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Effective Health Care

Bulletin on the effectiveness of health service interventions for decision makers

This bulletin summarises the effectiveness of interventions for the treatment and management of chronic fatigue syndrome/ myalgic encephalomyelitis

Interventions for the management of CFS/ME

- Estimates of prevalence of CFS/ME in the UK range from 0.4% to 2.6%. A general practice with 10,000 patients is likely to have 30-40 patients with CFS/ME.
- Seven different categories of intervention have been evaluated for their potential use in the management of CFS/ME: behavioural, immunological, antiviral, pharmacological, supplements, complementary/alternative and multi-treatment.
- Interventions for which there is evidence of effectiveness from randomised controlled trials include cognitive behavioural therapy and graded exercise therapy.
- Bed or wheelchair restricted patients have been excluded in some of the studies and only one study included young people under 18 years of age. This raises questions about the applicability of findings to all people with CFS/ME.
- Further research is needed into i) how sub-groups 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 pacing, ideally in comparison with CBT and GET.

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A. 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.[1-3] Children and adults present with similar symptoms.[4] Myalgic encephalomyelitis (ME) is sometimes reported to be a separate syndrome from CFS, characterised by muscle weakness, pain and neurological disturbance.[5] It has been suggested that CFS and ME are part of a group of similar symptom complexes such as postviral fatigue syndrome, fibromyalgia and neurasthenia.[2] 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.[6] In this *Effective Health Care* bulletin, the condition will be referred to as CFS/ME.

The cause of CFS/ME remains unknown although various hypotheses have been suggested that include one or more of the following factors: immunological, viral, psychological and neuroendocrine. Diagnosis is based entirely on symptoms reported by the patient. Definitions commonly used tend to be research criteria.[7] Two frequently used definitions for CFS are the UK (Oxford) criteria[1] and the US Centers for Disease Control and Prevention criteria.[2] 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 that must be present. 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.[7] This involves taking a full clinical history, a mental health evaluation, sleep evaluation and a physical examination. It is recommended that a series of basic screening tests be undertaken to exclude other conditions that can present as fatigue.[7]

Estimates of prevalence vary, and may be attributed to the diversity in diagnostic criteria and to variations in the extent to which alternative medical and psychiatric diagnoses have been excluded. One small UK study reported that the point prevalence of CFS was 0.6% (95% confidence interval 0.2 – 1.5%), using the UK (Oxford) criteria.[8] A larger UK study reported a prevalence ranging from 0.5%, when comorbid psychological disorders were excluded, to 2.6% when they were not.[9] Most commonly, onset is reported to be early twenties to mid-forties.[7] 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.[7] 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.[7]

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.[7] The findings from prospective natural history studies are varied.[10] 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 range from 15 – 20%.

B. Current service provision

The recent CFS/ME Working Group Report[7] 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.[7] Referrals from primary care are to one or more specialists such as 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.[7]

C. Treatment and management

A variety of interventions have been used in the treatment and management of CFS/ME. The CFS/ME Working Group Report[7] 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 Department of Health has now asked the Medical Research Council to develop a broad strategy for advancing biomedical and health services research on CFS/ME (http://www.doh.gov.uk/cmo/CFS/mereport/response.htm).

This *Effective Health Care* Bulletin summarises the evidence from a systematic review commissioned by the Department of Health (see full report for more details[11]). The results of the systematic review were found to be similar to those of another systematic review carried out in the USA at the same time[10] and the two have been

combined and published together in 2001.[12] This bulletin is based on evidence from RCTs. See appendix for further details of methods.

An overview of the included studies and main findings from the UK systematic review is presented in Table 1. To provide an overall estimate of whether each study found a positive, negative or no effect of the intervention, all studies were classified according to two separate methods: whether the study showed any effect of the intervention and whether it showed any overall effect. See appendix for further details.

D. Interpreting the findings

Some of the interventions have been evaluated in only one or two studies, which may limit the generalisability of the findings. Many studies had relatively small sample sizes, did not use standardised outcome measures and failed to use an intention-to-treat analysis. Much of the data presented in the studies were limited and, due to the differences between studies (e.g outcomes reported, types of data presented and interventions evaluated), it was not possible to calculate pooled summary statistics. Also of importance are the inclusion criteria specified in some trials, such as participants being eligible if they could physically get to the clinic. Those people who were unable to walk or to get out of bed were excluded and so it has not been possible to assess whether the interventions investigated would be effective, ineffective or even hazardous for a more severely disabled group of people. Uncontrolled studies of interventions for severely disabled people with CFS/ME are reported to have shown no evidence of harm.[13-15] However, these studies do not form part of the evidence base for this Bulletin.

In some of the trials, limited information was provided for patients who were ineligible or about the baseline functioning of many of those who were included. It is therefore difficult to extrapolate the findings to other people with CFS/ME. In those trials that did report baseline functioning, the majority of participants were unable to take part in full time employment. Another limitation of most of the trials was the duration of follow-up. The relapsing nature of the condition 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 persists for a relevant period of time.

Many different outcomes were reported and were measured using a variety of scales. Outcomes such as 'improvement', where participants were asked to rate themselves as better or worse after the intervention, were frequently used. 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 had increased their working hours, returned to work or increased their physical activities, and these outcomes were evaluated in some studies.

Some interventions have been evaluated using non-randomised controlled trials, including osteopathy, modified CBT (based on coping within limits set by symptoms) and other multi-treatment approaches. These have been reviewed elsewhere and have yet to be evaluated in RCTs.[11,12] RCTs are also needed evaluating the effectiveness of pacing. Pacing is an energy management strategy in which patients are encouraged to achieve an appropriate balance between rest and activity. This usually involves living within physical and mental limitations imposed by the illness, and avoiding activities to a degree that exacerbates symptoms or interspersing activity with periods of rest.[7,16] An understanding of the underlying mechanisms of CFS/ME is likely to aid in the development of effective treatment or management programmes.

E. Behavioural interventions

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[17] and chronic low back pain.[18]

See Table 2 for the main results of the included behavioural intervention studies.

Four RCTs evaluated weekly or biweekly sessions of CBT (see box for description of CBT). CBT was compared to routine medical care in one RCT (n=60),[19] to relaxation in a second RCT (n=60),[20] and to natural course (control) in a third RCT (n=270).[21] A fourth RCT (n=90) 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.[22]

Participants who received combined leukocyte extract and CBT showed a beneficial effect on general health compared to the other three groups.[22] The remaining three RCTs reported a beneficial effect of CBT when compared to control groups.[19-21] Two RCTs found a significant global improvement at follow-up.[19-20] All but the combined leukocyte extract/CBT study also found significant improvements in physical functioning and fatigue. Neither of the two studies that assessed depression found any differences between groups.[19,20]

Table 1 Summary of study results

Treatment	Duration of follow-up† (weeks)	Number of participants	Outcomes investigated	Any effect	Overall effect
BEHAVIOURAL					
Graded Exercise Therapy (GET)[26]	12	66	**PH**; PS; **LAB**; **QOL**	+	+
GET[28]	52 (26)	148	**PH**; **PS**; **QOL**	+	+
GET & Fluoxetine[27]	26	136	**PH**; PS; QOL	+	<>
Cognitive Behavioural Therapy (CBT)[20]	26	60	**PH**; PS; **QOL**	+	+
CBT[21]	61(35)	270	**PH**; **PS**; **QOL**	+	+
CBT[19]	52	60	**PH**; PS; **QOL**	+	+
CBT + Dialysable leukocyte extract (DLE)[22]	30 (16)	90	PH; PS; LAB; **QOL**	+	<>
IMMUNOLOGICAL					
Immunoglobulin [32]	26 (13)	71	**PH**	+	+
Immunoglobulin [31]	21	30	PH; **LAB**; QOL	+	<>
Immunoglobulin[30]	26 (13)	49	PS; **QOL**	+	<>
Immunoglobulin[33]	26 (13)	99	PH; PS; LAB; QOL	<>	<>
Gamma-globulin[29]	17	19	**QOL**	+	+
Ampligen[34]	26	92	**RU**; **PH**; **PS**	+	+
Terfenadine[35]	9	30	PH; QOL	<>	<>
ANTIVIRAL					
Alpha interferon[37]	12	30	**LAB**; QOL	+	<>
Interferon[36]	52 (12)	20	**PH**	+	+
Aciclovir[38]	18 (13)	27	PH; **PS**; LAB; QOL	–	<>
Ganciclovir[39]	26	11	QOL	<>	<>
PHARMACOLOGICAL					
Hydrocortisone[43]	9	32	**PH**; QOL	+	<>
Hydrocortisone[44]	12	70	PH; PS; **QOL**	+	<>
Fludrocortisone[46]	11 (9)	100	PH; PS; LAB; QOL	<>	<>
Fludrocortisone[45]	18	25	PH; PS; QOL	<>	<>
Fluoxetine[41]	12 (8)	107	PH; PS; QOL	<>	<>
Phenelzine[40]	6	24	PH; PS; QOL	<>	<>
Moclobemide[42]	6	90	PH; PS; LAB; QOL	<>	<>
Sulbutiamine[48]	4	326	PH; QOL	<>	<>
Galanthamine hydrobromide[47]	2	49	PH; PS; QOL	<>	<>
Oral NADH[50]	12	26	**QOL**	+	+
Growth hormone[49]	12	20	PH	<>	<>
SUPPLEMENTS					
Essential fatty acids*[52]	13	63	**LAB**; **QOL**	+	+
Essential fatty acids*[51]	13	50	PS; **QOL**	+	<>
Magnesium[53]	6	34	**PH**; **PS**; **LAB**; **QOL**	+	+
Liver extract[54]	2	15	PH; PS; QOL	<>	<>
General supplements[55]	7	12	**PH**	+	+
COMPLEMENTARY/ALTERNATIVE					
Any homeopathic remedy[58]	26	104	**PH**; PS	+	<>
Any homeopathic remedy[57]	52	64	**QOL**	+	+
Massage therapy[56]	5	20	**PH**; **PS**; **LAB**	+	+
MULTI-TREATMENT					
Multi-treatment[59]	13	72	**PH**; **QOL**	+	+

+ 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 is shown in brackets

Outcome codes: 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.

One of these RCTs also followed patients for five years after the intervention[20,23] and found that global improvement was 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.[23] However, no significant differences were reported between the groups for individual outcomes of 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.[24,25]

The studies evaluating CBT reported no adverse effects of the intervention except in one RCT in which two participants dropped out of the CBT group because they felt a deterioration in their symptoms was due to the intervention.[19] 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 dropouts were not reported.[21]

The effects of GET were investigated in three RCTs (n=66, n=148 and n=136), two of which found overall beneficial effects (see box for description).[26,28] One found some beneficial effects.[27] When exercise was combined with fluoxetine there was no additional effect.[27] One RCT assessed different interventions to encourage graded exercise and found benefits from GET when compared to standardised medical care for all outcomes investigated.[28] The studies did not report any specific adverse effects of GET although two studies did report withdrawals that may have been related to adverse effects of the intervention.

Cognitive Behavioural Therapy (CBT)

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 activities 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 thoughts and changing any unhelpful ideas which may be hampering progress with treatment

REF: http://www.babcp.org.uk/publications/leaflets/chronic_fatigue.htm

British Association for Behavioural and Cognitive Psychotherapies website

Graded Exercise Therapy (GET)

GET is a form of structured and supervised activity management that aims for gradual but progressive increases in aerobic activities such as walking or swimming.[7] The initial programme is designed 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 activities.

F. Immunological interventions

Five RCTs investigated the effects of Immunoglobulin G (an antibody fraction of blood); two found some positive effect (n=30, n=49),[30,31] two found an overall beneficial effect (n=19, n=71).[29,32] One was conducted in young people aged under 18.[32] The fifth and largest (n=99) found no effect of treatment.[33]

One RCT evaluated ampligen (n=92) and found an overall beneficial effect.[34] In this trial, participants were grouped according to whether they had evidence of human herpes virus 6 (HHV-6) infection and no differences were found between the groups in response to ampligen. Another RCT which assessed the combined effect of leukocyte extract and cognitive behavioural therapy (n=90) found no effect of leukocyte extract on its own but found a beneficial effect on general health in the group receiving both leukocyte extract and CBT.[22] A third RCT which evaluated the antihistamine terfenadine (n=30) reported no beneficial effects.[35]

Some severe adverse effects were noted in participants in the immunological intervention groups. Two people out of 99 had to withdraw from immunoglobulin treatment due to severe constitutional symptom reactions.[33] One recipient also withdrew due to mild but transient liver failure[30] and phlebitis has also been noted with immunoglobulin infusions.[30] It should be noted that immunoglobulins and leukocyte

Table 2 Results of behavioural intervention trials

Intervention	Author (Year), number of participants	RESULTS				
		Physical	**Psychological**	**Physiological**	**Quality of life and general health**	**Drop-outs/ Adverse effects**
CBT	Deale (1997)[20] 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
	Results at 5 year follow-up[23] n=53	*Physical functioning and fatigue:* no significant difference between two groups			***Global improvement and proportion completely recovered:* greater improvement in treatment than control (p<0.001)** *General health and proportion that no longer meet UK CFS/ME criteria:* no significant differences between groups ***Symptoms and relapses:* suggestion of greater improvement in treatment than control (p=0.05)**	
	Lloyd (1993)[22] 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 dialysable leucocyte extract (DLE) combined with CBT showed greater improvement than other intervention groups (p<0.05)**	2 dropped out, however, no participants dropped out due to adverse effects
	Prins (2001)[21] 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 drop out. 10 in CBT and 8 in support group did not start treatment. No adverse effects reported
	Sharpe (1998)[19] 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		***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

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

Table 2 (continued) Results of behavioural intervention trials

Intervention	Author (Year), number of participants	RESULTS				
		Physical	**Psychological**	**Physiological**	**Quality of life and general health**	**Drop-outs/ Adverse effects**
GET	Fulcher (1997)[26] 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	***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 dropped out, 4 in exercise group and 3 in control, 1 from each group dropped out due to worsening of symptoms
	Powell (2000)[28] n=148	***Physical functioning, fatigue:* greater improvement in all intervention groups than control (p<0.001)**, no significant difference between the 3 intervention groups ***Sleep problems:* greater improvement in all intervention groups than control (no measure of significance)**, no significant difference between the 3 intervention groups	***Depression and anxiety:* greater improvement in all intervention groups than control (no measure of significance)**, no significant difference between the 3 intervention groups		***Improvement, and patients report of improvement:* greater improvement in all intervention groups than control (p<0.01),** no significant difference between the 3 intervention groups	21 dropped out, 19 in intervention groups, dropped out during treatment: 8 for medical reasons, 7 for psychiatric reasons, 4 gave no reason, 1 emigrated, 1 was dissatisfied with treatment
	Wearden (1998)[27] 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 dropped out 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

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

extract are blood products and there are known risks associated with their use, such as the possible transfer of infectious diseases.

G. Antiviral interventions

Two RCTs evaluated interferon (an antiviral agent), one of which found an overall beneficial effect (n=20) and the other reported only within group differences and so no conclusion can be drawn from this study.[36,37] The effect of aciclovir was investigated in one small RCT (n=27) and a negative effect was reported for anxiety, depression and confusion with the control group showing a greater improvement in symptoms than the treatment group.[38] Another small RCT investigated the effects of ganciclovir (n=11) and found no significant differences between intervention and control groups.[39] Three people had to withdraw from aciclovir treatment due to reversible renal failure.[38] In the ganciclovir study, two participants out of 11 who were undergoing right ventricular endomyocardial biopsies experienced serious pericardial bleeding and so the study was ended prematurely.[39]

H. Pharmacological interventions

Antidepressants The effects of antidepressants were investigated in two RCTs.[40,41] No benefit was found in patients with CFS/ME from treatment with antidepressants (either in treating the symptoms of depression or any of the other outcome measures reported, n=24 and n=107).[40,41] The RCT of fluoxetine[41] also reported no differences in response between depressed and non-depressed participants. One RCT (n=90) investigated the effect of moclobemide (a monoamine oxidase inhibitor) and found no benefit of treatment.[42] This trial also found no differences in response between those with major depression or general psychological distress and those without, or between those with reduced immune responses and those without.[42]

Corticosteroids The effects of steroid treatment were investigated in four RCTs.[43-46] Two of these RCTs evaluated hydrocortisone (n=70, n=32) and both reported some beneficial effect.[43,44] The other two RCTs assessed fludrocortisone (n=25, n=100), and did not find any beneficial effects.[45,46] 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.[46]

Anticholinergic agents Two studies evaluated anticholinergic agents (drugs which inhibit the neurotransmitter acetylcholine at neuromuscular junctions, n=49 and n=326),[47,48] and reported no significant effects of the intervention.

Other pharmacological agents One study assessed the growth hormone Genotropin (n=20) and found no significant effects of the intervention.[49] Oral nicotinamide adenine dinucleotide (NADH) led to a greater improvement in symptoms (the only outcome investigated) in the intervention group compared to the control group in one small RCT (n=26).[50]

Adverse events serious enough to cause people to withdraw from the studies occurred with fludrocortisone,[46] moclobemide,[42] sulbutiamine,[48] galanthamine hydrobromide,[47] phenelzine[40] and fluoxetine.[41]

I. Supplements

Two RCTs investigated the effect of essential fatty acid supplements. One (n=50) reported some positive effects[51] and another (n=63) reported an overall beneficial effect.[52] Magnesium supplements were found to have an overall beneficial effect in one small RCT (n=34).[53] One very small RCT (n=15) of liver extract reported no beneficial effects.[54] Another RCT (n=12) evaluated general supplements and found an overall beneficial effect.[55]

The RCT of magnesium supplements reported that two participants left the intervention group after experiencing a generalised rash.[53] The other studies did not report any adverse effects.

J. Complementary/alternative interventions

An overall beneficial effect of massage therapy was found in one small RCT (n=20).[56] Two RCTs assessed the effectiveness of homeopathy.[57,58] One large RCT (n=104) found some positive effects (preliminary results)[58] and the second (n=64) reported an overall positive effect.[57] There were no reports of adverse events in any of these studies.

K. Multi-treatment

An overall beneficial effect on a range of symptoms was found in an RCT (n=72) of a symptom-based multi-treatment approach in people with CFS/ME and fibromyalgia.[59] This programme involved treating specific patient symptoms with a variety of medications. All patients, in both control and intervention groups, also received nutritional supplements.

L. Implications

- A total of 38 RCTs have investigated the effectiveness of

seven different categories of intervention: behavioural, immunological, antiviral, pharmacological, supplements, complementary/alternative and multi-treatment.

- Overall the interventions demonstrated mixed results in terms of effectiveness. All conclusions about effectiveness should be considered together with the methodological inadequacies in some of the studies.
- Interventions which have shown evidence of effectiveness include CBT and GET.
- There is insufficient evidence about how sub-groups of patients may respond differently to treatments and further studies investigating additional subgroups are needed.
- In some of the 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 is the only intervention that has been investigated in young people. Two studies of CBT in children aged 10-18 are ongoing, one of these is of family focused CBT.[60,61]
- 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. A study comparing the effects of CBT and GET is ongoing in patients with chronic fatigue (of whom 27% have a diagnosis of CFS/ME).[62]
- 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 with CBT and GET. The large number of outcome measures used makes standardisation of outcomes a priority for future research.

Appendix – review methods

Search strategy

Literature searches were initially undertaken to identify all study designs. Individual search strategies were developed for each electronic database searched. The following databases were searched: MEDLINE (1966 to June 2000), EMBASE (1980 to May 2000), PSYCLIT (1887 to March 1999), ERIC (1966 to March 2000), CCCTR (March 1999), Social Science Citation index (1981-1999), Science Citation Index (1981-1999), Index to Scientific and Technical Proceedings (1982-1999), PASCAL (1973 –2000), MANTIS (1880 – January 2000), JICST (1985 – 2000), Conference Proceedings Index (1973 – January 2000), AMED (1984 – January 1999), NTIS (1964 - July 2000), Inside Conferences (1993 - June 2000), Life Sciences (1982 - March 2000), CAB Health (1983 - April 2000), BIOSIS (1969 - June 2000), TGG Health & Wellness (1976 - June 2000). See CRD report[11] for the search terms used. Update searches of all the above databases, from the date on which they had previously been searched, were carried out in February 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, AltaVista, etc). A dedicated web-site was set up for the review (http://www.york.ac.uk/inst/crd/CFS/ME.htm) through which additional references could be submitted. The review advisory panel was contacted and asked to submit any references that they thought might meet inclusion criteria for the review.

Methods

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

Studies were selected for inclusion if they were RCTs (non-randomised controlled trials have also been included in the full report) of an intervention used with people with CFS/ME (see full report for more details).[11]

Validity assessment was carried out, using an existing validity assessment tool,[63] by one reviewer and checked by a second. Discrepancies were resolved by discussion or, when agreement could not be reached, by consultation with a third reviewer.

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.

Heterogeneity amongst interventions, participants and outcomes measured meant that data could not be pooled statistically. Results were synthesised narratively. Details of data extraction and methodological assessment are available from the full report.[11]

Studies were judged to show some effect of treatment if any of the outcomes measured showed a significant difference between the intervention and control groups. Studies were classified as having an overall effect (positive or negative) if they showed an effect for more than one clinical (i.e. not a physiological) outcome; if only one outcome was measured, studies were classified as having an overall effect if this outcome was found to show an effect.

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Effective Health Care

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