Interventions for the treatment, management and rehabilitation of patients with chronic fatigue syndrome/ myalgic encephalomyelitis: an updated systematic review

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J R Soc Med 2006;**99**:506–520

SUMMARY

Objectives To determine whether any particular intervention or combination of interventions is effective in the treatment, management and rehabilitation of adults and children with a diagnosis of chronic fatigue syndrome / myalgic encephalomyelitis (CFS/ME).

Design Substantive update of a systematic review published in 2002. Randomized (RCTs) and non-randomized controlled trials of any intervention or combination of interventions were eligible for inclusion. Study participants could be adults or children with a diagnosis of CFS/ME based on any criteria. We searched eleven electronic databases, reference lists of articles and reviews, and textbooks on CFS/ME. Additional references were sought by contact with experts.

Results Seventy studies met the inclusion criteria. Studies on behavioural, immunological, pharmacological and complementary therapies, nutritional supplements and miscellaneous other interventions were identified. Graded exercise therapy and cognitive behaviour therapy appeared to reduce symptoms and improve function based on evidence from RCTs. For most other interventions, evidence of effectiveness was inconclusive and some interventions were associated with significant adverse effects.

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

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INTRODUCTION

Chronic fatigue syndrome (CFS) is a debilitating condition characterized by fatigue on minimal exertion accompanied by a range of other symptoms such as headaches, sleep disturbance, cognitive difficulties and muscle pain.[1,2] The severity of the symptoms varies widely both between patients and over time; in severe cases patients may be confined to bed or to a wheelchair. CFS affects both adults and children. The nomenclature of the condition and the overlap between CFS and myalgic encephalomyelitis (ME) has been much debated. For this review we have used the term CFS/ME and included studies of people with a diagnosis of CFS/ME by any criteria.

The aetiology of CFS/ME remains uncertain and diagnosis is based on symptoms as reported by the patients. Case definitions developed for research purposes tend to be used to aid diagnosis, the most widely used being the US Centers for Disease Control and Prevention (CDC)[2] and the UK (Oxford)[1] criteria. Estimates of the prevalence of CFS/ME vary depending on the case definition used. In a study of 2376 primary care patients in England, 2.6% met criteria for CFS/ME but the prevalence fell to 0.5% when those with co-morbid psychological disorders were excluded.[3] The UK Department of Health Working Party on CFS/ME[4] estimated that a typical general practice with 10 000 patients is likely to have 30–40 patients with CFS/ME and that about half of these would require specialist services.

A variety of interventions have been used for the treatment and management of patients with CFS/ME and a number of groups have performed systematic reviews to assess the effectiveness of these interventions. Price and Couper[5] assessed the effectiveness of cognitive behaviour therapy (CBT) in adults and concluded that CBT appears to be an effective and acceptable treatment, although only three relevant randomized controlled trials (RCTs) were found. Edmonds and colleagues reviewed RCTs of exercise therapy.[6] Based on five RCTs they concluded that exercise therapy is a promising intervention, although they recommended more rigorous studies involving different patient groups and settings and a wider range of outcomes. A systematic review by Ross and colleagues examined how best to measure, monitor and treat disability in patients

with CFS/ME.[7] Disability was considered primarily in terms of ability to work. Although the authors found some small studies of interventions (including rehabilitation, CBT and graded exercise therapy [GET]) that reported improved employment outcomes, they concluded that no intervention has been proved to be effective in restoring the ability to work

More broadly, Mulrow and colleagues examined the definition and management of CFS/ME,[8] while a review of all available interventions for the treatment and management of CFS/ME in both adults and children was carried out at the NHS Centre for Reviews and Dissemination (CRD).[9] These two reviews only covered the period up to 2001, and many studies of CFS/ME have been published since then. We recently carried out a number of systematic and scoping reviews on CFS/ME to inform the process of guideline development by the UK National Institute for Health and Clinical Excellence (NICE). In this paper we present an updated systematic review of the literature on interventions for the treatment and management of CFS/ME in adults and children.

METHODS

Literature search

The following databases were searched: MEDLINE (1966 to May 2005), EMBASE (1980 to May 2005), PsycINFO (1872 to April 2005), CENTRAL (May 2005), Social Science Citation Index (1945 to 2005), Science Citation Index (1945 to 2005), Index to Scientific and Technical Proceedings (1982 to 2005), PASCAL (May 2005), Inside Conferences (May 2005), AMED (1985 to January 2005), and HEED (June 2005). Individual search strategies were developed for each electronic database and details of these can be obtained from the authors. The search was broad, with the objective of identifying all studies of CFS/ME and related synonyms and covering several research questions. No language restrictions were applied. Additional references were sought by screening reference lists of retrieved articles, textbooks on CFS/ME, and stakeholder submissions from the NICE Guideline Development Group on diagnosis and management of CFS/ME.

Inclusion criteria and study selection

Two reviewers independently assessed all titles and abstracts identified from the searches for potential relevance to the review questions, and potentially relevant papers were retrieved in full. Two reviewers independently assessed these studies for possible inclusion, using the specified inclusion criteria. A third reviewer resolved differences.

The inclusion and exclusion criteria were:

Intervention—any intervention or combination of interventions used in the treatment, management or rehabilitation of people with CFS/ME.

Population—adults and/or children aged five years or more with a diagnosis of CFS/ME based on any criteria.

Outcomes—all outcomes reported in included studies were considered.

Study design—only randomized or controlled clinical trials were eligible for inclusion.

Data extraction

Data were extracted from study reports by one reviewer and the results were checked by a second reviewer. Any discrepancies were resolved by reference to the original study, with a third reviewer being consulted if necessary. Only between-group comparisons were considered.

Validity assessment

The criteria for validity assessment described by Bagnall *et al*.[9] and based on the CRD recommendations[10] were used to allocate a validity score, ranging from 0 to 20, to each study. Assessment of validity was based on method of randomization and allocation concealment (randomized studies only); baseline comparability of groups; adjustment for confounding factors and appropriateness of the control group (controlled studies only); blinding; completeness of follow-up; handling of drop-outs and missing data; objectivity of outcome assessment; appropriateness of statistical analysis; whether the groups were treated identically apart from the named intervention; and sample size/statistical power. Validity was assessed by one reviewer and checked by another. Disagreements were resolved by discussion and reference to a third reviewer if necessary.

Data synthesis

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

Heading	*Subheading*	*Descriptor*	*Reported? (Y/N)*
Title		Identify the report as a meta-analysis (or systematic review) of RCTs	Yes
Abstract		Use a structured format	Yes
		Describe	
	Objectives	The clinical question explicitly	
	Data sources	The databases (i.e. list) and other information sources	Not all databases listed to save space
	Review methods	The selection criteria (i.e. population, intervention, outcome, and study design); methods for validity assessment, data abstraction, and study characteristics, and quantitative data synthesis in sufficient detail to permit replication	
	Results	Characteristics of the RCTs included and excluded; qualitative and quantitative findings (i.e. point estimates and confidence intervals); and subgroup analyses	
	Conclusion	The main results	
Introduction		The explicit clinical problem, biological rationale for the intervention, and rationale for review	Yes
Methods	Searching	The information sources, in detail (e.g. databases, registers, personal files, expert informants, agencies, hand-searching), and any restrictions (years considered, publication status, language of publication)	Yes
	Selection	The inclusion and exclusion criteria (defining population, intervention, principal outcomes, and study design	Yes
	Validity assessment	The criteria and process used (e.g. masked conditions, quality assessment, and their findings)	Yes
	Data abstraction	The process or processes used (e.g. completed independently, in duplicate)	Yes
	Study characteristics	The type of study design, participants' characteristics, details of intervention, outcome definitions, &c, and how clinical heterogeneity was assessed	Yes
	Quantitative data synthesis	The principal measures of effect (e.g. relative risk), method of combining results (statistical testing and confidence intervals), handling of missing data; how statistical heterogeneity was assessed; a rationale for any a-priori sensitivity and subgroup analyses; and any assessment of publication bias	Not applicable
Results	Trial flow	Provide a profile summarizing trial flow (see figure)	Yes
	Study characteristics	Present descriptive data for each trial (e.g. age, sample size, intervention, dose, duration, follow-up period)	Yes
	Quantitative data synthesis	Report agreement on the selection and validity assessment; present simple summary results (for each treatment group in each trial, for each primary outcome); present data needed to calculate effect sizes and confidence intervals in intention-to-treat analyses (e.g. 2×2 tables of counts, means and standard deviations, proportions)	Not applicable
Discussion		Summarize key findings; discuss clinical inferences based on internal and external validity; interpret the results in light of the totality of available evidence; describe potential biases in the review process (eg, publication bias); and suggest a future research agenda	Yes

Figure 1 **(A) QUORUM statement checklist of the systematic review**

RESULTS

The overall literature search identified 10,768 items, of which 70 met the inclusion criteria for the review (Figure 1). Two studies included in the review by Bagnall *et al.* were excluded from the updated review, one because it included patients with chronic mononucleosis[11] and one because a full report was subsequently published.[12] Fifteen papers that were ordered as potentially meeting inclusion criteria had not arrived at the time of writing.[13–27] One paper in the Russian language was identified as potentially meeting inclusion criteria but has not been translated.[28] The paper is about a yeast extract supplement but it is unclear whether patients all had CFS.

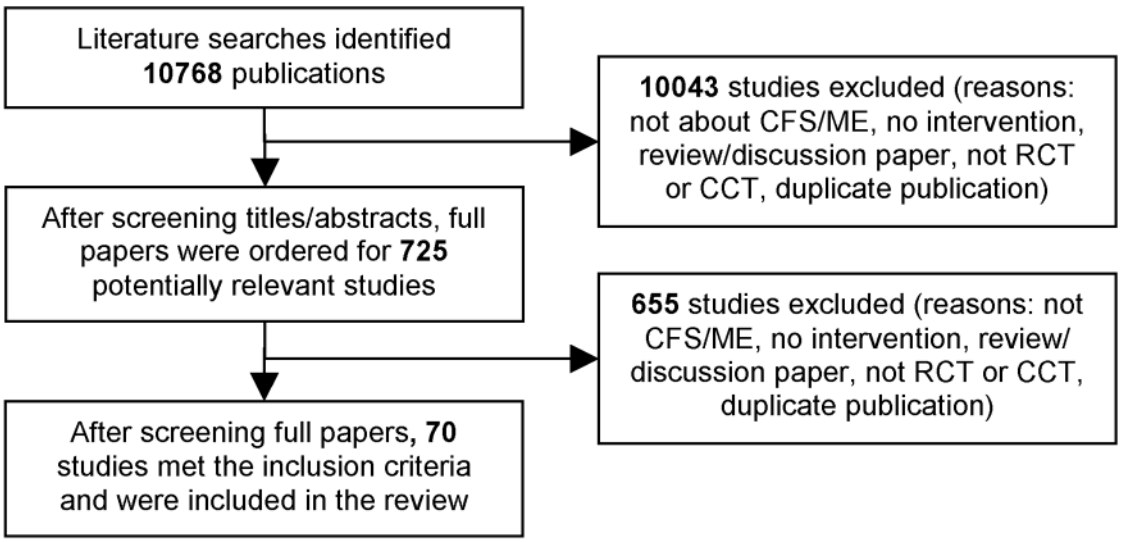

Figure 1 **(B) QUORUM statement flow diagram of the systematic review.** RCT, randomized controlled trial; CCT, controlled clinical trial

Of the studies included in the review, 59 were RCTs and the remainder non-randomized controlled trials (Table 1). Of the newly included studies (Table 2), 15 showed some beneficial effect of the intervention and eight showed an overall beneficial effect. Validity scores ranged from 2 to 19 for the included RCTs and from 0 to 14 for the controlled trials. Controlled trials generally scored less well than RCTs on all validity criteria. A high degree of heterogeneity in interventions and outcomes was evident.

The evidence supporting the effectiveness of CBT has been strengthened by one recent good quality RCT in children and adolescents[29] which found an overall positive effect of the intervention. CBT was associated with a significant positive effect on fatigue, symptoms, physical functioning and school attendance. Most other new studies of CBT and modified CBT have also favoured the treatment for one or more outcomes but these were either lower quality RCTs or non-randomized studies. GET has recently been studied in two moderate quality RCTs.[30,31] These studies have broadened the evidence base for GET because, unlike earlier studies, they involved non-UK settings and patients who met the 1994 CDC case definition criteria for CFS/ME. As with CBT, the overall results of studies to date suggest that this intervention may have positive effects on the symptoms of CFS/ME. Improvements in measures of physical function were also found in all five RCTs of GET published to date.[30–34] No severely affected patients were included in the studies of GET.

Two new studies of immunological therapies (a controlled trial of inosine pranobex[35] and a relatively low quality RCT of staphylococcus toxoid[36]) were added to the updated review. Both of these treatments showed benefits for some outcomes but were also associated with relatively high levels of adverse events. Overall there is still insufficient evidence about the effectiveness of therapies of this type.

Treatment of CFS/ME with pharmacological therapies has given disappointing results in most cases. A recent large RCT of the acetylcholinesterase inhibitor galantamine hydrobromide[37] found no significant differences between groups and 120 of 434 patients (27.6%) withdrew from the trial. An RCT of hydrocortisone published in 2002[38] found a significant difference between groups for fatigue, but this study scored poorly for validity. Two other recent studies of steroid treatment[39,40] found no significant effect, in line with the mixed results reported in 2002.

The only new study of complementary/alternative therapies was an RCT of homeopathic treatment[41] that showed significant differences favouring the treatment group for one of five measures of fatigue and one of five measures of functional limitations. This trial used rigorous methodology but there is also a published study showing no effect of homeopathic treatment[42] and further studies are clearly required. A supplement of acetyl-L-carnitine and propionyl-L-carnitine showed an overall positive effect in one moderate quality RCT published in 2004.[43] Other supplements (essential fatty acids[44] and magnesium[45]) have also given promising results in single studies, although a later study of essential fatty acids failed to replicate the results of the first study.[46] The trial of magnesium supplementation has apparently not been replicated. The evidence base for supplements and miscellaneous interventions for CFS/ME remains very limited.

There is limited evidence about adverse effects associated with behavioural interventions. Withdrawals

Table 1 **Summary of results of studies included in the review. Controlled studies are shaded in the table, all other studies are RCTs**

Treatment	*Number of patients*	*Outcomes investigated*	*Any effect*	*Overall effect*	*Validity score (Maximum 20)*
Behavioural					
CBT[60]	60	**PH**; PS; **QOL**	+	+	18
CBT[48]	270	**PH**; **PS**; **QOL**	+	+	16
CBT[47]	60	**PH**; PS; **QOL**	+	+	15
CBT[29]	69	**PH**; **QOL**	+	+	16
CBT + DLE[61]	90	PH; PS; LAB; **QOL**	+	=	13
Rehab[62]	47	**PH**; **QOL**	+	+	9
Rehab[63]	130	**PH**; **PS**; **QOL**	+	+	8
Rehab[64]	97	PH; PS; **QOL**	+	=	7
CBT[54]	65	PH; PS;QOL	=	=	3
CBT/rehab[49]	56	PH; **QOL**	+	=	2
CBT[65]	44	PH; PS; QOL	=	=	1
GET & Fluoxetine[34]	136	**PH**; PS; QOL	+	=	17
GET[32]	66	**PH**; PS; **LAB**; **QOL**	+	+	17
GET[33,53]	148	**PH**; PS; **QOL**	+	+	17
GET[31]	61	**PS**; **PH**; LAB	+	+	9
GET[30]	49	**PH**	+	+	9
Immunological					
Immunoglobulin[50]	71	**PH**	+	+	16
Immunoglobulin[66]	30	PH; LAB; QOL	=	=	15
Immunoglobulin[67]	49	PS; **QOL**	+	=	13
Immunoglobulin[68]	99	PH; PS; LAB; QOL	=	=	13
Staphylococcus toxoid[36]	98	**PH**	+	+	14
Staphylococcus toxoid[69]	28	PS; **QOL**	+	=	9
Alpha interferon[70]	30	**LAB**; QOL	+	=	11
Interferon[71]	20	PH	=	=	6
Acyclovir[51]	27	PH; **PS**; LAB; QOL	−	=	15
Ampligen[72]	92	**RU**; **PH**; **PS**	+	+	12
Terfenadine[73]	30	PH; QOL	=	=	12
Gancyclovir[74]	11	PH	=	=	4
Inosine pranobex[35]	16	PH; **LAB**; QOL	+	=	6
Pharmacological					
Hydrocortisone[75]	32	**PH**; QOL	+	=	18
Hydrocortisone[76]	70	PH; PS; QOL	=	=	14
Hydrocortisone[38]	120	**PH**; LAB	+	=	2
Hydrocortisone and fludrocortisone[39]	80	PH; PS; LAB; QOL	=	=	14
Fludrocortisone[77]	100	PH; PS; LAB; QOL	=	=	18
Fludrocortisone[78]	25	PH; PS; QOL	=	=	16
Topical nasal corticosteroids[40]	28	PH	=	=	3
Moclobemide[79]	90	PH; PS; LAB; QOL	=	=	19
Fluoxetine[80]	107	PH; PS; QOL	=	=	12
Selegiline[81]	25	PH; **PS**; QOL	+	=	11
Galantamine hydrobromide[37]	434	PH; PS	=	=	15
Galanthamine hydrobromide[82]	49	PH; PS; QOL	=	=	9
Oral NADH[83]	26	**QOL**	+	+	12

continued

Table 1 ***continued***

Treatment	*Number of patients*	*Outcomes investigated*	*Any effect*	*Overall effect*	*Validity score (Maximum 20)*
Pharmacological *(continued)*					
Oral NADH[84]	20	PH	=	=	3
Clonidine[85]	10	PS	=	=	12
Phenelzine[86]	24	PH; PS; QOL	=	=	10
Sulbutiamine[87]	326	PH; QOL	=	=	10
Dexamphetamine[88]	20	**PH**; QOL	+	=	8
Growth hormone[89]	20	PH	=	=	5
Melatonin[90]	30	**PH**; **PS**	+	+	5
Complementary / Alternative					
Homeopathy[41]	103	**PH**	+	=	17
Any homeopathic remedy[42]	64	QOL	=	=	6
Massage therapy[91]	20	**PH**; **PS**; **LAB**	+	+	9
Osteopathy[92]	58	PH; PS; QOL	=	=	0
Supplements					
General supplements[93]	53	PH	=	=	10
General supplements[94]	42	PH; QOL	=	=	10
General supplements[95]	12	PH	=	=	6
Essential fatty acids*[44]	63	**LAB**; **QOL**	+	+	17
Essential fatty acids*[46]	50	PS; QOL	=	=	16
Magnesium[45]	34	**PH**; **PS**; LAB; **QOL**	+	+	15
Liver extract[96]	15	PH; PS; QOL	=	=	10
Acetyl-L-carnitine and propionyl-L-carnitine[43]	90	**PH**; **PS**	+	+	10
Pollen extract[97]	22	PH; PS; QOL; LAB	=	=	9
Acclydine and amino acids[98]	90	PH; **LAB**	+	=	3
Medicinal mushrooms[99]	70	PH	=	=	3
Other interventions					
Combination[100]	72	**PH**	+	+	19
Combination[101]	71	QOL	=	=	3
Combination[102]	52	PS; **QOL**	+	=	2
Low sugar, low yeast diet (Hobday *et al.*, unpublished data)	57	PH; PS	=	=	11
Buddy/mentor[103]	12	**PH**; PS; QOL	+	=	4
Group therapy[104]	14	PH; QOL	=	=	1

+, positive effect of treatment; –, negative effect of treatment; =, no effect of treatment; rehab, rehabilitation; DLE, dialyzable leukocyte extract
*Essential fatty acids (both studies) were 36mg gamma-linoleic acid (GLA), 17mg eicosapentanoic acid (EPA), 11mg docosahexanoic acid (DHA), 255mg linoleic acid (LA), plus 10 IU vitamin E
Outcome codes: PH, physical; PS, psychological; LAB, laboratory and physiological; QOL, quality of life and general health; RU, resource use. Outcomes which showed a significant difference between intervention and control groups are highlighted in bold

Table 2 **Results of new studies included in the updated review**

		Results					
Intervention	***Author (Year), number of participants***	***Physical***	***Psychological***	***Physiological***	***Quality of life and general health***	***Drop-outs/ Adverse effects***	***Validity score***
Behavioural							
CBT	Whitehead (2002)[54] *n*=65	*Fatigue:* no significant difference between groups	*Anxiety and Depression:* no significant differences between groups		*Disability:* no significant differences between groups	At 6 months, 8 in treatment group and 11 in control group were lost to follow-up	3
Rehabilitation	Cox (2002)[64] *n*=97	*Physical functioning and fatigue:* no significant differences between groups	*Emotional distress:* no significant differences between groups		*Maintaining activity and accommodating to illness:* significant difference in favour of treatment group ($P<0.03$)	6 months after discharge, 14 in treatment group and 16 in control group did not return questionnaires	7 (NB controlled trial)
Rehabilitation	Cox (1999)[63] *n*=130	*Physical/functional status, fatigue, pain, symptoms:* significant difference between groups for fatigue symptoms ($P<0.02$) and pain ($P<0.05$)	*Perceived ability, anxiety, depression, emotional distress:* significant difference between groups for emotional distress ($P<0.03$)		*Illness management:* significant difference in favour of treatment group ($P<0.03$)	5 withdrew from experimental group, 18 from control group	8 (NB controlled trial)
Rehabilitation	Taylor (2004)[62] *n*=47	*Symptoms:* significant interaction ($P<0.05$)			*Quality of life:* significant interaction ($P<0.05$)	No withdrawals	9
CBT	Stulemeijer (2005)[29] *n*=69	*Physical functioning, fatigue, symptoms:* significant difference in favour of CBT group ($P<0.003$)			*School attendance:* significant difference in favour of treatment group ($P=0.04$)	6 patients dropped out during treatment. 7 were missing from CBT group and 2 from control group at final assessment	16
Modified CBT	Viner (2004)[49] *n*=56	*CFS severity:* better result in intervention group, significance not reported			*Global wellness, school attendance:* significantly better in treatment group ($P<0.05$)	No withdrawals	2 (NB controlled trial)
GET	Moss-Morris (2005)[30] *n*=49	*CGI, fatigue:* significant difference in favour of treatment group ($P<0.03$)				3/25 dropped out of treatment and 3/24 did not return questionnaires at 12 weeks	9

Table 2 **(continued)**

Behavioural *(continued)*							
GET	Wallman (2004)[31] *n*=61	*Fatigue:* significantly better in treatment group (*P*=0.027)	*Depression, anxiety:* significantly better in treatment group (*P*=0.027)	*Resting and target heart rate and blood pressure, exercise test values:* comparisons not made between groups		One excluded after randomization because BMI too high to participate in exercise test. None reported during the study	9
Immunological							
Inosine pranobex	Diaz-Mitoma (2003)[35] *n*=16	*Symptoms, fibromyalgia tender points:* no significant difference between groups	*Cognitive function:* no significant differences between groups	*Immune function:* significant improvements in treatment group ($P<0.03$)	*Global severity, activities of daily living, Karnofsky Performance Scale: no significant differences between groups*	1 withdrawal in each group. Transient elevation of serum uric acid (presumably in treatment group)	6
Staphylococcus toxoid	Zachrisson (2002)[36] *n*=98	*Global impression, symptoms, pain:* statistically significant difference in favour of treatment group for CGI ($P<0.001$) and 'feeling good' item on fibromyalgia impact questionnaire				10 dropouts during study. 13 patients in the treatment group and 7 in the placebo group experienced side effects.	14
Pharmacological							
Galantamine hydrobromide	Blacker (2004)[37] *n*=434	*Global impression, fatigue, symptoms:* no significant differences between groups	*Cognitive function:* no significant difference between groups			130 patients withdrew. 389 patients reported adverse events, of which 88 withdrew	15
Hydrocortisone	Cleare (2002)[38] *n*=120?	*Fatigue:* 'significantly' greater improvement in treatment group (*P* not reported)		*Hormone levels:* greater increase in cortisol response to HCRH in treatment group (significance not reported)			2
Hydrocortisone and fludrocortisone	Blockmans (2003)[39] *n*=80	*Fatigue:* no significant differences between groups	*Anxiety and depression:* no significant differences between groups	*Blood pressure:* no significant differences between groups	*SF-36, wellbeing:* no significant differences between groups	9 in treatment group and 11 in placebo group dropped out. Only one dropped out due to adverse events	14
Topical nasal corticosteroids	Kakumanu (2001)[40] *n*=28	*Fatigue, daytime sleepiness, muscle pain:* no significant improvement with treatment			*Daily activity:* no significant improvement with treatment		3

continued

Table 2 ***(continued)***

		Results					
Intervention	***Author (Year), number of participants***	***Physical***	***Psychological***	***Physiological***	***Quality of life and general health***	***Drop-outs/ Adverse effects***	***Validity score***
Pharmacological *(continued)*							
Oral NADH	Santaella (2004)[84] *n*=20	*Symptoms:* no significant difference between groups				11 dropped out of 31 initially randomized. No adverse events were reported in treatment group	3
Dexam-pheta-mine	Olson (2003)[88] *n*=20	*Fatigue, sleep:* significant difference in favour of treatment group for fatigue ($P<0.02$)			*SF36 scores:* no significant difference between groups	Reduced food consumption reported by 5 patients in treatment group, one in placebo group	8
Clonidine	Morriss (2002)[85] *n*=10		*Cognitive function:* no significant effects			One patient withdrew after GP prescribed fluoxetine	12
Melatonin vs phototherapy	Williams (2002)[90] *n*=30	*Symptoms, fatigue:* improved sleep ($P=0.03$), vitality ($P=0.016$) and mental health ($P=0.046$) with melatonin, worsening of bodily pain ($P=0.044$)	*Anxiety, depression:* no significant effects of treatment			12 of initial 42 patients withdrew, 10 due to time and social demands of the study	5
Complementary/Alternative							
Homeopathy	Weatherley-Jones (2004)[41] *n*=103	*Fatigue, functional limitations:* significant differences in favour of treatment group for fatigue ($P=0.04$) and some physical dimensions of the Functional Limitations Profile (*P* value not reported)				11 withdrew from treatment arm (5 did not complete treatment) and 8 from placebo arm (6 did not complete treatment)	17
Supplements							
Acetyl-L-carnitine and propionyl-L-carnitine	Vermeulen (2004)[43] *n*=90	*Global improvement, fatigue, pain:* significant improvement in general fatigue in PLC ($P=0.004$) and combined group ($P<0.001$); significant improvement in mental fatigue in ALC group ($P=0.015$)	*Attention, concentration:* 'significant' improvements in all groups			8 patients withdrew due to side effects and 8 withdrew due to lack of efficacy.	10

Table 2 ***(continued)***

Supplements *(continued)*							
Acclydine and amino acids	De Becker (2001)[98] *n*=90	*Global improvement, symptoms:* improvements seen in intervention group above control group but groups were not compared statistically		*IGF-1 levels:* significantly more improvement in intervention than placebo group ($P<0.0002$)			3 (NB controlled trial)
Pollen extract	Ockerman (2000)[97] *n*=22	*Fatigue, sleep, symptoms:* comparisons were not made between groups	*Depression:* comparisons were not made between groups	*Erythrocyte fragility:* comparisons were not made between groups		1 withdrawal due to moving away. 'Slight intestinal inconvenience' was the only side effect for a few days in 1 or 2 patients	9
RM-10: medicinal mushrooms	Rothschild (2002)[99] *n*=70	*Symptoms:* improved more in the treatment group (measure of significance not presented)				2 dropped out of treatment group, not reported for placebo group.	3
General supplements	Brouwers (2002)[93] *n*=53	*Fatigue, symptoms, improvement, functional impairment, activity:* no significant differences between groups				3 dropped out from the supplement group due to nausea, and one in each group for other reasons	10
Other interventions							
Group therapy	Soderberg (2001)[104] *n*=14	*Fatigue:* results not reported			*Quality of life:* comparisons were not made between groups	One withdrawal in control group	1
Low sugar low yeast diet	Hobday (2005, unpublished) *n*=57	*Fatigue:* no significant differences between groups	*Anxiety, depression:* no significant differences between groups		*General health:* no significant differences between groups	8 in the LSLY arm and 9 in the control arm were lost to follow-up	11

from treatment in RCTs suggest that there may be an issue but the evidence is often difficult to interpret because of poor reporting. In one RCT of CBT,[47] two patients attributed a deterioration in their symptoms to the effects of the treatment. Another RCT of CBT reported high withdrawal rates in all three intervention groups, but the reasons for withdrawal were not reported.[48] In the study of GET by Fulcher and White,[32] one patient in each group withdrew because of worsening symptoms. In the RCT of patient education to encourage GET,[33] 21 of 148 patients (14.1%) entering the trial withdrew; 19 of these were in the groups randomized to GET, but the reasons for withdrawal were not reported clearly enough to be sure how many were attributable to adverse events. Eleven patients withdrew because of adverse events in a RCT of GET with or without fluoxetine,[34] but it is not clear which intervention group they were in. New studies of behavioural interventions included in the update (Table 2) did not report any withdrawals caused by adverse events, although again the reasons for withdrawal were often not reported.

Several studies of immunological/antiviral, pharmacological and nutritional interventions have reported withdrawals because of adverse effects, including recent studies of Staphylococcus toxoid,[36] galanthamine hydrobromide[37] and hydrocortisone/fludrocortisone.[39]

Recent studies of CBT[29] and modified CBT[49] in children and young people both reported that school attendance was significantly better in the treatment group compared with controls. One study supported the effectiveness of immunoglobulin treatment in children[50] but this intervention may also have harmful effects.

DISCUSSION

Statement of principal findings

A number of RCTs suggest that behavioural interventions, including elements of CBT, GET and rehabilitation, may reduce symptoms and improve physical functioning of people with CFS/ME. Immunological and anti-viral treatments may have beneficial effects but are also associated with harmful side-effects. Most pharmacological treatments have not shown beneficial effects.

Strengths and weaknesses of the study

Review methodology

Our review was supported by a search of the literature that was designed to be as comprehensive as possible, with the objective of identifying all published studies of interventions for CFS/ME and related conditions that met pre-specified inclusion criteria. We searched for conference abstracts and dissertations as well as standard journal articles, and we attempted to locate unpublished reports and ongoing clinical trials.

Publication bias needs to be considered in any systematic review; studies with statistically significant or unexpected results are more likely to be published than those showing non-significant results. Various statistical tests to assess publication bias are available, notably funnel plots, but the reliability of these is questionable and they are no longer recommended by the Cochrane Collaboration. We decided not to assess publication bias statistically for this reason and because of the wide range of interventions and outcomes included in the review. However, the fact that only one included study[51] reported a negative effect of the intervention suggests that a degree of publication bias may be present in the CFS/ME literature.

A fundamental problem in evaluating interventions for CFS/ME is that the wide variety of outcome measures used in the included studies makes it difficult to compare the effects of interventions across studies. Even when studies evaluated the same outcome, they used a variety of scales and measures to do so. This heterogeneity made it impossible to combine studies by meta-analysis. Standardized measures of treatment effect (effect sizes) can be calculated when studies measure the same outcome in different ways but the data required for this (sample size, mean treatment effect and standard deviation in each group) were not reported in many included studies. We have summarized our results (Table 1) in a way designed to convey as much information as possible in a relatively small space, but this presentation has limitations. Achievement of statistically significant differences between groups may be influenced by sample size in the study and results may be statistically but not clinically significant. Our measure of 'overall effect' represents an attempt to deal with this issue by showing which studies reported a statistically significant treatment effect on two or more clinical outcomes. A summary of the results of all included studies showing the magnitude of treatment effects is available from the authors and will be included in an updated version of the report by Bagnall and colleagues[9] that will be available from the Centre for Reviews and Dissemination (www.york.ac.uk/inst/crd/index.htm).

Included studies

As noted above, development of standardized and objective outcome measures and agreement on their use in studies remain largely unmet goals. There is also a lack of long-term follow-up data for most interventions, although a five-year follow-up of the RCT of CBT by Deale and colleagues showed maintained benefit of the intervention for several outcomes[52] and a two-year follow-up of one RCT of GET was published in 2004.[53] The studies included in our review also show a lack of uniformity in terms of case definitions

for CFS/ME, study inclusion and exclusion criteria and the basic information provided about the participants. For example, baseline functional status and duration of illness are not always reported. It is therefore difficult to assess the generalizability of the findings of many of these studies.

Although we have discussed all the studies evaluating a particular intervention together, the treatment offered to patients receiving a particular type of therapy in practice may vary considerably, particularly for behavioural interventions. For example, in the CBT study by Stulemeijer *et al.*,[29] participants in the intervention group received ten individual therapy sessions over five months in a hospital child psychology department, whereas in the study by Whitehead *et al.*[54] the intervention was a form of 'brief CBT' delivered by general practitioners. Further standardization of methods for delivering behavioural interventions in research and practice would be desirable.

Strengths and weaknesses in relation to other studies

This updated systematic review confirms and extends the conclusions of previous reviews in this area.[5,6,8,9] Evidence reviews also informed guidelines for the treatment or management of CFS/ME published in Australia[55] and the Royal College of Paediatrics and Child Health (RCPCH) guidelines covering children and young people.[56] The Australian guidelines concluded that CBT and GET 'may be effective for some people with CFS' (based on level 1 and 2 evidence, respectively). This is similar to the conclusions of our review. The recommendations for children and young people were largely developed by consensus because of a lack of specific evidence for this age group. GET and CBT were recommended for consideration based on extrapolation from studies in adults. The effectiveness of CBT for adolescents is supported by a recent high-quality RCT,[29] although this had only 69 participants.

Meaning of the study and implications for clinicians/policy makers

Our results demonstrate that there are a considerable number of studies evaluating interventions for the treatment and management of CFS/ME and that many of them have used robust research methods; the majority of the included studies were RCTs and many of these were of high methodological quality (Table 1). However, RCTs generally scored poorly for concealment of treatment allocation and many failed to use an intention-to-treat analysis. These issues should be addressed in designing future clinical trials of interventions for CFS/ME. In view of the chronic nature of CFS/ME, future trials should be designed, as far as practicable, to collect long-term data on effectiveness and adverse events.

A number of issues may limit the uptake and availability of effective interventions for CFS/ME. Behavioural interventions require the participation of trained therapists and this may raise issues both of cost and the availability of personnel. This is particularly true for CBT, which is regarded as a valid therapy option for a range of conditions. Improving the organization and delivery of psychological therapies has been identified as a priority for the UK National Health Service.[57]

Unanswered questions/further research

Homeopathy and supplements (essential fatty acids and magnesium) have shown beneficial effects but only in one or two trials and further rigorous trials of these interventions would be helpful. Similarly, very few studies have assessed the effectiveness of interventions for children and young people and for severely affected patients. No rigorous evaluations of pacing were identified. A large trial known as PACE (Pacing, Activity and Cognitive behaviour therapy: a randomized Evaluation), involving patients attending specialist CFS/ME clinics across the UK, is underway and is due for completion in 2009. This trial is designed to compare specialist medical care against specialist medical care with the addition of adaptive pacing therapy, CBT or GET.

Patient perceptions and preferences regarding interventions have been investigated but are not generally reported in studies of effectiveness. Some studies of behavioural interventions have reported significant rates of withdrawal from treatment or loss to follow-up, as high as 20–40% in some studies.[48,54] Withdrawals not related to adverse events may reflect patient dissatisfaction with treatment. Our review did not find any new evidence of adverse effects (sufficient to cause withdrawal from treatment) associated with GET or CBT. However, reasons for withdrawals were often poorly reported and should be investigated in more detail in future studies.

The protocols for many clinical studies require patients to attend a clinic for treatment and/or assessment. These conditions may exclude people severely affected with CFS/ME from taking part and hence bias the sample towards those with less severe symptoms. Surveys by patient organizations highlight the fact that those with the worst symptoms often receive the least support from health and social services.[58] The balance between effectiveness and adverse effects of interventions may be different in more severely affected compared with less severely affected patients and methods of delivery/doses may need to be different. Research to evaluate the effectiveness of interventions for severely affected patients should be considered a priority. The FINE (Fatigue Intervention by Nurses Evaluation) trial is designed to evaluate a pragmatic

rehabilitation therapy delivered by nurses in patients' homes, and hence accessible to severely affected patients.[59] This trial is expected to end in 2008.

Acknowledgments We thank Vickie Orton for carrying out the literature searches and Paul Wilson for helpful comments.

Authors' contributions Carol Forbes prepared the project proposal and managed the project. All authors participated in designing the study, selection of studies for the review, data extraction, data analysis and interpretation, and writing the paper, and approved the final manuscript.

Guarantor Duncan Chambers is guarantor for this paper.

Ethical approval Was not required.

Funding/Support This project was funded by the National Institute for Health and Clinical Excellence who commissioned the National Collaborating Centre for Primary Care (part of the Royal College of General Practitioners) to produce guidelines for 'The Diagnosis and Management of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (or Encephalopathy) in Adults and Children'. The work forms part of the independent synthesis of research evidence to support the development of these guidelines. The views expressed in this publication are those of the authors and not necessarily those of the NCC-PC, RCGP or the Institute. The funding source had no influence on study design; in the collection, analysis, and interpretation of the data; in the writing of the report; and the decision to submit the paper for publication.

Competing interests None declared.

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