **Final treatment group:** 1: 9 (31%); 2:7 (24%); 3:11 (38%); 41: (3%); 5: 1 (3%); 6:0; 7:0 **Final 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 participants improved with exercise and 9/33 improved with flexibility treatment (chi2=4.06, p=0.04)	**Outcome:** Physiological variables **Comments**: Exercise group showed significant increase in: peak oxygen consumption and maximum ventilation but not in any other physiological measures compared to control.	**Outcome:** Symptom measure: Various symptomatic and functional measures **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

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (Year) Lloyd (1993)[26] **Study design:** RCT	**Intervention:** Immunologic **Number of participants in each arm:** CBT+DLE: 20; DLE+ clinic: 26; Placebo + CBT: 21; Placebo + clinic: 23 **Study duration**: 8 weeks **Length of follow-up:** 7 months **Purpose of intervention:** To evaluate the potential benefit of immunologic therapy with dialyzable leukocyte extract and/or CBT in patients with chronic fatigue syndrome **Intervention details:** **Intervention:** 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. **Control:** placebo (lyophilized normal saline). **Intervention:** CBT treatment as outpatients, 6 biweekly sessions lasting 30-60mins, aimed at re-establishing previous physical and social activity. **Control:** Clinic control. Patients randomised to either CBT + DLE, DLE + clinic, CBT + placebo or placebo + clinic	**Sub-groups:** None stated **Number:** 90 **Age:** 39.6 (sd=12.3, 17-65 years) **Sex:** 68 F, 22 M **Concurrent diagnoses:** Around 75% had major depression **Duration of fatigue:** mean 5.5 years, range 1-28 years **Further details:** Not stated **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	**Diagnostic criteria:** Lloyd/ Australia **Details:** 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 Inclusion criteria Patients capable of bringing themselves to the clinic at biweekly intervals for 4 month period. Had not received previous immunologic therapy	**Drop-outs:** 2 patients withdrew during the trial, 1 in DLE + clinic group and 1 in placebo + clinic group, both were excluded from the analysis **Adverse effects:** 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 Global well-being measured using 10 item visual analogue scales from which a cumulative score was calculated **Baseline:** **Placebo + CBT**: 406 **DLE + clinic:** 435 **DLE + CBT:** 458 **Placebo + clinic**: 445 **Final:** **Placebo + CBT**: 469 **DLE + clinic:** 498 **DLE + CBT**: 596 **Placebo + clinic:** 477 **Comments:** Significantly greater improvement in DLE + CBT group compared to other groups (F=1.49, p<0.05)	**Outcome** Physical capacity assessed by standardised diary of daily activities, measured as number of non-sedentary hours **Baseline:** **Placebo + CBT**: 5.5; **DLE + clinic**: 4.7 **DLE + CBT**: 4.3 **Placebo + clinic:** 5.4 **Final:** **Placebo + CBT**: 5.2 **DLE + clinic**: 4.9 **DLE + CBT**: 4.9 **Placebo + clinic:** 5.2 **Comments**: No significant difference between groups (F=1.18, p>0.05)	**Outcome** Functional status: Patients rated by one investigator on Karnofsky performance scale **Baseline:** **Placebo + CBT**: 71.2 **DLE + clinic:** 72.2 **DLE + CBT**: 71.5 **Placebo + clinic:** 70.5 **Final:** **Placebo + CBT**: 72.1 **DLE + clinic**: 74.8 **DLE + CBT:** 80.0 **Placebo + clinic:** 73.4 **Comments**: No significant difference between groups (F=1.11, p>0.05)	**Outcome** Fatigue assessed using Profile of mood states questionnaire **Baseline:** **Placebo + CBT**: 22.8 **DLE + clinic**: 22.0 **DLE + CBT**:21.1 **Placebo + clinic:** 20.8, **Final:** **Placebo + CBT**: 16.8 **DLE + clinic:** 16.9 **DLE + CBT**: 17.8 **Placebo + clinic**: 17.3, **Comments**: No significant difference between groups (F=1.15, p>0.05)
Outcome 5:	**Outcome 6:**	**Outcome 7:**	
Outcome Confusion assessed using Profile of mood states questionnaire **Baseline** : **Placebo + CBT**: 14.8 **DLE + clinic**: 12.3 **DLE + CBT:** 14.8 **Placebo + clinic:** 13.7 **Final:** **Placebo + CBT**: 12.8 **DLE + clinic:** 10.8 **DLE + CBT:** 14.4 **Placebo + clinic:** 11.6 **Comments:** F=0.39, p>0.05	**Outcome** Depression assessed using Profile of mood states questionnaire **Baseline:** **Placebo + CBT**: 18.2 **DLE + clinic**: 15.1 **DLE + CBT**: 14.3 **Placebo + clinic:** 17.1 **Final:** **Placebo + CBT:** 15.9 **DLE + clinic:** 10.1 **DLE + CBT:** 12.9 **Placebo + clinic:** 14.6 **Comments:** F=0.70, p>0.05	**Outcome** Immune outcomes CD4, CD8 cell counts and DTH skin response **Comments:** No significant difference between treatment groups (p>0.05)	

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Powell (2000)[45] **Study design:** RCT	**Intervention**: Graded exercise and discussion of symptoms **Number of subjects in each arm:** 34 in control, 37 in group 2, 39 in group 3, 38 in group 4 **Study duration:** 26 weeks **Length of follow-up:** 52 weeks **Purpose of intervention:** To assess the efficacy of an educational intervention explaining symptoms to encourage graded exercise in chronic fatigue syndrome patients, using different methods of delivery **Intervention details:** *Group 1:* standardised medical care, given pack without medical explanation but which encouraged regular activity and positive thinking. Intervention: *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.	**Sub-groups:** None stated **Number:** 148 **Age (mean):** *Group 1 & 2:* 34 , *Group 3 & 4:* 32 **Sex (% female):** *Group 1:* 24; *Group 2:* 28, *Group 3:*33; *Group 4:* 31 **Concurrent diagnoses:** Not stated **Duration of fatigue:** Mean (months): *Group 1: 48.6; Group 2:* 51.2; *Group 3:* 51.5 G*roup 4*: 55.0 **Further details:** Recruited from consecutive referrals to CFS and infectious diseases clinic. Randomisation was stratified by scores on HAD depression scale **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	**Diagnostic criteria:** Oxford **Details:** Not stated 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	**Drop-outs:** 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 effects:** Not stated

Results

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

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Prins (2001)[40] **Study design:** RCT	**Intervention:** CBT **Study duration**: 8 months **Length of follow-up:** 14 months **Number of subjects in each arm:** 92 in CBT group , 90 in support group, 88 in no treatment **Purpose of intervention:** To investigate the effects of CBT in the treatment of CFS **Intervention details:** **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-centred. **Natural course (control):** no interventions offered and no further requirements, patients could attend other examinations or treatments	**Sub-groups:** None stated **Number:** 270 **Age:** Mean (sd): CBT 36.2 (9.4), Support: 37.1 (10.6), control: 36.7 (10.3) **Sex:** 19-24% female **Concurrent diagnoses:** Not stated **Duration of fatigue:** Mean (sd) years: CBT: 4.9 (4.8), support: 6.6 (6.4), control: 5.3 (5.4) **Further details:** Recruited from outpatient clinics at departments of internal medicine **Baseline functioning:** Not stated	**Diagnostic criteria:** CDC (1994) **Details:** Did not have to meet 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 **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 hours travelling time of the 3 centres. Patients in CFS group could not undergo further medical examinations of other treatments for CFS during study period	**Drop-outs:** 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 effects:** Not stated

Results

General comments	Outcome 1	Outcome 2:	Outcome 3:	Outcome 4:
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)	**Outcome** Fatigue: CIS fatigue score. Results presented as change from baseline to follow-up and mean (SE). Results presented on ITT basis **CBT**: -11.8 (1.4) **Support:** -6.5 (1.2) **Control**: -6.6 (1.0) **Comments:** P<0.001 for differences between groups	**Outcome** Psychological well-being: Measured on SCL90. Results presented as mean(sd). Results presented on ITT basis **Baseline CBT**: 170 (38.5) **Baseline support**: 169 (41.5) **Baseline control**: 166 (36.0) **Final CBT:** 138 (35.1) **Final support**: 153 (33.9) **Final control:** 147 (32.8) **Comments:** F=4.96, p=0.001 for differences between groups (group x time)	**Outcome** Quality of life: Measured on EuroQol scale. Results presented on ITT basis **Baseline CBT**: 46 (17) **Baseline support**: 43 (16) **Baseline control**: 40(14) **Final CBT:** 57 (22) **Final support**: 44 (19) **Final control**: 49 (19) **Comments:** F=3.92, p=0.004 for differences between groups (group x time)	**Outcome** Work: Number of hours at work during 12 days. Results presented on ITT basis **Baseline CBT**: 16.3 (21.1) **Baseline support:** 12.8 (19.1) **Baseline control:** 13.5 (18.6) **Final CBT:** 23.1 (28.1) **Final support:** 11.0 (15.4) **Final 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 Fatigue: Proportion of participants with a clinically significant improvement in fatigue on CIS fatigue score **CBT:** 20/58=35% **Support:** 8/62=13% **Control:** 13/76=17% **Comments:** p=0.009 comparing CBT to support and 0.026 comparing CBT to control	**Outcome** Functional: Proportion of participants wth a clinically significant improvement in Karnofsky score **CBT:** 28/57=49% **Support**: 12/62=19% **Control:** 17/75=23% **Comments:** p=0.001 comparing CBT to support and 0.001 comparing CBT to control	**Outcome** Improvement: Proportion of participants with self-rated improvement **CBT:** 29/58=50% **Support:** 9/62=15% **Control:** 24/76=32% **Comments:** p<0.001 comparing CBT to support and 0.034 comparing CBT to control	**Outcome** Functional Impairment: Measured using Sickness Impact Profile. Results presented as change from baseline to follow-up and mean (SE). Results presented on ITT basis **CBT:** -590 (80) **Support:** -320 (80) **Control:** -390 (80) **Comments:** Measured using Sickness Impact Profile. Results presented as change from baseline to follow-up and mean (SE). Results presented on ITT basis

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Sharpe (1998)[25] **Study design:** RCT	**Intervention:** CBT **Number of participants in each arm:** 30 **Study duration**: 4 months **Length of follow-up**: 12 months **Purpose of intervention:** To evaluate the acceptability and efficacy of adding CBT to the medical care of patients presenting with CFS **Intervention details:** **Intervention:** CBT group given 16 1 hour individual sessions over 4 months, plus medical care. **Control:** Patients with medical care alone told to increase their level of activity as much as they felt able, and reassured that there was no organic cause for their illness.	**Sub-groups:** Not stated **Number:** 60 **Age:** 18-60 **Sex:** M:F: 12:18 in CBT group, 7:23 in standard care group **Concurrent diagnoses:** Not stated **Duration of fatigue:** In months: Median 17 in CBT group, 20 in control, mean 33.6 in CBT, 29.7 in control, range 6-91 months **Further details:** 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 **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.	**Diagnostic criteria:** Oxford **Details:** Also fulfilled CDC (94) criteria **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 history of bipolar affective disorder, schizophrenia, or substance misuse or were at significant risk of suicide or in need or urgent psychiatric treatment	**Drop-outs:** Complete data not available for one participant, did not attend 12 month follow-up. Phone call indicated no substantial change since previous evaluation, 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 effects:** 2 participants in CBT group attributed deterioration in symptoms to treatment

Results: at 12 month follow-up

Outcome 1	Outcome 2:	Outcome 3:	Outcome 4:
Outcome Proportion of participants with normal functioning at 12 months follow-up (achieved Karnofsky score of 80 or more) **Final treatment group:** 73% **Final control group:** 27% **Comments:** Difference in proportion = 47% (95% CI: 24-69), p<0.001, difference increased over time	**Outcome** Functioning: proportion of participants with at least 10 point improvement on Karnofsky scale at 12 months follow-up **Final treatment group:** 73% **Final control group:** 23% **Comments:** Difference in proportion = 50% (95% CI: 28-72), p<0.001, difference increased over time	**Outcome** Improvement in work status **Final treatment group**: 63% **Final control group:** 20%	**Outcome** Global improvement: proportion of participants reporting much improved or very much improved, or worse or very much worse, measured on CGI scale (7 point patient rated scale) **Final treatment group:** Improved: 60%, Deteriorated: 13% **Final control group:** Improved: 23%, Deteriorated: 10%
Outcome 5:	**Outcome 6:**	**Outcome 7:**	**Outcome 8:**
Outcome Illness beliefs: Proportion of participants reporting reduction in strength of illness beliefs, measured on Likert type scales **Final treatment group:** Illness mainly physical:33%, cause is a virus, 48%, illness is ME 17%, avoidance of exercise 60% **Final 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), except for the belief that illness is ME	**Outcome** Percentage interference with activities **Baseline treatment group:** 65 % **Baseline control group**: 64 % **Final treatment group**: 50 % **Final control group:** 37 % **Comments:** Difference in change between the groups = 14(95% CI: 3 to 25), p<0.05	**Outcome** Number of days in bed per week **Baseline treatment group**: 3.3 **Baseline control group**: 1.6 **Final treatment group**: 0.9 **Final control group**: 2.0 **Comments:** Difference in change between the groups = 2.8(95% CI: 1.7 to 4.0), p<0.05	**Outcome** Exercise, distance walked in 6 minutes (m) **Baseline treatment group**: 437 **Baseline control group**: 435 **Final treatment group**: 481 **Final control group**: 424 **Comments:** Difference in change between the groups = 55(95% CI: 17 to 94), p<0.05
Outcome 9:	**Outcome 10:**	**Outcome 11:**	
Outcome Fatigue severity, graded 0-10 **Baseline treatment group**: 7.8 **Baseline control group**: 7.9 **Final treatment group**: 4.3 **Final control group**: 6.3 **Comments**: Difference in change between the groups = 1.9(95% CI: 0.5 to 3.3), p<0.05	**Outcome** Anxiety, measured on hospital anxiety and depression scale **Baseline treatment group**: 6.3 **Baseline control group**: 8.4 **Final treatment group**: 4.4 **Final control group**: 6.8 **Comments**: Difference in change between the groups = 0.3(95% CI: -1.6 to 2.2), p>0.05	**Outcome** Depression, measured on hospital anxiety and depression scale **Baseline treatment group**: 6.7 **Baseline control group**: 6.8 **Final treatment group**: 3.6 **Final control group**: 5.8 **Comments**: Difference in change between the groups = 2.0 (95% CI: 0.0 to 4.1), p<0.06	

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Wearden (1998)[46] **Study design:** RCT	**Intervention:** GET & fluoxetine **Number of participants in each arm:** GET+F 33; GET+P 34; ExP+F 35; ExP+P 34 **Study duration:** 26 weeks **Length of follow-up**: 26 weeks **Purpose of intervention:** To assess the efficacy and acceptability of GET and fluoxetine for participants with chronic fatigue syndrome. **Intervention details:** **Interventions** : 1. Fixed daily dose 20mg fluoxetine plus graded exercise (n=33). 2. Graded exercise and placebo drug (n=34). 3. Exercise control (activity diaries) and fluoxetine (n=35). **Control:** Exercise control and placebo drug (n=34). Placebo controlled and controlled for the amount of therapist contact. Treatment by physiotherapist on 8 occasions over 6 months. Graded exercise: participants 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 participant'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: participants 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:** 136 **Age:** mean 38.7 (10.8) **Sex:** 97 F 39 M **Concurrent diagnoses:** none stated **Duration of fatigue:** Median: 28.0 (39.5) months **Further details:** 114 had changed their occupation. 35 were members of a self-help group. **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.	**Diagnostic criteria:** Oxford **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.	**Drop-outs:** 22 dropped out by 3 months and 40 by 6 months. More drop-outs in exercise vs non-exercise groups (25/68 vs 15/69, p<0.05). No sig difference in drop-out rates fluoxetine vs placebo (24/68 vs 16/69). 11 dropped out due to side effects (9 Fluoxetine, 2 Placebo), 16 due to lack of efficacy (which groups not stated) and 13 for other reasons or no reason. Drop-outs 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 effects:** not stated: 11 dropped out due to adverse effects

Results

General comments	Outcome 1	Outcome 2:	Outcome 3:	Outcome 4:
General comments: 21 drop-outs 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.	**Outcome:** Fatigue Chalder's 14 item fatigue scale, self-rated questionnaire. Primary outcome = change in score and % of participants scoring below case level on the fatigue scale. **Baseline treatment 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 control group:** ExP+P 34.0(32.3 to 35.7) **Final treatment 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) **Final control group:** ExP+P -2.7(-5.4 to 0.01) **Comments:** there were trends for exercise to improve fatigue scale scores at week 12 (mean change 2.1(-0.6 to 4.8, p=0.13) and at week 26 (mean change 2.9(-0.2 to 6.1, p=0.07). Fluoxetine had no effect on fatigue scale at week 12 or wk 26. At the beginning of the study no participants 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.	**Outcome** 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. **Comments:** No significant changes on any MOS scale. Values not reported.	**Outcome** Depression: Hospital anxiety and depression scales (HAD). Secondary outcome = change in score. **Baseline treatment group:** Ex+F 9.4(3.6), Ex+P 8.5(2.9). ExP+F 9.1(4.2) **Baseline control group:** ExP+P 8.1(3.3) **Final treatment 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) **Final 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** Physical: functional work capacity. Calculated as mL of oxygen consumed in the final minute of exercise per kg body weight. **Baseline treatment group:** Ex+F 23.1(9.3); Ex+P 19.9(6.5); ExP+F 22.7(8.7) **Baseline control group:** ExP+P 26.0(9.9) **Final treatment 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) **Final 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.

2. Immunological

Details of Lloyd (1993)[26] CBT/ immunological study are presented, under 'behavioural'.

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Andersson (1998)[27] **Study design:** Controlled trial	**Intervention:** Staphylococcus toxoid vaccine **Number of participants in each arm:** 14 **Study duration:** 12 weeks **Length of follow-up**: 12 weeks **Purpose of intervention:** To investigate the effect of prolonged treatment with staphylococcus toxoid on the symptomatology of CFS **Intervention details:** **Intervention:** Vaccine given at increasing dose of 0.01, 0.05, 0.1, 0.2, 0.5 and 1.0 ml of fully potent vaccine. **Control:** placebo (sterile water injection). Each dose given twice with one injection per week. Injection given subcutaneously in gluteal region by a nurse.	**Number:** 28 **Age**: 33-64 (mean 47, sd=7.3) **Sex:** All women **Concurrent diagnoses:** None stated **Duration of fatigue:** 5-37 years, mean = 12.9 years **Further details:** All had history of repeated infections and ongoing mild infections. All had been certified sick for at least 6 months **Baseline functioning:** No significant differences between 2 groups prior to treatment in any of the laboratory tests or psychometric variables	**Diagnostic criteria:** CDC (1994) **Details:** Participants had to meet criteria for CFS outlined by CDC and criteria for Fibromyalgia outlined by the American College of Rheumatology. **Inclusion criteria:** Participants had been granted a sickness pension or had been on the sick list, full-time or part-time, for at least six months	**Drop-outs:** Four participants 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 effects:** Not stated

Results

Outcome 1:	Outcome 2:	Outcome 3:
Outcome Depression Zung'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) **Baseline treatment group:** 39.5 (range 38-48)% **Baseline control group:** 47 (range 45-50)% **Final treatment group:** 38 (range 37-41)%, decrease was not significant **Final control group:** 39 (36-44)%, p-value for change from baseline <0.05 **Comments:** No significant intergroup differences	**Outcome** Comprehensive psychopathological rating scale (CPRS), 15 reported and observed items on 7 scale steps from 0 (normal) to 6 (maximum severity) **Baseline treatment group:** CPRS fatigue score: 5 (range 4-5) CPRS pain score: 5 (range 4-5) **Baseline control group:** CPRS fatigue score: 5 (range 4-5). CPRS pain score 4(range 4-5) **Final treatment group**: CPRS fatigue score: 3 (range 2-4), p<0.01 for change CPRS pain score: 4 (range 4-4), p<0.01 **Final 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** Clinical global improvement rated as whether or not due to treatment **Final treatment 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) **Final control group:** 3/11 minimally improved, remaining 8 unchanged
Outcome 4:	**Outcome 5:**	**Outcome 6:**
Outcome Pain Momentarily perceived pain measured using visual analogue scale (1-10), varying from no pain to worst pain imaginable. (median values presented) **Baseline treatment group:** 6.5 (95% CI: 3.5-6.5) **Baseline control group:** 6.5 (95% CI: 5.0-6.5) **Final treatment group:** 4.1 (95% CI: 2.8-5.0) **Final 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** Pain Average pain in last week measured using visual analogue scale (1-10), varying from no pain to worst pain imaginable (median values presented). **Baseline treatment group**: 6.0 (95% CI: 4.9-7.2) **Baseline control group:** 6.5 (95% CI: 5.2-6.5) **Final treatment group:** 4.2 (95% CI:3.0-6.0), p-value for change from baseline >0.05 **Final 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 assessment differed between the 2 groups	**Outcome** Pain Pressure pain threshold determined with hand-held electronic pressure algometer **Baseline treatment group**: 20 kPa (95% CI:1-56) **Baseline control group**: 32 kPa (95% CI:5-152) **Final treatment group**: 47 kPa (95% CI:14-124) p-value for change >0.05 **Final control group**: 76 kPa (95% CI:11-129) p-value for change >0.05

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) DuBois (1986)[54] **Study design:** RCT	**Intervention:** Gamma Globulin **Number of participants in each arm:** 76 gamma globulin and 63 placebo injections, 19 participants **Study duration:** 4 months **Length of follow-up:** 4 months **Purpose of intervention:** To assess the efficacy of gamma globulin in participants with chronic mononucleosis syndrome **Intervention details:** **Intervention:** Intramuscular gamma globulin at a dosage of 0.13 cc per kilogram. **Control:** Placebo control was bacteriostatic water for injection, kept refrigerated at same temperature as the gamma globulin. Doses were divided in half for injection into each buttock. Participants were allowed to determine the intervals of their injections as long as it was greater than one week. Study design allowed for cross-over so that each participant could receive either injection independent of previous injections. Study continued for 4 months. No participant received >10 injections	**Sub-groups:** None stated **Number:** 19, 139 courses **Age:** Not stated **Sex:** Not stated **Concurrent diagnoses:** Not stated **Duration of fatigue:** Not stated **Further details:** Not stated **Baseline functioning:** Not stated	**Diagnostic criteria:** Not stated **Details:** No details given, authors state that criteria for diagnosis have been previously described. This study looks specifically at chronic mononucleosis syndrome **Inclusion criteria:** Written consent obtained from all participants	**Drop-outs:** 6 injections (3 in each group) excluded because of inadequate questionnaire response. **Adverse effects:** Not stated
Results				
Outcome 1				
Outcome General health - Whether or not improvement had occurred (yes/no question). **Final treatment group:** 52% of injections resulted in improvement in participants **Final control group:** 32% of injections resulted in improvement in participants **Comments:** Difference in improvement between the 2 groups p<0.001				

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (Year) Lloyd (1990)[51] **Study design:** RCT	**Intervention:** Immunoglobulin G **Number of participants in each arm:** 23 in treatment arm, 26 in placebo **Study duration:** 3 months **Length of follow-up**: 6 months **Purpose of intervention:** To investigate the effect of immunoglobulin treatment in participants with CFS Intervention details: Intervention: intravenous immunoglobulin (2g(IgG)/kg). **Control:** placebo of 10% w/v maltose. 3 infusions lasting 24 hours administered at monthly intervals.	**Sub-groups:** None stated **Number:** 49 **Age:** 16 to 63 (mean=36) **Sex:** 25 males, 24 females **Concurrent diagnoses:** None stated **Duration of fatigue:** 12 to 180 months (median 47) **Further details:** Acute viral like illness precipitated onset in 37 participants, 40 had abnormal cell-mediated immunity **Baseline functioning:** 32 participants were unable to participate in work, none were able to undertake sport or vigorous leisure activity and social activities of 45 participants 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 participants, in CD4 subset in 9 participants, and in CD8 subset in 18 participants. Reduced DTH responses demonstrated in 33 participants, 40/49 participants had abnormal cell-mediated immunity evidenced by reduced DTH response and/or T-cell lymphopenia. 7/33 participants met criteria for current major depressive episode, 19 had mild depression	**Diagnostic criteria:** Similar to CDC (1988) **Details:** 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 participant's premorbid status. Other chronic infectious or immunodeficiency related disorders excluded **Inclusion criteria** No previous immunologic therapy	**Drop-outs** 2 immunoglobulin recipients with drew from study: one because of mild, but transient, abnormal liver function tests, other withdrew voluntarily after phlebitis had occurred with the first infusion **Adverse effects** Phlebitis and constitutional symptoms including headaches, worsened fatigue and concentration impairment occurred more commonly in the immunoglobulin recipients than in the participants who received placebo. Phlebitis occurred in 35/65 immunoglobulin infusions & with 1 placebo infusion, constitutional symptoms occurred in 53/65 immunoglobulin infusions and 19/78 placebo infusions.

Results

General comments:	Outcome 1	Outcome 2:	Outcome 3:
In 23 immunoglobulin recipients the % 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 cell count (r=0.4, p<0.05) and DTH (r=0.3, 0=0.08)	**Outcome:** Symptom measure: Symptoms and disability as assessed by the physician **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** Employment status: Measure of functional capacity **Comments**: 6/13 who responded (all immunoglobulin recipients) resumed pre-morbid employment status in full-time occupation or housework, 5 participants (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 participants (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 participants had little to no change in ability to participate in work, leisure and social activities.	**Outcome** 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 treatment group: 36 (sd=14) Baseline control group: 41(sd=16) Final treatment group: 36(sd=21) Final 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 4:	**Outcome 5:**	**Outcome 6:**
	Outcome Depression: 33 participants interviewed by psychiatrist completed self-report measures of depression (Zung scale) **Baseline treatment group:** 42(sd=8) **Baseline control group**: 38(sd=11) **Final treatment group**: 41(sd=11) **Final control group**: 40(sd=12) **Comments:** No significant differences when overall scores compared.	**Outcome** Depression: Psychiatrist rated participants on Hamilton Depression scale **Baseline treatment group:** 10.7(2.8) **Baseline control group**: 10.5(3.4) **Final treatment group**: 9(5) **Final 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** Immune outcomes: CD4 lymphocyte, PHA response and DTH response **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 participants 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 participant did not undergo immunologic testing at follow-up

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Peterson (1990)[48] **Study design:** RCT	**Intervention:** Immunoglobulin G **Number of participants in each arm:** 15 **Study duration:** 21 weeks **Length of follow-up:** 21 weeks **Purpose of intervention:** To evaluate its therapeutic benefit in participants with CFS **Intervention details:** **Intervention:** IV IgG (1g/kg) every 30 days for 6 months. **Control:** Placebo = IV 1% albumin solution every 30 days for 5 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.	**Sub-groups:** None stated **Number:** 30 **Age:** mean 40.8(11.2) **Sex:** 8M 22F **Concurrent diagnoses:** None stated **Duration of fatigue:** mean 3.8(2.2) **Further details:** 96.7% had viral-like onset of illness. All recruited from CFS research program at medical centre in Minnesota. **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	**Diagnostic criteria** CDC (1988) **Details:** Medical psychometric and psychiatric evaluations did not establish another explanation for chronic fatigue **Inclusion criteria:** No other explanation for chronic fatigue	**Drop-outs** 2 due to adverse events (1 from each group). **Adverse effects** 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 don't state which groups they were in.

Results

Outcome 1	Outcome 2:	Outcome 3:
Outcome Symptom measure: Self-assessment form - Symptom Checklist 90 **Baseline treatment 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 control group:** fatigue 14/14; prolonged postex fatigue 14/14; muscle weakness 11/14; myalgias 10/14; sleep disturbance 10/14; headac hes 7/14; arthralgias 11/14 **Final treatment 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 **Final 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** Functional measure: functional status and well-being, self-assessment form - Medical outcome short study form (0=worst, 100=best), sd given in brackets **Baseline treatment group:** physical 63.1(25.9); social 6.1(6.4); health perceptions 8.5(18.4); mental health 63.7(17.1) **Baseline control group:** physical 66.1(21.0); social 5.7(3.0); health perceptions 12.0(14.8); mental health 59.7(13.4) **Final treatment group**: physical 56.0(23.2); social 5.2(5.5); health perceptions 20.5(25.0); mental health 58.3(17.4) **Final control group:** physical 51.8(22.2); social 9.4(7.9); health perceptions 16.3(13.1); mental health 62.9(13.3)	**Outcome** Immune outcomes: IgG1 and IgG3 levels **Comments:** IgG1 levels of all pts receiving IgG fell within normal range following treatment - 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

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Rowe (1997)[55] **Study design:** RCT	**Intervention:** Immunoglobulin G **Number of participants in each arm:** IgG group 36, placebo group 35 (34 in analysis). **Study duration**: 13 weeks **Length of follow-up:** 26 weeks **Purpose of intervention:** To reduce symptoms and improve function. **Intervention details:** **Intervention:** Immunoglobulin G, 3 infusions of 1g/kg (max 1 L of 6g/100ml in 10% w/v maltose solution) given 1 month apart. **Control:** 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.	**Sub-groups:** None stated **Number:** 71 **Age:** Mean 15.3 - 15.6 (2.0) **Sex:** 18 M, 53 F **Concurrent diagnoses:** None stated **Duration of fatigue:** mean placebo group 16.9(11.4) months, mean IgG 19.2(13.2) months **Further details:** All referred to the Royal Children's Hospital, Melbourne **Baseline functioning:** Baseline mean percentage functional score placebo 25.9(20.5), IgG 23.9(19.7)	**Diagnostic criteria:** CDC (1994) **Details:** None given **Inclusion criteria:** Excluded if receiving steroid medication, NSAIDs, immunomodulatory agents or were currently receiving or had received intravenous IgG. Aged 11-18.	**Drop-outs:** One in the placebo group due to moving away. **Adverse effects:** 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 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 treatment group:** 23.9 (sd=19.7) **Baseline control group:** 25.9 (sd=20.5) **Final treatment group:** 49.9 at 3 months, 64.1 at 6 months (sd=28.2) **Final control group:** 44.6 at 3 months, 52.1 at 6 months (sd=31.4) **Comments:** Comparison between the 2 groups was significant ($p<0.04$). Nine in the IgG group returned to full function and 4 in the placebo group.	**Outcome** Functional measure: Categorised as 'improved' or 'not improved', improvement being defined as 25% improvement in mean functional score at 6 months **Final treatment group:** 26 improved **Final control group:** 15 improved **Comments:** $p<0.02$

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Steinberg (1996)[50] **Study design:** RCT	**Intervention:** Oral terfenadine (antihistamine) **Number of participants in each arm:** 15 (14 reported) **Study duration:** 9 weeks **Length of follow-up**: 9 weeks **Purpose of intervention:** To test effect of terfenadine on CFS symptoms and functional impairment. **Intervention details:** **Intervention**: Terfenadine 60mg b.d. **Control**: Placebo b.d. 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.	**Sub-groups:** None stated. **Number:** 30 **Age:** Mean 36.2 (11.4) range 19-74 **Sex:** 23 F 7 M **Concurrent diagnoses:** None stated. **Duration of fatigue:** Not stated. **Further details:** Recruited from CFS research programme, responded to a letter. 73% had an atopic history and 53% responded to skin tests. **Baseline functioning:** not stated	**Diagnostic criteria:** CDC (1988) **Details:** Thorough medical, psychometric and psychiatric examinations. **Inclusion criteria:** No attempt was made to preselect participants with atopic disease. Participants had to be aged 18 or more	**Drop-outs:** 2 participants (one from each group) withdrew from the study due to 'no improvement' **Adverse effects:** None stated

Results

Outcome 1	Outcome 2:
Outcome: 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 treatment 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 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) **Final treatment 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) **Final 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** Symptom measure: Self-assessment 4 point scale (none to severe) **Baseline treatment group:** Fatigue 10; postexertional fatigue 11; muscle weakness 7; myalgias 8; sleep disturbance 3; headaches 10; arthralgias 6 **Baseline control group:** Fatigue 12; postexertional fatigue 12; muscle weakness 6; myalgias 7; sleep disturbance 6; headaches 5; arthralgias 6 **Final treatment group:** Fatigue 12; postexertional fatigue 12; muscle weakness 8; myalgias 9; sleep disturbance 3; headaches 9; arthralgias 8 **Final 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

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Strayer (1994)[53] **Study design**: RCT	**Intervention:** Ampligen (RNA drug (Poly(I).Poly(C12U))) **Number of participants in each arm:** 45 received treatment, 47 placebo. Analysis on 41 in treatment group, 43 in placebo. **Study duration:** 26 weeks **Length of follow-up**: 26 weeks **Purpose of intervention:** To determine response of several laboratory and clinical variables to the drug. **Intervention details:** **Intervention**: ampligen 4 doses of 200mg and then 400mg twice weekly. **Control:** placebo group received equivalent volume of saline. Twice weekly intravenous infusion usually given over 35mins.	**Sub-groups:** HHV-6 **Number:** 92 **Age:** Mean: 36 in treatment group, 35 in placebo **Sex:** 23M, 69F **Concurrent diagnoses:** None stated **Duration of fatigue:** Mean: 6.1 years in treatment group, 4.4 years in placebo group (p-value of difference =0.08) **Further details:** 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, age 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. **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.	**Diagnostic criteria:** CDC (1988) **Details:** Modified not to exclude certain psychiatric disorders (particularly depression) **Inclusion criteria:** Severely debilitated participants with KPS (Karnofsky performance score) from 20-60 were eligible, CFS diagnosed more than 12 months earlier and underwent diagnostic workup to exclude other disorders whose symptomatology might mimic that of CFS, participants excluded if: pregnant/nursing	**Drop-outs** 8 participants dropped out, 4 from each group, 3 of the placebo participants and one of the treatment participants dropped out because symptoms intensified, 4 others withdrew for non-medical reasons related to economic concerns, domestic problems, or transportation issues. Two arms did not differ significantly with regard to missed doses, no participants missed more than 6 doses **Adverse effects** Relative frequencies of more than 200 adverse-event categories were compared, 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

Results

General comments:	Outcome 1	Outcome 2:	Outcome 3:	Outcome 4:
Subgroup analysis: Increases in Karnofsky scores were equivalent in patients presenting with and without HHV-6 reactivation. Incidence of non-exudative pharyngitis was significantly higher among HHV-6 positive participants than in those lacking this marker (93% vs 58%, p<0.02). Actual figures for subgroup not reported.	**Outcome** Functional measure: Measured by Karnofsky performance score, % change presented **Final treatment group:** +20 **Final 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** Cognitive function: Perceived cognitive deficit assessed by the SCL-90-R questionnaire, % change presented **Final treatment group**: +27.3 **Final 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** Exercise treadmill testing, conducted according to standardised progressive exercise programme, % change reported **Final treatment group**: +10.3 **Final 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** Activities of daily living assessed using Barthel's ADL index, % change reported **Final treatment group**: +23.1 **Final 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 Amount of work completed, assessed by treadmill test, % change presented **Final treatment group:** +11.8 **Final 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** Depression and anxiety dimension assessed using SCL-90-R **Comments:** Changes in levels of depression and anxiety were similar in both treatment groups	**Outcome** Medication use: Participants were asked to discontinue any concomitant medication use before start of treatment. **Comments:** The use of three classes of drugs and all medications increased significantly in placebo group compared to treatment group	

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Vollmer Conna (1997)[52] **Study design:** RCT	**Intervention:** Immunoglobulin **Number of participants in each arm:** 73 received immunoglobulin (22 0.5g/kg, 28 1g/kg & 23 2g/kg), 26 received placebo **Study duration:** 13 weeks **Length of follow-up:** 26 weeks **Purpose of intervention:** To examine whether potential benefits in the treatment of CFS with immunoglobulin are dependent on dosage of immunoglobulin **Intervention details:** **Intervention:** Participants received one of 3 different doses of immunoglobulin (0.5, 1 or 2g/kg). **Control:** 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	**Sub-groups:** none reported **Number:** 99 **Age:** 16-73 (mean 40 years) **Sex:** 75 women, 24 men **Concurrent diagnoses:** None stated **Duration of fatigue:** 1-34 years (mean = 6 years) **Further details:** Acute viral like illness appeared to precipitate onset of CFS in 75 cases, serologic confirmation available for 23 of these cases **Baseline functioning:** 23 participants were unable to participate in any work, 48 participants reported only 50% or less work attendance	**Diagnostic criteria:** Australia **Inclusion criteria:** Excluded if: pregnant, on any of following therapies (steroid medication, nonsteroidal anti-inflammatory drugs, immunomodulatory agents, cholinesterase inhibitors), had previously received immunologic therapy, had a recent history of asthma	**Drop-outs:** 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 participant received only 2 immunoglobulin infusions as he developed vesiculopapular skin eruption. These participants followed up at 6 months after enrolment and analysed with other immunoglobulin recipients on an intention-to-treat basis **Adverse effects:** No significant differences in occurences of symptoms between different groups

Results

Outcome 1	Outcome 2:	Outcome 3:	Outcome 4:
Outcome Functional measure: Measured by Karnofsky performance score (assessed by investigator), reflects ability of individuals to participate in daily activities on 100 point scale **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** **Quality of life:** assessed by participants using QoL visual analogue scale modified to include 10 aspects of physical or neuropsychological symptomatology typical of CFS **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** Mood: Profile of mood states questionnaire completed by participants **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** Immune outcomes: Absolute numbers of T suppressor/cytotoxic (CD8) cells, and T inducer (CD4) cells, DTH skin responses **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

3. Antiviral

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Brook (1993)[49] **Study design:** RCT	**Intervention:** Interferon **Number of participants in each arm:** 20 (crossover) **Study duration:** 12 weeks **Length of follow-up**: 12 months **Purpose of intervention:** To investigate the effect of interferon-alpha in the treatment of chronic fatigue syndrome **Intervention details:** **Intervention:** interferon alpha 2b. Three meaga-units of interferon - alpha 2b was administered subcutaneously thrice weekly for 12 weeks. **Control:** No treatment. Cross-over study - control group treated after 12 weeks.	**Sub-groups:** None stated **Number:** 20 **Age:** Not stated **Sex:** 14 women, 6 men **Concurrent diagnoses:** Not stated **Duration of fatigue:** 1-11 years **Further details:** Not stated **Baseline functioning:** ECOG score of all participants combined: 0:0; I: 8; II: 12	**Diagnostic criteria:** CDC (1988) **Details:** No further details **Inclusion criteria:** Performance status of ECOG (Eastern Co-operative Oncology Group) I or II.	**Drop-outs:** 1 participant in control group decided not to be treated. 1 participant in treatment group withdrew after 2 weeks due to adverse effects (increased fatigue). **Adverse effects:** Therapy was reasonably well-tolerated and side effects, which were most prominent during 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 persisted for up to a year in 2 women.
Results				
Outcome 1				
Outcome Activity: Graded according to ECOG scale: 0: able to carry out normal activity without restrictions; I: restricted in physically strenuous 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 treatment group**: Not stated **Baseline control group:** Not stated **Final treatment group:** 3/20 participants completely recovered (scored=0, baseline scores were I in 2 participants and II in 1 participant) . 2 /20 participants improved (both were II at start of trial) **Final control group:** 0/20 recovered significantly **Comments**: 4 participants that improved on treatment all reported acute virus-type illness at start of their disease. Improvements remained in all participants at 8 or 12 months follow-up.			

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Lerner (2001) **Study design:** RCT	**Intervention:** Ganciclovir **Study duration:** 6 months **Length of follow-up**: 6 months **Number of subjects in each arm:** 11 (crossover trial), only results for first half of study available **Purpose of intervention:** No stated purpose as such: the authors state the data are consistent with the hypothesis that subsets of cases of CFS result from cardiac disease due to a single persisting infection caused by Epstein-Barr virus or human cytomegalovirus in immunocompetent patients. **Intervention details:** 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 elevated EBV antibodies, oral valaciclovir 1g given q6h added to oral ganciclovir treatment.	**Sub-groups:** None stated **Number:** 11 **Age:** mean 42.7 years **Sex:** 10/11 F **Concurrent diagnoses:** none stated **Duration of fatigue:** 35.1 months (mean) **Further details:** 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. **Baseline functioning:** 1/11 had positive HCMV IgM titre. 4/11 had co-infection with EBV. Energy index (EI) score mean 3.5 (max 10). Mean symptom score (0-1) was 0.81.	**Diagnostic criteria:** Not stated **Details:** none stated **Inclusion criteria:** not stated	**Drop-outs:** see adverse events **Adverse effects:** 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 Energy Index (EI) point scores: score 0 = bedridden, 5=CFS, score 10= healthy. **Baseline treatment group:** mean 3.5 (n=7) **Baseline control group:** mean 4.4 (n=4) **Final treatment group:** 6 months (7 pts) mean 4.4. **Final control group:** 6 months (4 pts) mean 3.9	**Outcome** Symptom scores: e.g. chest pain, wooziness (light headedness and cognitive disturbance), palpitations at rest, muscle aches. Symptom score of 1 = presence of all 4 symptoms, 0= absence of all 4 symptoms. **Baseline treatment group:** mean 0.81 (11 pts) **Baseline control group**: mean 0.81 (11 pts) **Final treatment group**: 6 months (7 pts) 0.38. **Final control group**: 6 months (4 pts) mean 0.5.

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) See (1996)[36] **Study design:** RCT	**Intervention:** Alpha interferon **Number of participants in each arm:** 30 (crossover trial) **Study duration:** 12 weeks **Length of follow-up:** 12 weeks **Purpose of intervention:** Not stated. **Intervention details:** **Intervention:** Alfa 2a interferon (3 million units) s.c. 3 times per week. **Control:** Placebo (0.9% NaCl solution) s.c. 3 times p.w. 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	**Sub-groups:** None stated **Number:** 30 **Age:** mean 37.2 (7.4) years, range 22-58 **Sex:** 6 M 24 F **Concurrent diagnoses:** None stated **Duration of fatigue:** 4.6 years (1-12) **Further details:** Referred from secondary care. **Baseline functioning:** not stated	**Diagnostic criteria:** CDC (1988) **Details:** Chronic infections and other chronic disease exclusion criteria screened for at trial entry. **Inclusion criteria:** Excluded: participants 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.	**Drop-outs:** 4 withdrew- all were receiving interferon at the time: 2 had neutropenia, one palpitations and one worsened fatigue. **Adverse effects:** 4 participants had significant flu-like symptoms within 6 hrs of initial dose of interferon. 2 had new onset diarrhoea. 9 female participants complained of hair loss at some point during or after interferon therapy.

Results

Outcome 1	Outcome 2:
Outcome Immune outcomes: NK function, %NLP, CD4 count, CD8 count **Baseline treatment 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 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 **Final treatment group:** NK increased significantly to 129.3(20.7) p<.05, f=3.51. Mean %NLP did not change. **Final control group:** No significant changes **Comments:** CD4 and CD8 counts no significant changes except in one participant (CD4 rose from 422 to 673 after 12 weeks interferon).	**Outcome** Quality of life 0-60, 60 worst score **Comments:** Mean QoL score at baseline was 35.7(10.9) and did not change significantly with placebo 31.4(9.2) or interferon 28.4(13.8) therapy.

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Straus (1988)[56] **Study design:** RCT	**Intervention:** Aciclovir (antiviral) **Number of participants in each arm:** 27 (crossover trial) **Study duration:** 13 weeks **Length of follow-up:** 18 weeks **Purpose of intervention:** To provide 'temporary' benefit.. Relief of symptoms. **Intervention details:** **Intervention:** Aciclovir **Control:** Placebo. Crossover trial. Drugs given 1 week iv (500mg per sq m body surface) to hospitalised participants, 30 days orally (aciclovir 800mg qid), with a 6 week washout period before alternate treatment was given. Participants permitted to take vitamins, nonsteroidal and nonnarcotic analgesics, decongestants, antihistamines, oral contraceptives and antibiotics during the study.	**Sub-groups:** None stated **Number:** 27 **Age:** mean 34.1 (sem 1.5) yrs **Sex:** M 8 F 19 **Concurrent diagnoses:** None stated **Duration of fatigue:** Mean 6.8 (se 1.4) yrs **Further details:** Fatigue began insidiously in 4, during acute febrile illness in 10 and during mononucleosis-like illness in 7. **Baseline functioning:** 12/27 vocationally disabled, 10/27 working part time.	**Diagnostic criteria:** CDC (1988) **Details:** Initial screening, followed by psychiatric assessment. Full physical examination conducted at NIH at beginning of each study phase by 1 physician blinded to treatment. **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)	**Drop-outs:** 3 had reversible renal failure during aciclovir infusions and were withdrawn from the study. **Adverse effects:** Nausea/ upset stomach: aciclovir 10 iv, 4 oral; placebo 5 iv, 0 oral. Vomiting: aciclovir 2 iv, 1 oral; placebo 1 iv, 0 oral. Diarrhoea: aciclovir 3 iv, 3 oral; placebo 0 iv, 1 oral. Dizziness/ disorientation: aciclovir 7 iv, 0 oral; placebo 3 iv, 0 oral. Headache: aciclovir 4 iv, 1 oral; placebo 1 iv, 0 oral. Jitteriness: aciclovir 1 iv, 0 oral; placebo 1 iv, 0 oral. Rash: aciclovir 0 iv, 2 oral; placebo 0 iv 0 oral. Other: aciclovir 14 iv, 9 oral; placebo 10 iv, 5 oral.

Results

General comments:	Outcome 1	Outcome 2:	Outcome 3:	Outcome 4:
11 participants felt better during aciclovir treatment and 10 during placebo treatment. Neither aciclovir treatment nor clinical improvement correlated with alterations in laboratory findings, including titres of antibody to EBV or levels of circulating immune complexes or of leukocyte 2,5-oligoagenylate synthetase A negative score indicates improvement	**Outcome** Mood: Self-assessment, Profile of Mood States Questionnaire **Comments:** Aciclovir 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.	**Outcome** Personal wellbeing: Wellness scores self-assessment 0 for dying, 100 for being as well as they could imagine a person to be. **Comments:** aciclovir vs placebo: mean difference -1.08 SEM 3.01 p>0.5	**Outcome** Temperature: Oral temperature, self-measured **Comments:** Aciclovir vs placebo mean difference -0.02 SEM 0.03 p>0.5	**Outcome** Rest: hours/ day **Comments:** Aciclovir vs placebo mean -0.05 SEM 0.38 p>0.5

4. Pharmacological

Details of Wearden (1998)[46] GET/pharmacological study are presented, under 'behavioural'.

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Cleare (1999)[28] **Study design:** RCT	**Intervention:** Hydrocortisone **Number of participants in each arm:** 35 randomised, 32 treated (crossover trial) **Study duration:** 9 weeks **Length of follow-up**: 9 weeks **Purpose of intervention:** To improve fatigue in chronic fatigue syndrome **Intervention details:** **Intervention:** . First 16 participants given 5mg /day hydrocortisone, remainder given 10mg / day. **Control:** placebo. Randomly assigned to 1st treatment (hydrocortisone or placebo). 28 days each arm, 1 tablet per day	**Sub-groups:** None stated **Number:** 32 **Age:** mean 35.3yrs (range 19-58) **Sex:** 20 F, 12 M **Concurrent diagnoses:** 9 history of psychiatric illness **Duration of fatigue:** Mean 36 (range 28-45) months. **Further details** : 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. Participants from specialised CFS clinics in London and Cambridge. 19 participants had infection related onset. **Baseline functioning:** Mean baseline fatigue score 25.1 (23.7-26.5) points. Adrenal autoantibodies negative in all participants.	**Diagnostic criteria:** Oxford & CDC 1994 **Details:** All participants had physical examination and standard lab tests, also baseline endocrine assessment. Semi-structured psychiatric examination done by trained psychiatrists to exclude additional psychiatric disorders **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.	**Drop-outs:** Noon dropped out from the 32 treated, however 3 randomised dropped out - 1 before receiving medication and 2 due to 'protocol violation'. **Adverse effects:** 3 pts on hydrocortisone reported side effects (exacerbation of acne, nervousness, improvement in eczema), and one pt on placebo (episode of fainting)

Results

General comments:	Outcome 1	Outcome 2:	Outcome 3:
Results of endocrine assessment are provided in the paper	**Outcome** Fatigue: 11 item self-administered fatigue scale scored according to Likert 0,1,2,3 system to be sensitive to change. **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** Clinical global impression: clinician administered CGI scale **Comments:** 7/32 in the hydrocortisone group improved compared with 2/32 on placebo.	**Outcome** Disability: Work and social adjustment scale (WSAS) change scores **Baseline treatment group**: As above: combined measures **Baseline 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) **Final treatment group:** home -0.6; private leisure -1.0; social leisure -1.1; relationships -0.6; work -0.8; mean -0.7 **Final control group:** home -0.04; private leisure 0.06; social leisure -0.3; relationships -0.3; work -0.2; mean -0.05
	Outcome 4:	Outcome 5:	Outcome 6:
	Outcome Disability: Medical outcomes SF36 - physical function and role limitation subscales **Comments:** No significant improvement overall.	**Outcome** Psychological assessment: General Health Questionnaire (GHQ) **Comments:** No results given	**Outcome** Symptom measure: self-reported somatic symptoms **Baseline treatment group:** 16.9 **Baseline control group**: 17.2 **Final treatment group**: 14.3 (p=0.04) **Final control group:** 15.6 (p=0.21)

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Forsyth (1999)[31] **Study design:** RCT	**Intervention:** Oral NADH **Number of participants in each arm:** 26 (cross-over trial). 35 initially enrolled. **Study duration:** 12 weeks **Length of follow-up**: 12 weeks **Purpose of intervention:** To evaluate the efficacy of the reduced form of nicotinamide adenine dinucleotide (NADH), the stabilised oral form in participants with CFS **Intervention details:** **Intervention**: Given 10mg of NADH (2 5mg tablet formulation), took dosage of 2 tablets orally once a day in the morning before breakfast on an empty stomach with a glass of water **Control:** Placebo, 2 tablets as above. Received NADH/placebo at week 0 for 4 week period, at week 4 4-week wash out period began in which no drug was given, at week 8 final 4-week period commenced - participants crossed over to alternate regimen	**Sub-groups:** None stated **Number:** 26 **Age:** 26-57 years (mean 39.6) **Sex:** 65% females **Concurrent diagnoses:** Not stated **Duration of fatigue:** 1 to 16 years (mean 7.2) **Further details:** Participants allowed to continue taking prescribed medication. 25 participants Caucasian, 1 Afro-American. Participants referred by variety of physicians, self-referred or recruited from the Georgetown University Medical Center. **Baseline functioning:** 100% of participants 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, 69% had swelling of lymph nodes	**Diagnostic criteria:** CDC (1994) **Inclusion criteria:** Participants 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, participants with history of established medical condition that could be contributing to fatigue, use of antidepressants, lithium, neuroleptics and monoamine inhibitors generally considered exclusionary criteria	**Drop-outs** 2/35 participants dropped out due to non-compliance. 9 were dropped from the analysis because they were using psychotropic drugs. **Adverse effects:** 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				
General comments: 35% of patients guessed correctly when asked which drug they thought they were on	**Outcome 1** **Outcome** 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 **Final treatment group:** 8/26 showed 10% improvement **Final control group:** 2/26 showed 10% improvement p-value for difference = <0.05			

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author Year) Hickie (2000)[61] **Study design:** RCT	**Intervention:** Moclobemide (monoamine oxidase inhibitor) **Number of participants in each arm:** 47 in moclobemide arm, 43 in placebo **Study duration:** 6 weeks **Length of follow-up**: 6 weeks **Purpose of intervention**: to provide symptomatic benefit. **Intervention details:** **Intervention:** 300-600mg/day moclobemide **Control**: 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.	**Sub-groups:** Analysed separately: general psychological distress, major depression, reduced immune responsiveness **Number:** 90 **Age:** 18-65 (mean 42.2-44.9) **Sex:** 49 F, 41 M **Concurrent diagnoses:** None stated. **Duration of fatigue:** mean 84.2-90.9 weeks **Further details:** Recruited from infectious disease and immunology outpatient clinics in Australia. **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 response.	**Diagnostic criteria:** Australia **Exclusion criteria:** Alternative medical 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.	**Drop-outs:** 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 effects:** see 'drop-outs'.

Results

General comments:	Outcome 1	Outcome 2:	Outcome 3:	Outcome 4:
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 the most impressive difference between groups on KPI.	**Outcome** Global improvement (self-assessed): No details of scales given **Final treatment group:** 24/47 **Final control group:** 14/43 **Comments:** ITT analysis with last observation carried forward (LOCF). OR 2.16 (95% CI 0.9, 5.1) **Subgroups** : *General psychological distress* Final treatment group: 13/32 Final control group: 7/29 *Major depression* Final treatment group: 8/14 Final control group: 8/17 *Reduced immune responsiveness* Final treatment group: 6/16 Final control group: 6/20	**Outcome** Disability - Karnofsky performance index score **Baseline treatment group:** 74.3 (5.0) **Baseline control group:** 75.9 (4.5) **Final treatment group:** change score +0.86 (1.2) **Final control group:** change score +0.58 (1.3) **Comments:** mean difference between groups 0.28 (-0.2, 0.8), not significant. ITT, LOCF. **Subgroups:** *General psychological distress* Final treatment group: +0.84 (1.2) Final control group: +0.43 (1.2) *Major depression* Final treatment group: +1.11 (1.2) Final control group: +0.97 (1.3) *Reduced immune responsiveness* Final treatment group: +1.16 (1.2) Final control group: +0.36 (1.0)	**Outcome** Mood: POMS subscale scores: fatigue, vigour, depression **Baseline treatment group:** fatigue 18.0 (5.6); vigour 8.2 (5.3); depression 12.9 (13.4) **Baseline control group:** fatigue 18.0 (5.8); vigour 8.8 (5.1); depression 14.1 (12.2) **Final treatment group:** change scores: fatigue -0.05 (0.37); vigour +0.51 (1.2); depression -0.06 (1.0) **Final 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. **Subgroups:** *General psychological distress* Final treatment group: fatigue –0.06 (1.3); vigour 0.62 (1.1); depression –0.07 (1.2). Final control group: fatigue +0.03 (0.3); vigour –0.17 (1.0); depression –0.10 (0.9). *Major depression* Final treatment group: fatigue –0.17 (0.37); vigour +0.93 (1.1); depression –0.99 (1.5). Final control group: fatigue –0.01 (0.33); vigour +0.08 (1.0); depression –0.19 (0.9). *Reduced immune responsiveness* Final treatment group: fatigue +0.05 (0.42); vigour +0.40 (1.3); depression +0.16 (0.0). Final control group: fatigue +0.03 (0.32); vigour –0.04 (0.8); depression –0.17 (0.8).	**Outcome** Immunologic: CD4 T cell count, CD8 T cell count, size of delayed type hypersensitivity skin response (mm). **Baseline treatment group:** CD4 0.89 (0.31); CD8 0.83 (0.26) **Baseline control group:** CD4 0.05 (0.04); CD8 0.51 (0.15) **Final treatment group:** change scores: CD4 +0.03 (0.29); CD8 +0.01 (0.19); skin test 0.00 (0.73) **Final 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, significant); 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

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) McKenzie (1998)[32] **Study design:** RCT	**Intervention:** Hydrocortisone **Number of participants in each arm:** 35 in each arm **Purpose of intervention:** To evaluate the efficacy and safety of low-dose oral hydrocortisone as a treatment for CFS, to determine whether CFS symptoms could be ameliorated through cautious hormonal supplementation to approximately normal levels. **Intervention details:** **Intervention:** 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 **Control:** Equivalent volume of placebo pills.	**Sub-groups:** None stated **Number:** 70 **Age:** mean 36.7 (sd=7.2) in hydrocortisone group, 38.3 (SD=7.5) in placebo group **Sex:** 20% male **Concurrent diagnoses:** None stated **Duration of fatigue:** Mean 46.9 (sd=27.3) months in hydrocortisone group, 59.9 (sd=31.7) in placebo group **Further details:** Withheld prescribed medication for duration of study and for 2-6 weeks prior to the study starting **Baseline functioning:** Similar in both groups, 73% impaired employment	**Diagnostic criteria:** CDC (1988) **Details:** Diagnosis ascertained by participant history routine physical examination and laboratory tests to exclude other relevant diagnoses **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	**Drop-outs:** 7 participants withdrew from trial 3 in each group as considered that intervention was ineffective, and one in placebo group because of a rash **Adverse effects:** 21 adverse reactions identified, 3 of which occurred significantly more frequently in treatment group: increased appetite, weight gain and difficulty in sleeping, actual participant weights confirmed reports

Results

Outcome 1	Outcome 2:	Outcome 3:	Outcome 4:
Outcome General health: Participants 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 **Final treatment group:** 6.3 (sd=11.7), p-value for difference in change = 0.06 (value calculated from 2 sided Wilcoxon rank sum test) **Final control group:** 1.7 (sd=8.8) **Comments:** The proportions of participants 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** Mood: Participants completed profile of mood states questionnaire **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** Symptom measure: Participants completed symptom checklist-90-R. Mean change in scores for general severity index presented **Final treatment group:** -0.1 (sd=0.2) **Final control group:** -0.1 (sd=0.2) p-value for difference between 2 groups = 0.20 (value calculated from 2 sided Wilcoxon rank sum test)	**Outcome** Symptom measure: Sickness impact profile **Final treatment group:** -2.5(sd=6.4) **Final control group**:-2.2 (sd=6.8) p-value for difference between 2 groups = 0.85 (value calculated from 2 sided Wilcoxon rank sum test)
Outcome 5:	**Outcome 6:**	**Outcome 7:**	
Outcome Depression: Beck depression inventory **Final treatment group:** -2.1 (sd=5.1) **Final 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)	**Outcome** Activity: 10 point activity scale developed by authors **Final treatment group:** 0.3 (sd=1.1) **Final control group**: 0.7 (sd=1.4) p-value for difference between 2 groups = 0.32 (value calculated from 2 sided Wilcoxon rank sum test)	**Outcome** Depression: Participants interviewed by psychiatric specials who administer Hamilton Depression Rating scale **Final treatment group**: -0.8 (sd=3.8) **Final control group**: 0.1 (sd=2.9) p-value for difference between 2 groups = 0.25 (value calculated from 2 sided Wilcoxon rank sum test)	

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Moorkens (1998)[34] **Study design:** RCT	**Intervention:** Growth hormone **Number of participants in each arm:** 10 **Study duration:** 12 weeks **Length of follow-up**: 12 weeks **Purpose of intervention:** To demonstrate therapeutic efficacy of GH therapy in people with CFS who had low GH peak levels during stage-controlled sleep **Intervention details:** **Intervention:** Growth hormone 6.7 ug/kg/day (0.02 IU/kg/day). **Control:** Placebo. Double blind.	**Sub-groups**: none stated **Number:** 20 **Age:** 30-60 years **Sex:** 7 M, 13 F **Concurrent diagnoses:** None stated **Duration of fatigue:** not stated **Further details:** Recruited from CFS clinic at Antwerp University Hospital. All had nocturnal peak levels of GH <10ug/L **Baseline functioning:** Not stated.	**Diagnostic criteria:** CDC (1994) **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	**Drop-outs:** 3 withdrew - 1 due to lack of motivation, 1 due to anxiety, 1 due to nervousness. Not stated which group they were in. **Adverse effects:** None stated.

Results

Outcome 1	Outcome 2:	Outcome 3:	Outcome 4:
Outcome Physical: Weight, muscle strength, skinfold thickness, fat mass, fat free mass, total body water, BMI **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** Laboratory measures **Comments:** only reported after 12 months (following 9 month open label administration)	**Outcome** Quality of life **Comments:** only reported after 12 months (following 9 month open label administration)	**Outcome** Return to work **Comments:** only reported after 12 months (following 9 month open label administration)

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Natelson (1996)[59] **Study design:** RCT	**Intervention:** Phenelzine **Number of participants in each arm:** 15 in active treatment, 9 in placebo, 9 in each group evaluated **Study duration:** 6 weeks **Length of follow-up**: 6 weeks **Purpose of intervention:** To investigate whether CFS symptoms respond quickly to low dose treatment with monoamine oxidase inhibitor **Intervention details:** **Intervention:** phenelzine. **Control:** placebo. In 1st 2 weeks all participants 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	**Sub-groups:** None stated **Number:** 24 **Age:** 37.9 (se =2.6) in drug group, 31.2 (se=2.9) in placebo group **Sex:** 9 women in drug group, 6 women and 3 men in placebo group **Concurrent diagnoses:** None stated **Duration of fatigue:** Not stated **Further details:** Not stated **Baseline functioning:** Not stated	**Diagnostic criteria:** CDC (1988) **Details:** Only 7 minor symptoms were required for entry into trial. All participants also filled CDC 1994 criteria **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	**Drop-outs** 6 participants, 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 effects** 3 participants dropped out due to adverse effects when on full dose of phenelzine

Results

General comments: Of the 20 tests there were 11 tests for which a plurality of drug-treated patients improved and none for which a plurality worsened, there were 5 tests for which plurality of placebo-treated patients improved and 4 tests for which a plurality worsened	Outcome 1	Outcome 2:	Outcome 3:
	Outcome Functional measure: Functional status questionnaire: data on 11 variables assessed **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 participants reported no change for most of the tests comprising the FSQ	**Outcome** Mood: Profile of mood states questionnaire (POMS), 6 variables were assessed including fatigue, vigour, depression and confusion **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** Depression: Centers for Epidemiological Studies of Depression (CES-D), pencil and paper test for depression used **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 4:	**Outcome 5:**	**Outcome 6:**
	Outcome Illness severity: Illness severity scale (modification of Karnofsky, expanding areas of mild to moderate disability) used **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** Fatigue: Fatigue severity scale used **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** Symptom measure: 16-question symptom severity checklist used, 0-4 scale **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.

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Natelson (1998)[60] **Study design:** Controlled trial	**Intervention:** Selegiline (Antidepressant) **Number of participants in each arm:** 25 participants (one treatment arm only) **Study duration**: 6 weeks **Length of follow-up**: 6 weeks **Purpose of intervention:** To perform a clinical trial of selegiline in 25 participants with CFS to improve symptoms independently of effect on mood (effect on mood was not expected) **Intervention details:** **Intervention**: selegiline. **Control:** placebo. For first 2 weeks all participants took 2 placebo pills per day, next 2 weeks took 1 5mg tablet selegiline and 1 placebo for final 2 weeks all took 2 5mg tablets selegiline.	**Sub-groups:** None stated **Number:** 25 **Age:** Not stated **Sex:** Not stated **Concurrent diagnoses:** Not stated **Duration of fatigue:** Not stated **Further details:** All participants were from the University CFS centre identified serially **Baseline functioning:** Not stated	**Diagnostic criteria:** CDC (1988) **Details:** Only 7 minor symptoms were required for entry into study **Inclusion criteria:** Participants 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	**Drop-outs:** 6 participants 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 effects:** None stated

Results

Outcome 1	Outcome 2:	Outcome 3:
Outcome Functional measure: Functional status questionnaire: data on 9 variables assessed **Comments:** Wilcoxon matched paired tests of the difference in participants response to placebo compared to drug: Sexual relations were improved for the 12 participants 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 participants at either time point studied	**Outcome** Mood: Profile of mood states questionnaire (POMS), 6 variables were assessed including fatigue, vigour, depression and c onfusion **Comments:** Wilcoxon matched paired tests of the difference in participants 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 participants showed improvement on all 6 scales, on placebo majority showed improvement on 2 scales and worsening on 4 scales	**Outcome** Depression: Centers for Epidemiological Studies of Depression (CES-D), pencil and paper test for depression used **Comments:** Wilcoxon matched pair tests of the difference in participants response to placebo compared to drug showed no significant differences. Most of the participants showed improvement in depression scores on drug, but worsening on placebo
Outcome 4:	**Outcome 5:**	**Outcome 6:**
Outcome Illness severity scale (modification of Karnofsky, expanding areas of mild to moderate disability) **Comments:** Wilcoxon matched pair tests of the difference in participants response to placebo compared to drug showed no significant differences. Most of the variables from this scale did not change for the plurality of participants at either time point studied	**Outcome** Fatigue severity scale **Comments:** Wilcoxon matched pair tests of the difference in participants response to placebo compared to drug showed no significant differences. Most of the participants showed improvement on drug and worsening on placebo.	**Outcome** Symptom measure: 16-question symptom severity checklist used **Comments:** Wilcoxon matched pair tests of the difference in participants response to placebo compared to drug showed no significant differences. Most of the participants showed improvement on both drug and placebo

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Peterson (1998)[62] **Study design:** RCT	**Intervention:** Fludrocortisone **Number of participants in each arm:** 25 in each **Study duration:** 18 weeks **Length of follow-up:** 18 weeks **Purpose of intervention:** To provide a preliminary assessment of the efficacy and safety of fludrocortisone in the treatment of CFS **Intervention details** : Intervention: fludrocortisone acetate 0.1mg 1 tablet orally, if no improvement dose doubled after 2 weeks. Placebo: as above with dummy pills. (dose doubled for 8 participants on drug, 11 on placebo). Participants received fludrocortisone or placebo for 6 weeks, followed by 6 week wash out period then entry into opposite arm of the study	**Sub-groups:** None stated **Number:** 25 **Age:** 39.7 (SD 10.9) **Sex:** 76% female **Concurrent diagnoses:** None stated **Duration of fatigue:** 7.0 (sd=4.9) **Further details:** All participants were white. Onset of illness described as acute infection disease like episode in 22/25 participants. **Baseline functioning:** At initiation of treatment, in both arms the severity of most of the symptoms associated with CFS was high.	**Diagnostic criteria:** CDC 94 & 88 **Details:** Participants already enrolled in research programmes at Hennepin County Medical Center, Minneapolis or from Park Nicollett Clinic CFS Program, Min **Exclusion criteria:** Fatigue severity during previous month of less than 5, taking fludrocortisone or another medication that could confound interpretation of results	**Drop-outs:** Five participants 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 effects:** None reported

Results

Outcome 1	Outcome 2:	Outcome 3:
Outcome Symptom measure: 10 cm visual analogue scale with 0 being no problem to 10 of worst it could be **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** Functional measure: 36 item medical short form health survey used to assess functional status **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** Mood state assessed using the positive and negative affect scale **Baseline treatment group**: 22.9 (sd=6.0) **Baseline control group**: 22.7 (sd=6.3) **Final treatment group**: 22.7 (sd=8.3) **Final control group**: 21.7 (6.7)
Outcome 4:	Outcome 5:	
Outcome Cognitive function: Speed of cognitive function assessed using Hick paradigm reaction time **Baseline treatment group**: 0.35 (sd=0.05) **Baseline control group:** 0.37 (sd=0.07) **Final treatment group**: 0.35 (sd=0.07) **Final control group**: 0.36 (sd=0.08)	**Outcome** Exercise & work: Duration of walking on a treadmill (mins) at 1mph until feeling exhausted for a maximum of 30 mins **Baseline treatment group**: 19.3 (sd=11.2) **Baseline control group**: 20.0 (sd=11.7) **Final treatment group:** 22.8 (sd=9.2) **Final control group**: 20.2 (sd=11.5)	

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Rowe (2001)[30] **Study design:** RCT	**Intervention:** fludrocortisone **Intervention duration**: 5-6 months **Number of subjects in each arm:** 50 **Purpose of intervention:** To examine the efficacy of fludorcortisone as monotherapy for the subset of adults with both CFS and NMH. Intervention details: Duration: 9 weeks 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)	**Sub-groups:** stratified by disease duration (<3 or >=3 years) **Number:** 100 **Age:** mean 36.2(7.4) fludrocortisone group; 37.3(9.3) placebo group **Sex:** not stated. **Concurrent diagnoses:** neurally mediated hypotension **Duration of fatigue:** mean 6.0(4.9) years in placebo group; 6.9(6.4) years in fludrocortisone group. **Further details:** 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. **Baseline functioning:** All able to walk without assistance. 53-56% currently working. Baseline wellness score 40.7(16.3) placebo group; 46.8(16.0) fludrocortisone group.	**Diagnostic criteria:** CDC 1994 **Details:** clinical evaluation. **Inclusion criteria:** Neurally 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 enrolled in another CFS study, had depression or other psychiatric diagnoses, or abused drugs or alcohol.	**Drop-outs:** 21 overall: 8 placebo(1 developed hypertension, 1 refused to comply, 1 developed panic and tachicardia, 1 had increased fatigue, 1 had severe light-headedness, 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 discomfort, 1 had unrelated medical illness, 1 was found to have major depression and 2 had worsening symptoms). **Adverse effects:** No one had a change in 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 Improvement: at least 15 point improvement in global Wellness scores **Final treatment group**: 14% improved **Final control group**: 10% improved **Comments:** ITT analysis. No difference in those who had CFS <3 years or who were younger than 30 years.	**Outcome** Wellness: global wellness scale score (o-100, 0 bad, 100 good) **Baseline treatment group**: 46.8 (16.0) **Baseline control group**: 40.7 (16.3) **Final treatment group**: 50.4 (18.2) **Final control group**: 43.1 (17.6) **Comments :** p baseline = 0.06; p on treatment = 0.07.	**Outcome** Fatigue: Wood mental fatigue index **Baseline treatment group**: 16.3(9.7) **Baseline control group**: 18.3(8.2) **Final treatment group**: 14.1(10.9) **Final control group**: 13.3(9.6) **Comments:** p baseline 0.28; p final 0.73	**Outcome** Depression: BDI **Baseline treatment group**: 14.7(8.2) **Baseline control group**: 15.0(5.5) **Final treatment group**: 10.4(7.2) **Final control group**: 10.8(6.8) **Comments**: p baseline 0.82; p final 0.82
Outcome 5:	**Outcome 6:**	**Outcome 7:**	**Outcome 8:**
Outcome Mood: POMS vigour and fatigue subscales **Baseline treatment group**: vigour 7.9(4.7); fatigue 19.6(5.1) **Baseline control group**: vigour 6.7(4.3); fatigue 21.3(4.6) **Final treatment group**: vigour 8.8(6.1); fatigue 16.2(7.3) **Final 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** General health: SF36 physical function and mental health **Baseline treatment group**: PF: 54.8(22.5); MH: 63.7(18.1) **Baseline control group**: PF: 45.1(22.7); MH 66.3(16.3) **Final treatment group**: PF: 58.9(21.9); MH: 68.6(19.1) **Final 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** Activity: Duke Activity Status Index **Baseline treatment group**: 7.8(9.3) **Baseline control group**: 5.0(6.2) **Final treatment group**: 9.2(10.6) **Final control group**: 6.7(7.3) **Comments:** p baseline 0.09, p final 0.23	**Outcome** tilt test outcomes: NMH in stage 1, 2 (N) **Baseline treatment group**: 34, 16 **Baseline control group**: 33, 17 **Final treatment group**: 20, 6 **Final control group:** 17, 14 **Comments:** NMH in stage 1, 2 (N)

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Snorrason (1996)[35] **Study design:** RCT	**Intervention:** Galanthamine hydrobromide (a selective acetylcholinesterase inhibitor) **Number of participants in each arm:** 49 participants, 25 initially on galanthamine, 24 on placebo. **Study duration**: 2 weeks **Length of follow-up:** 2 weeks **Purpose of intervention:** To search for a means of diminishing the plight of participants with CFS and to test the hypothesis that central to the pathogensis of CFS is a cholinergic defect. **Intervention details:** **Intervention**: Galanthamine hydrobromide 10 mg t.i.d., reached by schedule of escalating dosage. **Control**: Matched treatment with placebo tablets. Optional cross-over trial. Participants who failed to improve or whose symptoms worsened after 2 weeks on treatment switched to alternative treatments, participants assessed 1,2, 4 and 8 weeks after change in treatment. If no improvement evident after 2 weeks on second treatment participants reverted to pre-trial therapy.	**Sub-groups:** Not stated **Number:** 49 **Age:** 18 - 67, mean 43.4 on galanthamine, 44.5 on control **Sex:** 7 male, 42 female **Concurrent diagnoses:** Not stated **Duration of fatigue:** 13.7 years on galanthamine, 11.8 on placebo **Further details:** Participants selected from University outpatient clinic and rheumatologicial outpatient clinic. **Baseline functioning:** Not stated	**Diagnostic criteria:** Not stated **Details:** Symptoms of fatigue occurring for more than 50% of waking hours and lasting more than 6 months, major sleep disturbances and myalgia. Participants taken off all medication 2 weeks prior to entering trial **Inclusion criteria:** CFS patients with minor psychiatric symptoms including depression and anxiety eligible for inclusion. People with medical conditions known to produce symptoms of fatigue, or those with major psychiatric diagnosis defined by DSM-III-R interview excluded.	**Drop-outs:** 5 participants (3 active, 2 placebo) did not progress past first 2 weeks of trial. After first 2 weeks 24 participants changed to alternative therapy (21 from placebo, 3 from galanthamine) at end of week 2. P<0.0001 **Adverse effects:** In 30% of participants dosage was reduced because of adverse effects, mainly nausea. 30% of participants on galanthamine suffered mild nausea at onset of treatment, disappeared with time. 4 participants had severe nausea on only 5mg. 9 reported headaches, 3 had severe headaches, 1 withdrew from trial. Dizziness occurred in 4 participants, 1 withdrew from study. 1 participant complained of nightmares. 2 participants developed redness and itching of skin around eyes on 10mg, disappeared when reduced to 5mg, 2 participants suffered from profuse sweating, diarrhoea, vomiting, confusion and hallucinations at 20mg dose

Results

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

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Tiev (1999)[63] **Study design:** RCT	**Intervention:** Sulbutiamine **Number of participants in each arm:** A=106; B=111; C=109 **Study duration:** 4 weeks **Length of follow-up:** 4 weeks **Purpose of intervention:** To investigate the effects of 2 different doses of sulbutiamine on chronic postinfectious fatigue (CPIF) **Intervention details:** **Intervention**: group A had 400mg sulbutiamine daily; group B had 600 mg sulbutiamine daily. **Control**: Placebo.	**Sub-groups:** None stated **Number:** 326 **Age:** 42.4 (sd=15.5), range = 18-87 **Sex:** 36% female **Concurrent diagnoses:** Not stated **Duration of fatigue:** 27 days to 2 years. **Further details:** Participants recruited by 120 GPs. Participants 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 relaxants 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. **Baseline functioning:** No difference in baseline functioning as measured by the MFI fatigue scale.	**Diagnostic criteria:** Not stated **Details:** Patients suffering from chronic postinfectious fatigue (CPIF). Febrile episode (after the disappearance of the initial infection - flu, bronchitis, common cold, gastro-enterisits etc.) accompanied by persistent 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. **Inclusion criteria:** Age more than 18 years. Participants with ongoing infection (e.g. chronic hepatitis), those who had experienced a traumatic situation in the previous quarter (e.g. bereavement), those with ongoing chronic illness with severe prognosis (e.g. cancer, aids, psychiatric or depressive illness), those with liver, renal endocrinological, cardiovascular, metabolic or auto-immune diseases requiring hospitalisation or surgical intervention were excluded. Women who were or were trying to become pregnant were also excluded.	**Drop-outs:** 16 participants 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 participants in placebo group stopped because they wanted to, 1 participant in 600mg and one in 400mg sul group judged the treatment not to work so stopped, 2 participants in 400 mg sul were not observed and 2 participants were lost to follow-up. **Adverse effects:** 9 participants in sul 400mg experienced side effects, 6 in 600mg sul group and 12 in placebo, side effects included agitation, palpitations, diarrhoea, cystitis, bronchitis, arthritic pain, back pain, asthma, abdominal pain, insomnia, constipation, gastro-enteritis, diffuse pain, sinusitis, headache, renal coli, vertigo, pharyngitis, tracheitis.

Results

Outcome 1	Outcome 2:	Outcome 3:
Outcome Fatigue as measured by MFI score, divided into general fatigue, physical fatigue, activity, motivation, and psychological fatigue. Combined results presented as mean (sd) **Baseline treatment group 400mg**: 16.7 (2.3) **Baseline treatment group 600mg**: 16.8 (2.3) **Baseline control group**: 16.6 (2.2) **Final treatment group 400mg**: 8.6 (3.4) **Final treatment group 600mg:** 8.9 (3.8) **Final 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** Clinical global impression: Global impression of severity of illness (CGI item 1). Reported as mean change (sd) **Final treatment group 400mg**: -2.06 (1.48) **Final treatment group 600 mg:** 1.98 (1.51) **Final 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** Activity: Baecke's measure of activity, divided into work, sport and leisure activity **Comments:** No difference in change in scores between the groups
Outcome 4:	**Outcome 5:**	
Outcome Illness severity: Ferreri's score of incapacity, reported as mean change (sd) **Final treatment group 400mg:** -12.9 (8.8) **Final treatment group 600mg:** -12.5 (9.1) **Final control group:** -12.1 (7.9) **Comments:** No significant differences between treatment groups	**Outcome** Fatigue: EVA scale **Final treatment group 400mg**: -4.5 (2.3) **Final treatment group 600mg**: -4.7 (2.3) **Final control group**: -4.3 (2.2) **Comments:** No significant differences between the groups	

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Vercoulen (1996)[58] **Study design:** RCT	**Intervention:** Fluoxetine **Number of participants in each arm:** 53 in placebo, 54 in treatment arm **Study duration**: 8 weeks **Length of follow-up:** 12 weeks **Purpose of intervention:** To assess the effect of fluoxetine in depressed and non-depressed participants with CFS **Intervention details:** **Intervention**: Fluoxetine (20mg) capsules taken once a day. **Control**: Placebo capsules taken once a day.	**Sub-groups:** Depressed and non-depressed participants **Number:** 48 depressed, 59 non-depressed **Age:** Mean 38-40 **Sex**: 80F, 27M **Concurrent diagnoses:** None stated **Duration of fatigue:** Median 5-6 years range 1-30 years **Further details:** Participants all on one CFS database at one hospital. **Baseline functioning:** See inclusion criteria	**Diagnostic criteria:** Oxford **Details:** No further details **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 participants had to have score on depression index of 16 or more, non-depressed participants 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	**Drop-outs:** 15% of treatment group stopped treatment because of side effects compared to 4% in placebo group. 11 participants dropped out altogether: 9/54 in treatment group and 2/53 in placebo group. **Adverse effects:** Two participants 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 participants complained of tremor (p=0.006) and perspiration (p=0.008).

Results

General comments	Outcome 1	Outcome 2:	Outcome 3:
General comments: No difference between fluoxetine 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 disturbance, neuro-psychological functioning, social interactions or cognitions. Depression subgroup: results only reported for outcome 3.	**Outcome** 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 **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** Depression **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** Recovery: change in status **Final treatment group:** Depressed: 1 improved, 12 unchanged, 8 worse. Non-depressed: 2 improved, 13 unchanged, 8 worse. **Final control group:** Depressed: 3 improved, 14 unchanged, 6 worse. Non-depressed: 3 improved, 21 unchanged, 4 worse. **Comments:** No participant reported complete recovery, no effects on self-reported change at follow-up testing

5. Supplements

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Behan (1990)[65] **Study design:** RCT	**Intervention:** Essential fatty acids **Number of participants in each arm:** 39 in treated group, 24 in placebo **Purpose of intervention:** To investigate the effects of high doses of essential fatty acids on the post-viral fatigue syndrome **Intervention details:** **Intervention**: Essential fatty acids. Each capsule contained 36mg gamma-linolenic acid (GLA), 17mg of eicosapentaenoic acid (EPA), 11mg of docosahexaenoic acid (DHA) and 255mg of linoleic acid. **Control:** Placebo. Placebo capsules contained 50mg linoleic acid in liquid paraffin. Participants took 8 capsules per day of either active preparation or placebo divided into 4 doses for 3 months, participants told to swallow capsules whole as the oils tasted slightly different. 10 IU of vitamin E was present in all capsules.	**Sub-groups:** None stated **Number:** 63 **Age:** 21-63 (mean 40) **Sex:** 27 men, 36 women **Concurrent diagnoses:** None stated **Duration of fatigue:** 1-3 years **Further details:** A febrile illness with upper respiratory or gastrointestinal symptoms of such severity that the participant was confined to bed for several days was the precipitating factor in all cases, all participants also complained at some time of palpitations, shooting pains in the chest and unsteadiness **Baseline functioning:** Not stated	**Diagnostic criteria:** Not stated **Details:** All participants 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 **Inclusion criteria:** Participants selected because of severity of symptoms, symptoms present for 1-3 years, all symptoms followed definite viral infection	**Drop-outs** No drop-outs **Adverse effects** No adverse effects stated

Results

Outcome 1	Outcome 2:	Outcome 3:
Outcome 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 treatment group**: 1.9 **Baseline control group**: 1.8 **Final treatment group**: 2.8 **Final control group**: 2.0 **Comments:** Mean difference between interventions = 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** General health: Participants overall condition evaluated as to whether felt worse, unchanged or better compared to baseline, made by doctor in consultation with the participant **Final treatment group:** 0 worse, 15% unchanged, 85% improved (p of difference between 2 groups using likelihood ratio test <0.0001) **Final control group:** 9% worse, 75% unchanged, 17% improved	**Outcome** Fatty acid concentration of erythrocyte membrane phospholipids **Comments:** Compared with normal controls at the beginning of the trial all participants 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

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Cox (1991)[67] **Study design:** RCT	**Intervention:** Magnesium **Number of participants in each arm:** 15 participants on active treatment (17 randomised) and 17 in control group. **Study duration:** 13 weeks **Length of follow-up:** 13 weeks **Purpose of intervention:** To test the hypothesis that participants with CFS have low red blood cell magnesium and that magnesium treatment would improve the wellbeing of such cases **Intervention details:** **Intervention**: 50% magnesium sulphate (1g in 2ml). **Control:** Placebo (2ml injectable water). Given as intramuscular injection in the gluteal region every week for 6 weeks.	**Sub-groups:** None stated **Number:** 34 **Age:** 18-56, mean 36 & 37 **Sex:** 11 male, 23 female **Concurrent diagnoses:** Not stated **Duration of fatigue:** 6-18 months **Further details:** Participants recruited from Centre for Study of Complementary medicine and from GPs in Southampton **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 plasma, whole blood and red blood cells)	**Diagnostic criteria:** Australian **Details:** No further detials **Inclusion criteria:** Duration of illnes greater than 6 months less than 18 months. Informed consent.	**Drop-outs:** 4 participants excluded before randomisation as did not satisfy diagnostic criteria. 2 treatment group participants dropped out, generalised rash developed in 1 participant, and the other could not get the co-opertion of his GP. **Adverse effects:** Not stated

Results

Outcome 1	Outcome 2:
Outcome General health: Nottingham health profile score (energy, pain emotional reactions, sleep, social isolation, physical mobility) **Baseline treatment group:** 284.9 (sd=71.5) **Baseline control group:** 261.1 (sd=91.6) **Final treatment group:** Change in score: -143.51 **Final control group:** Change in score: -24.74 **Comments:** p-value for difference in 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 Laboratory measures: Change in magnesium concentrations of plasma, whole blood and red blood cells (mmol/l) **Baseline treatment group:** Plasma: 0.80(sd=0.082) Whole blood: 0.99 (sd=0.07), Red blood cell: 1.29 (0.079) **Baseline control group:** Plasma: 0.81(sd=0.058) Whole blood: 1.00 (sd=0.046), Red blood cell: 1.28 (0.067) **Final treatment group:** Change after treatment: Plasma: 0.09(sd=0.09) Whole blood: 0.29 (sd=0.09), Red blood cell: 0.57 (0.19) **Final 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 magnesium was within the normal range in all group A participants but in only 1 group B participant.

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Kaslow (1989)[66] **Study design:** RCT	**Intervention:** Liver extract - folic acid - cyanocobalamin (LEFAC) **Number of participants in each arm:** 15 in each arm (cross-over trial), only 14 evaluated **Study duration:** 2 weeks **Length of follow-up:** 2 weeks **Purpose of intervention:** Participants with CFS were studied to evaluate the efficacy of treatment with LEFAC in alleviating symptoms **Intervention details: Intervention:** Extract of bovine liver (10ug/mL, cyanocobalamin equivalent) with folic acid (0.4mg/mL) and cyanocobalamin (100ug/mL). **Control**: 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.	**Sub-groups:** Not stated **Number:** 15 **Age:** 30 to 48 **Sex:** 3 male, 11 female **Concurrent diagnoses:** Not stated **Duration of fatigue:** Not stated **Further details:** Not stated **Baseline functioning:** Karnofsky (functional status) score at baseline ranged from 50 to 80, all participants had experienced previous treatment failures or had not tried any treatment. Normal values for blood tests, minor symptom scores 6-10, 9 had fever	**Diagnostic criteria** CDC (1988) **Details:** Not stated **Inclusion criteria:** Not stated	**Drop-outs:** 1 participant dropped out - participant that dropped out completed treatment but did not return questionnaire **Adverse effects:** None stated

Results

General comments:	Outcome 1	Outcome 2:	Outcome 3:	Outcome 4:
Trial continued for further 2 weeks during which time all participants that continued (n=11) were given LEFAC and knew that they were getting this. Significant improvements were found in all outcomes assessed as before, compared to scores on entry into the study (p=0.036, 0.01, 0.002 and 0.01 respectively)	**Outcome** Activity: Daily activity - subset of Karnofsky score (Functional status questionnaire) **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** Psychological assessment: Mental health - subset of Karnofsky score **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** Energy levels measured using Likert scales from 1 to 10 **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** Symptoms measured using Likert scales from 1 to 10 **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.

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Martin (1994)[68] **Study design:** Controlled trial	**Intervention:** Supplements **Number of participants in each arm:** 21 in each arm. Only 19 completed full crossover trial. **Study duration:** 26 weeks **Length of follow-up:** 26 weeks **Purpose of intervention:** To measure the effect of vitamin and mineral supplementation on symptoms of participants diagnosed as CFS in general practice **Intervention details: Intervention:** Vitamin and mineral mixture, contained mix of 35 vitamins and minerals. **Control:** Placebo. 2 tablets taken 4 times a day. Cross over trial with active ingredient/placebo taken for 3 months and then other taken for further 3 months. No washout.	**Sub-groups:** None stated **Number:** 42 **Age:** F mean 41.6(14.5), M mean 37.3(9.1) **Sex:** 13 M, 37 F **Concurrent diagnoses:** None stated **Duration of fatigue:** 3 to 120 months, mean 27 months **Further details:** All from one GP practice: Brechin & district **Baseline functioning:** Not stated	**Diagnostic criteria:** Author's own **Details:** 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: participant well before illness, exclusion of other cause of symptoms **Inclusion criteria:** Coxsackie B antibodies present	**Drop-outs:** 30 participants (15 in each group) completed 3 months of treatment, 19 (10 in one group, 9 in other) completed 6 months of treatment **Adverse effects:** None stated

Results

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

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Stewart (1987)[21] **Study design:** RCT	**Intervention:** Supplements **Number of participants in each arm:** 12 (cross-over trial) **Study duration:** 7 weeks **Length of follow-up**: 7 weeks **Purpose of intervention:** To investigate the effect of nutritional supplements on ME sufferers in New Zealand **Intervention details: Intervention:** 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. **Control:** Placebo capsules of similar colour and smell containing non-allergenic lactose-sugar free fillers. For 1st week no supplements given to either group, then one group of participants given supplements for 3 weeks. After first 3 weeks crossed over trial arms for further 3 weeks.	**Sub-groups:** None stated **Number:** 12 **Age:** Not stated **Sex:** Not stated **Concurrent diagnoses:** Not stated **Duration of fatigue:** Mean 7 years, range 2.5 to 16 years **Further details:** Diagnosed cause was judged to be a virus in 7 cases and 245T poisoning in 3, most participants had tried almost all available treatments **Baseline functioning:** Wide variability in participants of their condition, and also variable from one day to the next	**Diagnostic criteria:** Not stated **Details:** Participants diagnosed as having ME by their GPs and the study authors (no further diagnosis details) **Inclusion criteria:** Not stated	**Drop-outs:** 2 participants dropped out **Adverse effects:** None reported

Results

Outcome 1	Outcome 2:
Outcome 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 participants, no details on scales used **Comments:** 5/8 participants showed reduction in tiredness and improvement in well-being accompanying better digestion, for one other digestion improved but no effect on tiredness, in 1 participant improvement in tiredness occurred during follow-up period, for one other participant digestion improved, tiredness did not improve but overall condition did. Average % improvement in tiredness was 33% for 7 participants that showed positive change on this measure. During control conditions only 2 participants showed improvement (this was in first 3 week section of study) of 36% and 17%, one participant got worse by 23%. Two participants in control condition showed decrease in digestive scores (11% and 42% decrease), 2 participants maintained their improvement from experimental to control phase & 2 continued to improve	**Outcome** Bowel movements **Comments:** Cascara caused increase in bowel movements for nearly all participants during intervention, increased bowel movements nearly always accompanied improvement in digestion. For 8 participants showing digestive improvement, average improvement was 35%.

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Warren (1999)[64] **Study design:** RCT	**Intervention:** Essential fatty acids **Number of participants in each arm:** 24 in treatment group, 26 in placebo group **Study duration:** 26 weeks **Length of follow-up:** 26 weeks **Purpose of intervention:** To improve physical symptoms and depressive symptoms. **Intervention details: Intervention:** Efamol Marine 2x 500mg capsules taken 4 times a day. 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). **Control**: Placebo (same number of capsules containing sunflower oil). Placebo capsules did not contain EPA or DHA. Both intervention and placebo capsules contained 10IU vitamin E and trace riboflavin.	**Sub-groups:** None stated **Number:** 50 **Age:** 18-59 years, mean 37.1(11.9) **Sex:** 21 M, 29 F **Concurrent diagnoses:** None stated **Duration of fatigue:** Mean 4.0 (2.7) years **Further details:** 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. **Baseline functioning:** No significant differences between treatment and placebo groups with regard to physical symptoms, Beck scores or erythrocyte fatty acid profiles.	**Diagnostic criteria:** Oxford **Details:** Diagnosis confirmed by physicians in outparticipant setting. **Inclusion criteria:** Not pregnant, not receiving EFA supplements. Beck Depression Inventory score <30 at entry. Aged 18-65.	**Drop-outs:** 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 effects:** None stated.

Results

Outcome 1	Outcome 2:	Outcome 3:
Outcome 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 treatment group:** 7.0 (range 3-13) **Baseline control group:** 7.5 (range 5-13) **Final treatment group**: 5.5 (range 3-13) change in symptom score -1.0 (range -7 to 3) **Final control group**: 6.0 (range 1-14) change in symptom score -1.5 (range -7 to 9) **Comments**: p for difference in change = 0.54.	**Outcome** Beck Depression Inventory Self-questionnaire 21 items each scoring 0-3 in severity. **Baseline treatment group:** 15.0 (range 1-26) **Baseline control group:** 15.0 (range 4-26) **Final treatment group:** 12.0 (range 5-23) change -2.5 (-10 to 8) **Final control group**: 11.0 (range 1-46) change -4.0 (-26 to 8) **Comments:** p for difference in change = 0.09.	**Outcome** Participant assessment of whether they had improved or not **Final treatment group:** 29% improved **Final control group**: 46% improved **Comments:** p for difference = 0.09.

6. Complementary/alternative medicine

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Awdry (1996)[33] **Study design:** RCT	**Intervention:** Homeopathy **Number of participants in each arm:** 32 **Study duration**: 52 weeks **Length of follow-up:** 52 weeks **Purpose of intervention:** To investigate the effectiveness of homeopathy in treating CFS/ post viral fatigue syndrome **Intervention details: Intervention**: Variety of homeopathic remedies 'as indicated', assessed by homeopath. **Control:** Placebo - identical but inert powder or tablet.	**Sub-groups:** None stated **Number:** 64 **Age:** mean 39.9FH, 37.7MH, 42.8FP, 37.5MP **Sex:** H: 8M 22F; P: 10M 21F **Concurrent diagnoses:** none stated **Duration of fatigue:** Homeopathy: 4.8yrs M, 5.0yrs F. **Placebo:** 5.8yrs M, 5.0yrs F. **Further details:** All volunteers having read about trial in literature produced by Action for ME and the ME association. **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.	**Diagnostic criteria:** Oxford **Details:** Independent verification of their ME diagnosis from their doctor or consultant. In writing from the relevant clinic. **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	**Drop-outs:** 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 effects:** none stated

Results

Outcome 1	Outcome 2:
Outcome Daily graphs completed by each participant **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** End of trial self-assessment charts completed by each participant 5 categories: fatigue, disability, mood disturbance, myalgia, sleep disturbance. **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.

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	With-drawals
Author (year) Field (1997)[69] **Study design:** RCT	**Intervention:** Massage therapy **Number of participants in each arm:** 10 **Study duration:** 5 weeks **Length of follow-up**: 5 weeks **Purpose of intervention:** To examine the effects of massage therapy on the well-being of participants with chronic fatigue syndrome (expected to reduce depression, anxiety and stress hormones) **Interve ntion details: Intervention:** Massage therapy given twice a week for 5 weeks and consisted of gentle pressure to arms, torso, legs and head. **Control:** Control group received tactile stimulation from Electro-Acuscope which was not switched on, rolled over same body parts as massage group. 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.	**Sub-groups:** None stated **Number:** 20 **Age:** 47 (mean) **Sex:** 80% women **Concurrent diagnoses:** Not stated **Duration of fatigue:** Not stated **Further details:** Primarily middle SES, 80% white, 20% Hispanic, 55% married, 85% graduates, 30% employed, 56% had never had a massage	**Diagnostic criteria:** Not stated **Details:** Participants with chronic fatigue immunodeficiency syndrome **Inclusion criteria:** Not stated	**Drop-outs:** Not stated **Adverse effects:** Not stated

Results

Outcome 1	Outcome 2:	Outcome 3:
Outcome Depression: CESD depression score - 20 item self-report scale **Baseline treatment group**: 22.8 **Baseline control group:** 27.6 **Final treatment group:** 14.8 **Final control group:** 26.6 **Comments:** p-value for before-after comparison using ANOVA: f(2,17)=12.18, p<0.005	**Outcome** Profile of fatigue symptoms scores (fatigue and somatic symptoms) **Baseline treatment group:** fatigue: 54.8, emotional distress: 34.6, cognitive distress: 37.7, somatic symptoms: 37.2 **Baseline control group:** fatigue: 53.4, emotional distress: 43.6, cognitive distress:35.8, somatic symptoms: 43.6 **Final treatment group**: fatigue: 47.6, emotional distress: 23.2, cognitive distress:31.4, somatic symptoms: 27.4 **Final 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** Pain in last week **Baseline treatment group**: 4.1 **Baseline control group**: 5.0 **Final treatment group**: 2.8 **Final control group**: 6.6 **Comments:** p-value for before-after comparison using ANOVA: f(2,17)=13.65, p<0.005
Outcome 4:	**Outcome 5:**	
Outcome Sleep – number of hours of sleep **Baseline treatment group**: 6.8 **Baseline control group**: 6.5 **Final treatment group**: 7.5 **Final control group**: 6.2 **Comments**: p-value for before-after comparison using ANOVA: f(2,17)=4.72, p<0.05	**Outcome** Laboratory measures Norepinephrine, epinephrine, dpamine and Cortisol **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)	

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Perrin (1998)[20] **Study design:** Controlled trial	**Intervention:** Osteopathy **Number of participants in each arm:** 35 in participant group, 40 in control group. **Study duration**: 52 weeks **Length of follow-up:** 52 weeks **Purpose of intervention:** To reduce the detrimental effect of the symptoms associated with ME. **Intervention details: Intervention**: Osteopathic manipulation of the thoracic spine. 20 sessions over 1 year. 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. **Control:** were allowed to receive any other treatments.	**Number:** 58 **Age:** 18-55 **Sex:** 39 F, 18 M (1 uncertain) **Concurrent diagnoses:** None stated **Duration of fatigue:** Not stated **Further details:** 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'. **Baseline functioning:** Not clear	**Diagnostic criteria:** CDC (1988) **Details:** CDC (1988) criteria for CFS; London criteria for ME **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.	**Drop-outs** Two drop-outs in the participant group, 17 drop-outs in the control group. **Adverse effects** None stated

Results

General comments:	Outcome 1	Outcome 2:	Outcome 3:	Outcome 4:
Values taken from graphs so not very accurate, 0% = symptom free, 100% = worst symptoms possible. Final measurements are at 6 months interim at 3 months. O	**Outcome** Fatigue: Profile of fatigue related states **Baseline treatment group**: 41.5 **Baseline control group**: 62 **Final treatment group:** 32.5 **Final control group**: 59 **Comments:** Interim: control 59.5, treatment 56.	**Outcome** General health questionnaire: developed for this study based on 26 common ME symptoms. High=poor. **Baseline treatment group**: 80% **Baseline control group**: 68% **Final treatment group**: 68% **Final control group**: 67.5% **Comments**: Interim: control 65%, treatment 70%	**Outcome** Back pain questionnaire **Baseline treatment group**: 76.5% **Baseline control group**: 61.5% **Final treatment group**: 68% **Final control group**: 61.5% **Comments:** Interim: control 60.5%, treatment 67.5%	**Outcome** Depression - BDIRevised **Baseline treatment group:** 25% **Baseline control group**: 27% **Final treatment group**: 20% **Final control group**: 21.5% **Comments:** Interim: control 24%, treatment 18%
	Outcome 5:	**Outcome 6:**	**Outcome 7:**	**Outcome 8:**
	Outcome Anxiety: Beck anxiety inventory **Baseline treatment group**: 32.5% **Baseline control group**: 25.5% **Final treatment group**: 25.5% **Final control group**: 28.5% **Comments:** Interim: control 25%, treatment 22%	**Outcome** Sleep: Morgan-Gledhill sleep questionnaire **Baseline treatment group**: 126.5 **Baseline control group**: 133 **Final treatment group**: 113 **Final control group**: 126.5 **Comments**: Interim: control 128%, treatment 107%	**Outcome** Nottingham health questionnaire **Baseline treatment group**: 41.5% **Baseline control group**: 38% **Final treatment group**: 32.5% **Final control group**: 37.5% **Comments:** Interim: control 35%, treatment 33.5%	**Outcome** Cognitive function: Broadbent's cognitive function questionnaire **Baseline treatment group**: 58% **Baseline control group**: 57% **Final treatment group**: 54.5% **Final control group**: 61.5% **Comments:** Interim: control 58.5%, treatment 53.5%

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Weatherley-Jones (2001) **Study design:** RCT	**Intervention:** Homeopathy **Study duration:** 6 months **Length of follow-up**: 6 months **Number of subjects in each arm:** 53 in treatment arm, 51 in placebo **Purpose of intervention:** To test whether patients with CFS treated by a homeopath with homeopathic remedies showed clinically significant improvement compared to patients treated by a homeopath with placebo. **Intervention details:** 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	**Sub-groups:** None stated **Number:** 104 **Age:** Greater than 18 **Sex:** Not reported **Concurrent diagnoses:** None reported **Duration of fatigue:** Not reported **Further details:** Participants were recruited from two outpatient departments in UK hospitals. **Baseline functioning:** Not reported	**Diagnostic criteria:** Oxford **Details:** None reported **Inclusion criteria:** Patients aged over 18 years old	**Drop-outs:** 11 withdrew from treatment arm, 8 from placebo group **Adverse effects:** Not reported

Results

General comments:

Outcome 1	Outcome 2:	Outcome 3:
Outcome MFI general fatigue (Multidimensional Fatigue Inventory) **Final treatment group:** Post treatment improvement mean = 2.79 (sd=3.93). Number showing clinical benefit = 20 (47.6) **Final control group:** Post treatment improvement mean = 1.27 (sd=2.62). Number showing clinical benefit = 11 (26.8%) **Comments:** Analysis of covariance for difference in post treatment improvement mean p = 0.026, chi2 for difference in number showing clinical benefit = 0.041	**Outcome** MFI physical fatigue **Final treatment group:** Post treatment improvement mean = 2.29 (sd=3.92). Number showing clinical benefit = 17 (40.5%) **Final control group:** Post treatment improvement mean = 1.24 (sd=2.76). Number showing clinical benefit = 11 (26.8%) **Comments:** Analysis of covariance for difference in post treatment improvement mean p = 0.162, chi2 for difference in number showing clinical benefit = 0.139	**Outcome** MFI mental fatigue **Final treatment group:** Post treatment improvement mean = 2.60 (sd=4.13). Number showing clinical benefit = 18 (45.0%) **Final control group:** Post treatment improvement mean = 1.88 (sd=2.54). Number showing clinical benefit = 15 (36.6%) **Comments:** Analysis of covariance for difference in post treatment improvement mean p = 0.324, chi2 for difference in number showing clinical benefit = 0.293
Outcome 4:	**Outcome 5:**	**Outcome 6:**
Outcome MFI reduced activity **Final treatment group:** Post treatment improvement mean = 2.38 (sd=4.11). Number showing clinical benefit = 17 (42.5%) **Final control group:** Post treatment improvement mean = 1.63 (sd=2.71). Number showing clinical benefit = 13 (32.5%) **Comments:** Analysis of covariance for difference in post treatment improvement mean p = 0.264, chi2 for difference in number showing clinical benefit = 0.244	**Outcome** MFI reduced motivation **Final treatment group:** Post treatment improvement mean = 1.29 (sd=4.18). Number showing clinical benefit = 15 (35.7%) **Final control group:** Post treatment improvement mean = 1.63 (sd=3.06). Number showing clinical benefit = 17 (41.5%) **Comments:** Analysis of covariance for difference in post treatment improvement mean p = 0.80, chi2 for difference in number showing clinical benefit = 0.377	**Outcome** Improvement in all primary outcomes **Comments:** 8 patients in the treatment group and 3 in the placebo group showed improvement in all 5 primary outcomes. Chi2 for the difference in the number p= 0.089

7. Other

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Goudsmit (1996)[73] **Study design:** Controlled trial	**Intervention:** Combination **Intervention duration:** 5-6 months **Number of subjects in each arm:** 25 in treatment group, 27 in control group (22 in each arm analysed) **Purpose of intervention:** To assess the effectiveness of the Ho-Yen programme in the management of people with post-infectious CFS. **Intervention details: 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.	**Sub-groups:** Depression, anxiety, fatigue, duration of illness **Number:** 52 **Age:** Intervention group mean 39.6 (13.4) youngest 15. Control group mean 37.7, youngest 14 **Sex:** 35 F, 17 M **Concurrent diagnoses:** Additional illnesses in 23 participants included asthma, epilepsy, arthritis, ulcers, diverticulitis, hiatus hernia, sinusitis and kidney infections **Duration of fatigue:** 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 **Further details:** 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). **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.	**Diagnostic criteria:** Other **Details:** Post-infectious fatigue syndrome diagnosed using Dr Ho-Yen's criteria **Inclusion criteria:** None stated.	**Drop-outs:** 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 contraceptives, and one was lost to follow up after 3 months. **Adverse effects:** None reported as such: 9% of intervention group and 18% of control group 'felt worse' after treatment duration.

Results

General comments:	Outcome 1	Outcome 2:	Outcome 3:	Outcome 4:
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.	**Symptoms**: Subscales of profile of fatigue related symptoms: fatigue(F), cognitive difficulty(CD), somatic symptoms(SS). Mean(sd) **Baseline treatment group:** F 3.5(1.61); CD 2.53(1.33); SS 1.94(1.34) **Baseline control group:** F 4.2(1.14); CD 3.06(1.44); SS 2.29(1.04) **Final treatment group:** F 2.68(1.41); CD 2.28(1.42); SS1.54(1.15) **Final 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).	**Mood:** Mishel uncertainty in illness scale-community form: uncertainty(U); self-efficacy(SE) mean(sd) **Baseline treatment group:** U 64.77(7.88); SE 47.05(17.97) **Baseline control group:** U70.19(15.87); SE 62.71(14.05) **Final treatment group:** U 54.3(12.14); SE 62.14(14.55) **Final 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	**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 treatment group:** MA 3.22(0.85); AI 4.00 (0.88); FS 3.6(0.83); SI 3.21(0.91) **Baseline control group:** MA 3.42(0.83); AI 4.17(0.83); FS 3.67(1.08); SI 3.29(1.11) **Final treatment group:** MA 2.59(0.79); AI 4.45(0.86); FS 3.46(1.05); SI 3.46(0.86) **Final 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.	**Anxiety and depression:** Hamilton anxiety and depression scale (HAD) **Baseline treatment group:** A 8.77(4.9); D 7.95(3.84); D corrected 5.82(3.26) **Baseline control group:** A 8.81(4); D 9.59(4.04); D corrected 6.86(3.89) **Final treatment group:** A 7.14(3.86); D 6.59(4.12); D corrected 4.91(3.58) **Final 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: Functional impairment scale **Baseline treatment group**: 22.81(4.74) **Baseline control group**: 22.91(4.73) **Final treatment group**: 20.86(6.24) **Final control group**: 22.73(5.71)			

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Marlin (1998)[71] **Study design:** Controlled trial	**Intervention:** Multi treatment (medical treatment of symptoms plus anxiety/ affective disorder, CBT & social) **Number of participants in each arm:** 51 in treatment programme, 20 untreated. Assessed: 17 in treatment programme, 5 untreated. **Study duration**: 52 weeks **Length of follow-up:** 52 weeks **Purpose of intervention:** To improve overall functional and symptomatic status and maintain improvements over time. **Intervention details: Intervention:** 1. Bringing participant under optimal medical management, 2. Treating any ongoing affective or anxiety disorder pharmacologically and 3. Implementing comprehensive CBT programme. Average duration of treatment was 6 months (range 2-12).Participants were seen at home 2-3 x per week by behavioural medicine field researcher. Program tailored to each participant 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. **Control:** No treatment.	**Sub-groups:** None stated **Number:** 71 **Age:** mean 40-43 years, range 31-59. **Sex**: 6 M 16 F **Concurrent diagnoses:** none **Duration of fatigue:** mean 54-56 months, range 5-117. **Further details:** 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 follow-up. **Baseline functioning:** All were disabled with regard to 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.	**Diagnostic criteria** CDC (1994) **Details:** Assessment at privately funded multi-disciplinary clinic. Assessment by general internist, psychiatrist, clinical psychologist and kinesiologist. Inclusion criteria none stated.	**Drop-outs:** 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 effects:** None reported
Results				
Outcome 1				
Outcome Employment status Participants either returned to work or work equivalent (education retraining, job searching or other non-paid activity) or remained disabled. **Baseline treatment group:** all 17 disabled **Baseline control group:** all 5 disabled **Final treatment group:** 11 had returned to work , 4 were 'work equivalent', 2 were still disabled **Final control group:** 1 had returned to work, 1 was 'work equivalent', 3 were still disabled.				

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Shlaes (1996)[72] **Study design:** Controlled trial	**Intervention:** Buddy and mentor programme **Duration of intervention:** 4 months **Duration of follow-up**: 4 months **Number of participants in each arm:** 6 **Purpose of intervention:** The buddy/mentor program was created to try to fill the need for support and to evaluate if social support is an effective means of reducing stress in people who have CFS. It was hypothesised that the group who received the buddy/mentor services would experience improvements in both physical and psychological functioning. **Intervention details:** Half participants given buddies and mentors during study period, other half told they would receive buddy 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.	**Sub-groups:** None stated **Number:** 12 **Age:** 36-57 **Sex:** 3 male, 9 female **Concurrent diagnoses:** None stated **Duration of fatigue:** Not stated **Further details:** 11 Caucasian, 1 Asian/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 Chicago-area CFS newsletters and a letter sent out through the Chicago CFS Association **Baseline functioning:** Not reported	**Diagnostic criteria** Not stated **Details:** Participants with CFS **Inclusion criteria** Participants were individuals with CFS who felt that they would benefit from information, emotional support and help with weekly tasks.	**Drop-outs** 2 participants, one in each group, could not complete post-test measures due to severity of illness. **Adverse effects** None reported

Results

General comments:	Outcome 1	Outcome 2:	Outcome 3:	Outcome 4:
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.	**Outcome** Fatigue severity: Fatigue self-rating scale (validated) **Comments:** Participants in intervention group showed significant decrease in fatigue severity compared to control ($p<0.03$) - fatigue increased in control group	**Outcome** Positive thinking: Life Orientation test (revised) **Comments:** Participants in intervention group showed increases in positive thinking control group showed decreases, difference approached significance ($p=0.08$)	**Outcome** Depression: CES-D scale **Comments:** No significant differences between groups	**Outcome** Psychological distress: Brief Symptom inventory **Comments:** No significant differences between groups
	Outcome 5:	**Outcome 6:**	**Outcome 7:**	
	Outcome Perceived stress: Perceived stress scale, short version **Comments:** No significant differences between groups	**Outcome** Coping strategies: COPE scales **Comments:** No significant differences between groups	**Outcome** Perceived social support: Interpersonal support evaluation list short form **Comments:** No significant differences between groups	

Study details	Intervention details	Participant details	Diagnosis and inclusion criteria	Withdrawals
Author (year) Teitelbaum (2001) **Study design:** RCT	**Intervention:** Multi treatment (includes supplements) **Study duration:** approximately 3 months **Length of follow-up**: approximately 3 months **Number of participants in each arm:** 38 in active group, 34 in placebo. **Purpose of intervention:** To test the efficacy of an integrated treatment approach based on simultaneously treating various problems associated with CFS and or Fibromyalgia (FMS). Intervention details: 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	**Sub-groups:** None stated **Number:** 72 **Age:** mean 44.6 (sd=8.1), range 23-61. Placebo patients were an average 4 years older than intervention patients. **Sex:** 92% female **Concurrent diagnoses:** All patients had FMS **Duration of fatigue:** mean = 8.3 years (sd=6.5), range 0.5 - 34 years. **Further details:** 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. **Baseline functioning:** Entry visit mean analogue 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).	**Diagnostic criteria:** CDC (1994) **Details:** All patients were required to meet 1990 American College of Rheumatology criteria for FMS (fibromyalia). Patients were excluded if they had major intercurrent illnesses (e.g. cancer, multiple sclerosis, poorly controlled diabetes, emphysema, or lupus) that could cause their symptoms. All but three also met CFS criteria. **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.	**Drop-outs:** 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 effects:** 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

General comments:	Outcome 1	Outcome 2:	Outcome 3:	Outcome 4:
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.	**Outcome** 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 treatment group:** 176.1 (70.3) **Baseline control group:** 177.1 (57.6) **Final treatment group:** 310.3 (111.3) **Final 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** FIQ scale: Fibromyalgia Impact Questionnaire (disability index) scored from 0-100, the higher the score the higher the disability. **Baseline treatment group:** 54.8 (10.3) **Baseline control group:** 51.4 (8.4) **Final treatment group:** 33.2 (18.2) **Final 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** TPI: Tender Point Index, calculated by multiplying the number of positive tender points by their degree of tenderness. Maximum score of 72. **Baseline treatment group:** 31.7 (10.5) **Baseline control group:** 35.0 (10.6) **Final treatment group:** 15.5 (9.5) **Final control group:** 32.3 (11.4) **Comments:** p-value for t-test of difference between values at final readings <0.0001	**Outcome** Patient's overall response **Final treatment group:** much better = 16, better = 14, same = 2, worse = 0, much worse = 1 **Final control group:** Much better= 3, better = 9, , same = 11, worse = 6, much worse =4 **Comments:** Cochran-Mantel-Haenszel trend test, p<0.0001

APPENDIX C: STRUCTURED ABSTRACT OF CBT SYSTEMATIC REVIEW

Authors
Price JR, Coupler J

Title
Cognitive behaviour therapy for adults with CFS

Author's objective
To systematically review all randomised controlled trials of cognitive-behaviour therapy (CBT) for adults with chronic fatigue syndrome (CFS). To test the hypothesis that CBT is more effective than orthodox medical management or other interventions in adults with CFS.

Type of intervention
Treatment

Specific interventions included in the review
Cognitive Behavioural therapy, interventions which met the following criteria::
1. A psychological therapy which incorporated both attempted modification of though and beliefs about symptoms and illness and attempted modification of behavioural responses to symptoms and illness, such as rest, sleep and activity. Two types of CBT:
Type A: attempted to increase activity and reduce rest time in a systematic manner, independent of symptoms, towards normal level
Type B: Attempted to tailor the participant's rest and activity towards levels which were compatible with the limitations imposed by the disorder.
2. Individual or group treatment
Controls: trials which included orthodox medical management (elements of clinic attendance, investigation, reassurance and simple advise) or other intervention which did not meet the criteria for CBT as control treatment were included in the review. Trials of experimental intervention which included drug treatment, or self-help treatments as part of the intervention were excluded.

Participants included in the review
Participants over the age of 16 who fulfilled the following criteria for CFS were included, irrespective of gender, culture, or setting:
1. Fatigue is the principal symptom
2. Fatigue is medically unexplained
3. Fatigue is of sufficient severity to significantly disable or distress the participant
4. Fatigue is of duration of over 6 months
Trials which included several disorders were included if over 90% of participants had CFS according to the above criteria.

Outcomes assessed in the review
Physical functioning, usually measured by rating scales. Trials had to measure one or more aspects of physical functioning or of symptoms, quality of life, health service resource use, compliance with and acceptability of intervention.

Study designs of evaluations included in the review
Randomised controlled trials in which participants with CFS receiving CBT were compared with a control group receiving orthodox medical management or another intervention. Trials which randomised therapists rather than participants to intervention or control group were included, provided that the specific aim of the study was to examine the effect of the intervention. Trials had to measure outcomes at least one month after the cessation of treatment.

What sources were searched to identify primary studies?
The following electronic database were searched: MEDLINE (1966 to June 1988), EMBASE (1980 to May 1998), PsychLIT (1974 to September 1997), Biological Abstracts (January 1985 to March 1998), SIGLE (1970 to 1995), Index to Scientific and Technical Proceedings (1982 to 1998) and Science Citation Index. A comprehensive search strategy was developed to search these databases (further details in paper). Known specialists in the field and principal authors of studies identified in the

literature searches were contacted to help identify further studies. Both published and unpublished studies were included. Studies published in any language were considered.

On what criteria was the validity of primary studies assessed?
Trials were allocated to 3 quality categories: A (high quality; all of criteria met), B (moderate quality; one or more criteria only partially met), and C (low quality; one ore more criteria not met). The following quality criteria were assessed:

1. Concealment of treatment allocation
2. Presentation of outcomes of participants who withdrew from the study
3. Clear definition of outcome measures, blinding of assessors and appropriateness of duration of follow-up
4. Reporting and comparability of baseline characteristics
5. Comparability of care programmes, other than interventions
6. Definition of inclusion criteria

Trials of category C were excluded from the review.

How were decisions on the relevance of primary studies made?
Each reviewer (2) independently decided whether each potential trial fulfilled inclusion criteria.

How were judgements of validity made?
Each reviewer independently assessed the quality of included studies.

How was the data extracted from primary studies?
Data was extracted independently by the reviewers. When there was disagreement, this was discussed and a consensus decision was reached. Information was collected on: characteristics of participants, characteristics of interventions, characteristics of outcome measures and results. If any information was not available in the published trial, it was sought by correspondence with the trial authors.

Number of studies included
3 RCTs (n=164; 60 in 2 trials, in third trial 44 randomised to 2 arms of relevance to the review out of total sample size of 90).

How were the studies combined?
Two comparisons were made: Type A CBT versus other intervention and Type B CBT versus alternate intervention. The initial analysis of dichotomous outcomes used the odds ratio (OR). When appropriate, ORs were combined across studies using Peto's fixed effect method to give the pooled OR with 95% confidence intervals. The number needed to treat, with 95% confidence intervals, was also calculated. Continuous outcome measures were transformed, where possible, to dichotomous outcome measures. Where this was not possible, the effect size, with confidence intervals, was calculated for each study.

How were differences between studies investigated?
Not stated

Results of the review
Treatment duration varied between 4-6 months. Length of follow-up post-treatment varied from 3-7 months. Two trials were conducted in the UK and 1 in Australia. All three trials included adult outpatients with CFS. 2 trials used the Oxford criteria for diagnosis of CFS, the other trial used the Australian criteria. All 3 trials used CBT type A on an individual basis with weekly/bi-weekly sessions. One study compared CBT with relaxation, one with routing medical care, and one compared CBT with placebo injections to routine medical care and placebo injections.

Two of the studies were rated as 'high' and one of 'moderate' methodological quality.

Physical function: 2 trials found a beneficial treatment with CBT at final follow-up compared to relaxation (OR: 0.15, 95% CI: 0.05, 0.41) or routine medical care (OR: 0.16, 0.06 to 0.44). The beneficial effect of one of these trials appeared mainly at the end of the formal treatment programme. Other measures of physical function including SF-36 score, Work and Social Adjustment Scale score, and the long-term goals rating also demonstrated a beneficial effect of CBT compared to relaxation.

The second study found a significant benefit of CBT compared with routine medical care on interference with activities, weekly days in bed, and distance walked in 6 minutes. The third trial did not report functional results in such a way as to allow reliable interpretation, however it does appear that the groups do not have significantly different outcomes.

Fatigue: This was addressed by all three trials but different measures were used in each trial. CBT was found to reduce fatigue compared to relaxation and routine medical care, again the third study did not present results in a manner which permitted interpretation.

Quality of life*:* CBT appears to benefit quality of life as assessed by 2 studies

Health service resource use*:* other treatments commenced during the trial was measured in 2 trials and did not show significant differences between treatment and control groups.

Compliance and acceptability of intervention*:* the number of treatment completers was available for 2 of the trials, there was no significant difference in treatment completion between CBT and either relaxation or routine medical care. The perceived usefulness of treatment was greater with CBT than with relaxation but this difference was not significant.

Other outcomes: Participants receiving relaxation were significantly more likely to continue to satisfy diagnostic criteria for CFS than those receiving CBT (OR 0.12, 95% CI: 0.04, 0.37), and were more likely to be dissatisfied with their treatment (OR: 0.34, 95% CI:0.12, 0.95). Participants receiving CBT were more likely to rate themselves as globally improved than those receiving either relaxation (OR: 0.23, 95% CI: 0.08, 0.64) or routine medical care (OR: 0.23, 95% CI: 0.08, 0.63).

Was any cost information reported?
None reported

Author's conclusions
CBT is a more effective treatment for adult out-participants with CFS than either routine medical care or relaxation.

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
Hickie	1998	Good	Good	Yes	Yes	Good	Good	Good	Good	Good	Good	Adequate	19
Teitelbaum	2001	Good	Adequate	Yes	Yes	Good	Good	Good	Good	Good	Good	Good	19
Rowe	2000	Good	Not stated	Yes	Yes	Good	Good	Good	Good	Good	Good	Good	18
Cleare	1999	Good	Good	Yes	Yes	Good	Good	Adequate	Good	Good	Good	Adequate	18
Deale	1997	Good	Good	No	Yes	Good	Good	Good	Good	Good	Good	Adequate	18
Fulcher	1997	Good	Good	No	Yes	Good	Good	Good	Adequate	Good	Good	Adequate	17
Behan	1990	Good	Good	Yes	Yes	Good	Good	Good	Good	Good	Not stated	Adequate	17
Wearden	1998	Good	Not stated	Yes	Yes	Good	Good	Good	Good	Good	Good	Adequate	17
Powell	2000	Good	Good	Not stated	Not stated	Good	Good	Good	Good	Good	Good	Adequate	17
Peterson	1998	Good	Good	Yes	Yes	Not stated	Good	Poor	Good	Good	Good	Good	16
Prins	2001	Good	Good	No	No	Good	Poor	Good	Good	Good	Good	Good	16
Rowe	1997	Adequate	Not stated	Yes	Yes	Good	Good	Adequate	Good	Good	Good	Good	16
Warren	1999	Adequate	Good	Yes	Yes	Good	Good	Poor	Good	Good	Good	Adequate	16
Straus	1988	Adequate	Adequate	Yes	Yes	Good	Adequate	Poor	Good	Good	Good	Good	15
Peterson	1990	Good	Not stated	Yes	Yes	Adequate	Good	Poor	Good	Good	Good	Good	15
Cox	1991	Good	Not stated	Yes	Yes	Good	Good	Poor	Good	Good	Good	Adequate	15
McKenzie	1998	Not stated	Not stated	Yes	Yes	Good	Good	Adequate	Good	Good	Good	Adequate	14
Sharpe	1998	Good	Not stated	Not stated	Not stated	Poor	Good	Good	Good	Good	Good	Adequate	13
Vollmer Conna	1997	Not stated	Not stated	Yes	Yes	Good	Good	Good	Good	Good	Not stated	Adequate	13
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
Steinberg	1996	Not stated	Not stated	Yes	Yes	Good	Adequate	Poor	Good	Adequate	Good	Good	12
Forsyth	1999	Not stated	Not stated	Yes	Yes	Good	Good	Adequate	Good	Good	Not stated	Adequate	12
Vercoulen	1996	Good	Not stated	Yes	Yes	Good	Adequate	Poor	Good	Good	Not stated	Adequate	12
Strayer	1994	Adequate	Not stated	Yes	Yes	Good	Good	Poor	Good	Good	Not stated	Adequate	12
See	1996	Not stated	Not stated	Yes	Yes	Good	Good	Adequate	Good	Poor	Not stated	Good	11
DuBois	1986	Good	Good	Yes	Not stated	Not stated	Good	Poor	Good	Good	Not stated	Not stated	11
Kaslow	1989	Not stated	Not stated	Yes	Yes	Adequate	Good	Poor	Good	Adequate	Adequate	Adequate	10
Tiev	1999	Not stated	Not stated	Yes	Yes	Good	Adequate	Poor	Good	Good	Not stated	Adequate	10
Field	1997	Adequate	Not stated	No	Yes	Good	Not stated	Not stated	Good	Good	Not stated	Adequate	9
Snorrason	1996	Not stated	Not stated	Yes	Yes	Good	Good	Poor	Good	Poor	Not stated	Adequate	9
Weatherley-Jones	2001	Not stated	Not stated	Yes	Yes	Not stated	Adequate	Poor	Adequate	Good	Good	Not stated	8
Natelson	1996	Not stated	Not stated	Yes	Yes	Poor	Good	Poor	Good	Adequate	Not stated	Adequate	8
Awdry	1996	Not stated	Not stated	Yes	Yes	Good	Poor	Poor	Good	Poor	Not stated	Not stated	6
Stewart	1987	Adequate	Not stated	Yes	Yes	Good	Poor	Poor	Poor	Poor	Not stated	Adequate	6
Brook	1993	Good	Not stated	Not stated	Not stated	Not stated	Good	Poor	Good	Poor	Not stated	Not stated	6
Moorkens	1998	Not stated	Not stated	Yes	Yes	Not stated	Poor	Poor	Good	Poor	Not stated	Adequate	5
Lerner	2001	Not stated	Not stated	Yes	Yes	Not relevant	Not stated	Not stated	Not stated	Not stated	Not stated	Not clear	4

b. Controlled trials

Study details		Participant blinding	Investigator blinding	Baseline comparability of groups	Follow-up	Drop-outs (Intention-to-treat)	Outcome objectivity	Statistical Analysis	Appropriateness of control	Sample-size calculation	Control for confounding	Comparability of treatment of groups	VS
Natelson	1998	Yes	Not stated	Good	Good	Poor	Good	Adequate	Good	Not stated	Not stated	Adequate	11
Martin	1994	Yes	Yes	Good	Poor	Poor	Good	Adequate	Good	Poor	Poor	Adequate	10
Andersson	1998	Yes	Yes	Good	Poor	Poor	Good	Poor	Good	Not stated	Not relevant	Adequate	9
Schlaes	1996	No	No	Not stated	Adequate	Poor	Adequate	Good	Adequate	Poor	Poor	Poor	4
Marlin	1998	No	No	Poor	Poor	Poor	Good	Poor	Poor	Not stated	Poor	Adequate	3
Goudsmit	2000	No	No	Poor	Poor	Poor	Adequate	Adequate	Poor	Not stated	Poor	Not stated	2
Friedberg	1994	No	No	Poor	Not stated	Not stated	Adequate	Poor	Poor	Poor	Poor	Not stated	1
Perrin	1998	No	No	Not stated	Poor	Poor	Not stated	Poor	Poor	Not stated	Poor	Poor	0

APPENDIX E: LIST OF EXCLUDED STUDIES

Author	Year	Intervention?	CFS?	Study?	Study Design
Anonymous[81]	1993	Yes	Yes	No	
Anonymous[82]	1992	Yes	Yes	No	
Ablashi[83]	1996	Yes	Yes	Yes	Case Study
Adams[84]	1998	No	No	No	
Adolphe[85]	1988	Yes	Yes	Yes	Case Study
Allen[86]	1992	Yes	Yes	Yes	Case Study
Altura[87]	1994	Yes	Yes	No	
Amjad[88]	1998	Yes	Yes	Yes	Treatment cohort
Anderson[89]	1997	No	Yes	Yes	
Anderson[90]	1992	No	Yes	Yes	
Anderson[91]	1988	Yes	Yes	Yes	Treatment cohort
Andersson[27]	1998	Yes	Yes	Yes	Controlled trial
Ashar[92]	1999	Yes	Yes	Yes	Case Study
Balter[93]	1997	Yes	Yes	Yes	Treatment cohort
Baschetti[94]	1999	No	Yes	No	
Baschetti[95]	1999	Yes	Yes	No	
Baschetti[96]	1999	No	Yes	No	
Baschetti[97]	1995	Yes	Yes	Yes	Case Study
Baschetti[98]	1998	No	Yes	No	
Basseleur[99]	1995	No	No	No	
Bates[100]	1994	No	Yes	Yes	
Bazelmans[101]	2001	No	Yes	Yes	
Behan[102]	1985	No	Yes	Yes	
Behan[103]	1995	Yes	No	Yes	
Behan[104]	1994	Yes	Yes	Yes	Treatment cohort
Behan[105]	1994	Yes	Yes	Yes	Treatment cohort
Bell[106]	1994	Yes	Yes	No	
Bell[107]	1992	No	Yes	No	
Bennett[108]	1998	Yes	No	Yes	
Berkhof[109]	1991	Yes	Yes	No	
Bertagnolli[110]	1997	Yes	Yes	Yes	Case Study
Best[9]	2000	Yes	Yes	No	
Blackwood[111]	1998	No	Yes	Yes	
Blakely[112]	1991	No	Yes	No	
Blenkiron[113]	1999	Yes	No	No	
Blondel Hill[114]	1993	Yes	Yes	No	
Bombardier[15]	1995	No	Yes	Yes	
Bone[115]	1993	Yes	Yes	Yes	Case Study
Bonner[116]	1994	No	Yes	Yes	
Borish[117]	1998	No	Yes	No	
Brady[118]	1991	No	Yes	No	
Bralley[119]	1994	Yes	Yes	Yes	Treatment cohort
Breau[120]	1999	No	Yes	No	
Brickman[121]	1993	No	Yes	No	
Brooks[122]	1989	Yes	Yes	No	
Buchwald[123]	1991	Yes	Yes	Yes	Treatment cohort
Butler[124]	1991	Yes	Yes	Yes	Treatment cohort
Cabrera[125]	1993	Yes	Yes	Yes	Case Study
Calkins[126]	1998	No	No	No	
Carpman[127]	1995	No	Yes	No	
Caruso[128]	1990	Yes	No	Yes	
Cathebras[129]	1993	No	Yes	No	
Cathebras[130]	1995	No	Yes	Yes	
Cathebras[131]	1998	No	No	No	
Chalder[132]	1997	Yes	No	Yes	
Chalder[133]	1995	Yes	Yes	No	
Chalder[134]	1996	Yes	Yes	Yes	Treatment cohort
Charnock[135]	1999	No	No	No	
Chatfield[136]	1992	Yes	Yes	Yes	Case Study
Chaudhury[137]	2001	No	Yes	No	
Cheney[138]	1989	No	Yes	Yes	
Chiave[139]	1982	No	No	No	
Chilton[140]	1996	Yes	Yes	No	
Chisholm[141]	2001	Yes	No	Yes	
Clague[142]	1992	No	Yes	Yes	
Clapp[143]	1999	Yes	Yes	Yes	Treatment cohort
Cleare[144]	1996	Yes	Yes	No	
Cleare[145]	1999	Yes	Yes	No	
Collignon[146]	1991	Yes	Yes	No	

Author	Year	Intervention?	CFS?	Study?	Study Design
Cott[147]	1990	Yes	No	Yes	
Cox[148]	1998	Yes	Yes	Yes	Survey
Cox[149]	1994	Yes	Yes	No	
Cox[150]	1998	Yes	Yes	Yes	Case Study
Cox[151]	2000	Yes	Yes	Yes	Treatment cohort
Cunliffe[152]	1998	Yes	No	Yes	
De Becker[153]	1981	No	Yes	Yes	
De Schepper[154]	1990	Yes	Yes	Yes	Treatment cohort
Deale[155]	1994	Yes	Yes	Yes	Case Study
Deale[156]	1998	Yes	Yes	No	
Deale[157]	1994	Yes	Yes	Yes	Case Study
Deale[80]	1998	Yes	Yes	No	
Deale[158]	1998	Yes	Yes	No	
Delbanco[159]	1998	Yes	Yes	Yes	Case Study
DeLuca[160]	1994	No	Yes	No	
DeLuca[161]	1997	No	Yes	Yes	
Denz Penhey[162]	1993	No	Yes	Yes	
Dessein[163]	1999	No	Yes	No	
Deulofeu[164]	1991	No	Yes	Yes	
De Vinci[165]	1996	Yes	Yes	Yes	RCT, but control group received treatment
Dowsett[166]	1997	Yes	Yes	No	
Dowson[167]	1993	Yes	Yes	No	
Dykman[168]	1999	Yes	Yes	Yes	Treatment cohort
Dykman[169]	1998	Yes	Yes	Yes	Survey
Dykman[170]	1998	Yes	Yes	Yes	Treatment cohort
Dykman[171]	2001	Yes	Yes	Yes	Treatment cohort
Eaton[172]	1996	Yes	Yes	No	
Ehrlich[173]	2000	No	Yes	No	
Ehrlich[174]	1999	No	Yes	No	
Eichner[175]	1990	Yes	Yes	No	
Elliott[176]	1999	No	Yes	No	
Engleberg[177]	1996	Yes	Yes	No	
Essame[178]	1998	Yes	Yes	Yes	Treatment cohort
Evengard[179]	1998	No	Yes	Yes	
Featherstone[180]	1998	Yes	Yes	Yes	Survey
Findley[181]	1998	No	Yes	Yes	
Finestone[182]	1998	Yes	Yes	No	
Franklin[183]	1997	Yes	Yes	No	
Frazer[184]	1996	Yes	Yes	Yes	Treatment cohort
Friedman[185]	1999	Yes	Yes	No	
Fudenberg[186]	1994	Yes	Yes	No	
Fujisaki[187]	1993	Yes	Yes	Yes	Case Study
Fukuda[4]	1994	No	Yes	No	
Fukuda[188]	1995	Yes	Yes	No	
Fulcher[189]	1998	No	Yes	No	
Furst[190]	1994	No	Yes	No	
Gantz[191]	1989	Yes	Yes	No	
Gantz[192]	1993	Yes	Yes	No	
Gibbons[193]	1996	Yes	Yes	No	
Gibson[194]	1999	Yes	Yes	Yes	Treatment cohort
Gilbert[195]	2000	No	Yes	No	
Goldstein[196]	1986	Yes	Yes	No	
Goodnick[197]	1999	Yes	Yes	Yes	Case Study
Goodnick[198]	1990	Yes	Yes	Yes	Case Study
Goodnick[199]	1992	Yes	Yes	Yes	Treatment cohort
Goodnick[200]	1993	Yes	Yes	No	
Goodnick[201]	1996	Yes	Yes	Yes	Case Study
Goodnick[202]	1993	Yes	Yes	No	
Goodnick[203]	1993	Yes	Yes	No	
Gottfries[204]	1998	Yes	Yes	No	
Gracious[205]	1991	Yes	Yes	Yes	n=1
Gregg[206]	1995	Yes	Yes	Yes	Case Study
Gremillion[207]	1998	No	Yes	No	
Gruber[208]	1996	Yes	Yes	No	
Hana[209]	1996	Yes	Yes	Yes	Treatment cohort
Harthoorn[210]	1997	Yes	Yes	Yes	Treatment cohort
Heath[211]	1994	Yes	Yes	Yes	Treatment cohort
Heijmans[212]	1998	No	Yes	Yes	
Hickie[213]	1999	Yes	Yes	Yes	Treatment cohort
Himmel[214]	1999	Yes	Yes	Yes	Treatment cohort
Ho-Yen[215]	1990	Yes	Yes	No	

Author	Year	Intervention?	CFS?	Study?	Study Design
Ho-Yen[216]	1988	No	No	No	
Hotopf[217]	2000	No	No	Yes	
HoYen[218]	1996	Yes	Yes	No	
Hume[219]	1997	No	Yes	No	
Ishida[220]	1993	Yes	Yes	Yes	Case Study
Jacobs[221]	1997	No	Yes	No	
Jain[222]	1998	No	Yes	No	
James[223]	1992	No	Yes	No	
James[224]	1996	Yes	Yes	Yes	Case Study
Jason[225]	1999	No	Yes	Yes	
Jason[226]	1999	No	Yes	Yes	
Jason[227]	1999	No	Yes	Yes	
Jiang[228]	1994	Yes	Yes	Yes	Case Study
Jiaxu[229]	1999	No	No	No	
Jill[230]	1999	No	Yes	No	
Jordan[231]	1998	No	Yes	No	
Joyce[232]	1998	No	Yes	No	
Joyce[b]	1997	No	Yes	Yes	
Jungmayr[233]	1999	Yes	Yes	No	
Kawa-Ha[234]	1987	Yes	Yes	Yes	Case Study
Kelly[235]	1999	Yes	Yes	Yes	Survey
King[236]	1992	Yes	Yes	No	
Klimas[237]	1993	Yes	Yes	No	
Kodama[238]	1996	Yes	Yes	Yes	Case Study
Komaroff[239]	2000	No	Yes	No	
Krilov[240]		No	Yes	Yes	
Krupp[241]	1991	No	Yes	No	
Krupp[242]	1996	Yes	Yes	No	
Kumar[243]	2000	No	Yes	Yes	
Labunsky[244]	1997	Yes	Yes	No	
LaManca[245]	1998	No	Yes	Yes	
Lane[246]	1998	No	Yes	Yes	
Lapp[247]	1998	Yes	Yes	No	
Lawrie[12]	1995	No	Yes	Yes	
Lawrie[248]	1996	Yes	Yes	No	
Lawyer[249]	1992	Yes	Yes	Yes	Treatment cohort
Lee[250]	1992	Yes	Yes	No	
Lerner[251]	1997	Yes	Yes	Yes	Treatment cohort
Leyton[252]	1992	Yes	Yes	Yes	Treatment cohort
Lightfoot[253]	1993	Yes	No	Yes	
Lloyd[254]	1991	No	Yes	No	
Lubitz[255]	1999	Yes	Yes	Yes	Treatment cohort
Luit[256]	1998	No	Yes	Yes	
Lynch[257]	1998	Yes	Yes	No	
Lynch[258]	1991	Yes	Yes	No	
MacLean[259]	1994	No	Yes	No	
Marcovitch[260]	1997	No	Yes	No	
Marit Mengshoel[261]	1995	No	Yes	No	
McBride[262]	1991	Yes	Yes	No	
McClusky[263]	1993	No	Yes	No	
McCully[264]	1996	Yes	Yes	No	
McDonald[265]	1993	No	Yes	Yes	
McDonald[266]	1993	No	Yes	No	
Mechanic[267]	1993	No	Yes	No	
Mehta[57]	1995	Yes	Yes	Yes	n=1
Morris[268]	1993	Yes	Yes	No	
Morriss[269]	1998	No	Yes	Yes	
Morriss[270]	1998	No	Yes	Yes	
Morriss[271]	1998	Yes	Yes	No	
Mortimore[272]	1996	Yes	Yes	Yes	Treatment cohort
Moyer[273]	1998	Yes	Yes	Yes	Treatment cohort
Murtagh[274]	1995	No	Yes	No	
Myers[275]	1999	No	Yes	Yes	
Naranch[276]	1999	No	Yes	Yes	
Nishikai[277]	1992	No	Yes	Yes	
Noyes[278]	1998	Yes	Yes	Yes	Treatment cohort
Nutt[279]	1998	Yes	No	No	
O'Neill[280]	1995	Yes	No	Yes	
Packer[281]	1997	No	Yes	Yes	
Pagano[282]	1989	No	Yes	No	
Panay[283]	1998	Yes	Yes	No	
Pawlikowska[284]	1994	No	No	Yes	

Author	Year	Intervention?	CFS?	Study?	Study Design
Peakman[285]	1997	No	Yes	Yes	
Pearce[286]	1996	Yes	Yes	No	
Peel[287]	1988	No	Yes	Yes	
Pemberton[288]	1997	No	Yes	Yes	
Pemberton[289]	1994	No	Yes	No	
Peterson[290]	1991	Yes	Yes	No	
Peterson[291]	1994	Yes	No	Yes	
Petrie[292]	1995	No	Yes	Yes	
Pizzigallo[293]	1999	No	Yes	No	
Plioplys[294]	1997	Yes	Yes	Yes	Treatment cohort
Plioplys[295]	1997	No	Yes	No	
Plioplys[294]	1997	Yes	No	Yes	
Plioplys[296]	1994	Yes	Yes	Yes	Treatment cohort
Powell[297]	1999	Yes	Yes	Yes	Case Study
Price[298]	1992	No	Yes	Yes	
Rappaport[299]	1998	Yes	Yes	Yes	Treatment cohort
Ray[300]	1997	No	Yes	Yes	
Ray[301]	1993	No	Yes	Yes	
Ray[302]	1992	No	Yes	Yes	
Rea[303]	1999	No	Yes	No	
Reid[304]	2000	Yes	Yes	No	
Ridsdale [305]	2000	Yes	No	Yes	
Rowe[306]	1998	Yes	Yes	No	
Russo[307]	1998	No	Yes	No	
Sadler[308]	1997	Yes	Yes	No	
Scharf [309]	1999	Yes	Yes	No	
Schweitzer [310]	1994	No	Yes	Yes	
Shanks[311]	1995	No	Yes	Yes	
Sharpe[312]	1997	No	Yes	No	
Sharpe[313]	1991	Yes	Yes	No	
Sharpe[314]	1996	Yes	Yes	No	
Sharpe[315]	1997	Yes	Yes	No	
Sharpe[79]	1998	Yes	Yes	No	
Sharpe[316]	1995	Yes	Yes	No	
Sharpe[317]	1996	Yes	Yes	No	
Sharpe[318]	1993	Yes	Yes	No	
Sharpe[319]	1994	No	Yes	No	
Sharpe[3]	1991	No	Yes	No	
Sharpe[320]	1998	Yes	Yes	No	
Sharpley[321]	2000	No	Yes	Yes	
Shaw[322]	1962	Yes	No	Yes	
Shepherd[323]	1997	Yes	Yes	No	
Shepherd[324]	1999	No	Yes	No	
Shepherd[325]	1996	Yes	Yes	No	
Shlaes[326]	1999	No	Yes	Yes	
Simpson[327]	1997	No	Yes	No	
Sisto[328]	1998	No	Yes	Yes	
Small[329]	1989	No	Yes	No	
Spring[330]	1997	No	Yes	No	
Stark[331]	1999	No	Yes	No	
Steinbach[332]	1994	Yes	Yes	Yes	Treatment cohort
Steinhart[333]	1996	Yes	No	Yes	
Straus[334]	1990	Yes	Yes	No	
Straus[335]	1999	Yes	Yes	No	
Straus[336]	1990	Yes	Yes	No	
Strayer[337]	1995	Yes	Yes	Yes	Treatment cohort
Studd[338]	1997	Yes	Yes	No	
Surawy[339]	1995	No	Yes	No	
Sutton[340]	1996	No	Yes	Yes	
Swartz[341]	1989	No	Yes	No	
Taerk[342]	1994	Yes	Yes	Yes	Case Study
Tansey[343]	1993	Yes	Yes	Yes	Case Study
Teitelbaum[344]	1995	Yes	Yes	Yes	Treatment cohort
Teitelbaum[345]	1999	Yes	Yes	No	
Tiersky[346]	1997	No	Yes	No	
Turgeon[347]	1989	No	Yes	No	
Ullman[348]	1992	Yes	Yes	Yes	Case Study
Valdini[349]	1989	No	Yes	No	
Vallings[350]	1998	Yes	Yes	Yes	Treatment cohort
Vedhara[351]	1997	Yes	No	Yes	
Vercoulen[352]	1994	No	Yes	Yes	
Vercoulen[353]	1997	No	Yes	No	

Author	Year	Intervention?	CFS?	Study?	Study Design
Vercoulen[354]	1996	No	Yes	Yes	
Vereker[355]	1992	Yes	Yes	Yes	Treatment cohort
Wachsmuth[356]	1991	Yes	Yes	Yes	Case Study
Wade[357]	1990	Yes	Yes	Yes	Treatment cohort
Wessely[358]	1995	No	Yes	Yes	
Wessely[359]	1991	No	Yes	No	
Wessely[13]	1997	No	Yes	Yes	
Wessely[360]	1989	No	Yes	No	
Wessely[361]	1999	No	Yes	No	
Wessely[362]	1989	No	Yes	Yes	
Westin[363]	1994	Yes	No	Yes	
White[364]	2000	Yes	Yes	Yes	Treatment cohort
White[365]	1997	Yes	Yes	Yes	Treatment cohort
White[366]	1997	Yes	Yes	No	
Wilke[367]	2001	Yes	Yes	Yes	
Wilson[368]	1994	Yes	Yes	No	
Wilson[16]	1994	No	Yes	Yes	
Wolf[369]	2000	Yes	Yes	No	
Wright[370]	1999	No	Yes	Yes	
Zucker[371]	1997	No	No	No	

APPENDIX F: LIST OF INCLUDED STUDIES AND DUPLICATE REPORTS

RCTs and controlled trials

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Goudsmit 1996 [73]
Hickie 2000[61]
Kaslow 1989[66]
Lerner 2001[19]
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Lloyd 1993[26,376]
Marlin 1998[71]
Martin 1994[68]
McKenzie 1998[32]
Moorkens 1998[34]
Natelson 1996[59]
Natelson 1998[60]
Perrin 1998[20]
Peterson 1990[48]
Peterson 1998[62]
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Rowe 1997[55]
See 1996[36]
Sharpe 1996[25,378]
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Snorrason 1996[35]
Steinberg 1996[50]
Stewart 1987[21]
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Teitelbaum 2001[22]
Tiev 1999[63]
Vercoulen 1996[58,382]
Vollmer Conna 1997[52]
Warren 1999[64]
Wearden 1998[46,156,158]
Weatherley-Jones 2001[70]

Systematic Review

1. Price 2000[23]