Chronic fatigue syndrome

Search date July 2002

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QUESTIONS

INTERVENTIONS

Key Messages

- **Cognitive behavioural therapy** One systematic review has found that cognitive behavioural therapy versus standard care or relaxation therapy administered by highly skilled therapists in specialist centres improves quality of life and physical functioning. One additional multicentre RCT has found that cognitive behavioural therapy administered by less experienced therapists compared with guided support groups or no intervention may also be effective.
- **Evening primrose oil** One small RCT found no significant difference with evening primrose oil versus placebo in depression scores at 3 months.
- **Graded aerobic exercise** RCTs have found that a graded aerobic exercise programme versus flexibity and relaxation training or general advice significantly improves measures of fatigue and physical functioning. One RCT has found a significant improvement in measures of physical functioning, fatigue, mood, and sleep at 1 year with an educational package to encourage graded exercise versus written information only.
- **Immunotherapy** Small RCTs found that immunoglobulin G versus placebo modestly improved physical functioning and fatigue at 3–6 months, but was associated with considerable adverse effects. Small RCTs found insufficient evidence on the effects of interferon alfa versus placebo.
- **Magnesium (intramuscular)** One small RCT found that magnesium injections versus placebo significantly improved symptoms at 6 weeks.
- **Prolonged rest** We found no RCTs on the effects of prolonged rest. Indirect observational evidence in healthy volunteers and in people recovering from a viral illness suggests that prolonged rest may perpetuate or worsen fatigue and symptoms.
- **Antidepressants; corticosteroids; oral nicotinamide adenine dinucleotide** RCTs found insufficient evidence on the effects of these interventions.

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DEFINITION Chronic fatigue syndrome (CFS) is characterised by severe, disabling fatigue and other symptoms, including musculoskeletal pain, sleep disturbance, impaired concentration, and headaches. Two widely used definitions of CFS, from the US Centers for Disease Control and Prevention[1] and from Oxford, UK,[2] were developed as operational criteria for research (see table 1, p 13). There are two important differences between these definitions. The UK criteria insist upon the presence of mental fatigue, whereas the US criteria include a requirement for several physical symptoms, reflecting the belief that CFS has an underlying immunological or infective pathology.

INCIDENCE/ PREVALENCE Community and primary care based studies have reported the prevalence of CFS to be 0–3%, depending on the criteria used.[3,4] Systematic population surveys have found similar prevalence of CFS in people of different socioeconomic status, and in all ethnic groups.[4,5]

AETIOLOGY/ RISK FACTORS The cause of CFS is poorly understood. Women are at higher risk than men (RR 1.3–1.7 depending on diagnostic criteria used).[6]

PROGNOSIS Studies have focused on people attending specialist clinics. A systematic review of studies of prognosis (search date 1996) found that children with CFS had better outcomes than adults: 54–94% of children showed definite improvement (after up to 6 years' follow up), whereas 20–50% of adults showed some improvement in the medium term and only 6% returned to premorbid levels of functioning.[7] Despite the considerable burden of morbidity associated with CFS, we found no evidence of increased mortality. The systematic review found that outcome was influenced by the presence of psychiatric disorders (depression and anxiety), and beliefs about causation and treatment.[7]

AIMS To reduce levels of fatigue and associated symptoms; to increase levels of activity; to improve quality of life.

OUTCOMES Severity of symptoms and their effects on physical function and quality of life. These outcomes are measured in several different ways: the medical outcomes survey short form general health survey (SF-36),[8] a rating scale measuring limitation of physical functioning caused by ill health (score range 0–100, where 0 = limited in all activities and 100 = able to carry out vigorous activities); the Karnofsky scale,[9] a modified questionnaire originally developed for the rating of quality of life in people undergoing chemotherapy for malignancy; the Beck Depression Inventory,[10] a checklist for quantifying depressive symptoms; the sickness impact profile,[11] a measure of the influence of symptoms on social and physical functioning; the Chalder fatigue scale,[12] a rating scale measuring subjective fatigue (score range 0–11, where scores ≥ 4 = excessive fatigue); the clinical global impression scale,[13] a validated measure of overall change compared with baseline at study onset, with seven possible scores from "very much worse" (score 7) to "very much better" (score 1); and self reported severity of symptoms and levels of activity, the Nottingham health profile[14] contains questions in 6

categories — energy, pain perception, sleep patterns, sense of social isolation, emotional reactions, physical mobility (weighted scores give maximum 100 for answer yes to all questions, and minimum 0 for someone with no complaints).

METHODS *Clinical Evidence* search and appraisal July 2002.

QUESTION What are the effects of treatments?

OPTION ANTIDEPRESSANTS

RCTs found insufficient evidence about the effects of antidepressants in people with chronic fatigue syndrome.

Benefits: We found one systematic review (search date 2000), which did not report quantified results.[15] **Fluoxetine:** The review identified two RCTs.[16,17] The first RCT (107 depressed and non-depressed people with chronic fatigue syndrome [CFS]) compared fluoxetine versus placebo for 8 weeks.[16] It found that fluoxetine versus placebo significantly improved the Beck Depression Inventory (mean difference between fluoxetine and placebo in improvement in Beck Depression Inventory –0.19, 95% CI –0.35 to –0.02), but the difference may not be clinically important. It found no significant difference with fluoxetine versus placebo in the sickness impact profile (mean difference between fluoxetine and placebo measured by fatigue subscale of Checklist Individual Strength –0.16, 95% CI –0.64 to +0.31).[18] The second RCT (136 people with CFS) compared four groups: fluoxetine plus graded exercise; drug placebo plus graded exercise; fluoxetine plus general advice to exercise; and drug placebo plus general advice to exercise. It found no significant difference in the level of fatigue, although there were modest improvements in measures of depression at 12 weeks (Hospital Anxiety and Depression scale, mean change 1.1, 95% CI 0.03 to 2.2).[17,19] **Phenelzine:** The review identified one RCT.[15,20] The RCT (30 people with CFS) compared phenelzine versus placebo, using a modified Karnofsky scale and other outcome measures (including functional status questionnaire, profile of mood states, Centres for Epidemiological Study of Depression fatigue severity scale, and symptom severity checklist).[19] This study concluded that there was a pattern of improvement across several measures (significance tests for individual measures not carried out). **Moclobemide:** The review identified one RCT but did not report quantified results.[15,21] The RCT (90 people with CFS) compared moclobemide (450–600 mg daily) versus placebo.[21] It found that moclobemide was associated with a non-significant increase in subjectively reported global improvement (moclobemide 24/47 [51%] *v* placebo 14/43 [33%]; OR 2.16, 95% CI 0.9 to 5.1), and a non-significant improvement in the clinician rated Karnofsky scale. **Sertraline versus clomipramine:** We found one RCT comparing sertraline versus clomipramine in people with CFS.[22] It found no significant difference between sertraline and clomipramine. There was no placebo group, making it difficult to draw useful conclusions.

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Harms:

Fluoxetine: One RCT assessed separately the symptoms (which could be attributed to either CFS or to known adverse effects of fluoxetine) before starting treatment, after 2 weeks, after 6 weeks, and at the end of treatment (wk 8). It found that more people taking fluoxetine complained of tremor and perspiration compared with placebo at 8 weeks (tremor: P = 0.006; perspiration: P = 0.008).[16] It found no significant difference between fluoxetine and placebo at 2 and 6 weeks. More people taking fluoxetine withdrew from the trial because of adverse effects (9/54 [17%] *v* 2/53 [4%]).[16] The second RCT also found more people taking fluoxetine withdrew from the trial (24/68 people [36%] with fluoxetine withdrew *v* 16/69 people [24%] with placebo).[17] **Phenelzine:** Three of 15 people (20%) taking phenelzine withdrew because of adverse effects compared with none taking placebo.[20] **Sertraline versus clomipramine:** The RCT provided no information on adverse effects.[22]

Comment:

Clinical trials were performed in specialist clinics. **Fluoxetine:** The first RCT[16] used a shorter duration of treatment and studied people with a longer duration of illness compared with the second RCT.[17]

OPTION CORTICOSTEROIDS

Four RCTs found insufficient evidence about the effects of corticosteroids versus placebo in people with chronic fatigue syndrome.

Benefits:

We found one systematic review (search date 2000), which did not report quantified results.[15] **Fludrocortisone:** The systematic review[15] identified two RCTs.[23,24] The first large RCT (100 people with chronic fatigue syndrome [CFS] and neurally mediated hypotension) compared fludrocortisone (titrated to 0.1 mg daily) versus placebo for 9 weeks. It found no significant difference on a self rated global scale of "wellness" (recorded improvement of ≥ 15 points: fludrocortisone 14% *v* placebo 10%; P = 0.76; raw data not provided).[23] The second randomised crossover trial (20 people), which measured change in symptom severity (visual analogue scale of symptoms from 0–10 corresponding to "no problem" to "could not be worse") and functional status (using the SF-36) for 6 weeks. It found no significant difference between fludrocortisone and placebo.[24] **Hydrocortisone:** The review identified two RCTs.[15,25,26] The first RCT (65 people) compared hydrocortisone (25–35 mg daily) versus placebo for 12 weeks. It found that people taking hydrocortisone had a greater improvement in a self rated scale of "wellness" (recorded improvement of ≥ 5 points: hydrocortisone 53% *v* placebo 29%; P = 0.04). Other self rating scales did not show significant benefit (Beck Depression Inventory: hydrocortisone –2.1 *v* placebo –0.4, P = 0.17; activity scale: hydrocortisone 0.3 *v* placebo 0.7, P = 0.32; sickness impact profile: hydrocortisone –2.5 *v* placebo –2.2; P = 0.85).[25] The second randomised crossover trial (32 people) compared a lower dose of hydrocortisone (5 or 10 mg daily) versus placebo for 1 month. It found that more people taking hydrocortisone had short term improvement in fatigue (self report fatigue scale: hydrocortisone 28% *v* placebo 9%; results before crossover not provided).[26]

Harms: **Fludrocortisone:** In the first RCT, more people on fludrocortisone withdrew because of adverse events (12/50 [24%] *v* 4/50 [8%]; RR 3, 95% CI 1.04 to 8.67; NNT 6, 95% CI 3 to 8).[23] Four people withdrew from the trial because of worsening symptoms.[24] **Hydrocortisone:** One RCT (using 25–35 mg daily doses of hydrocortisone) found that 12 people (40%) experienced adrenal suppression (assessed by measuring cortisol levels).[25] Another RCT (using 5 or 10 mg daily doses of hydrocortisone) reported minor adverse effects in up to 10% of participants. Three people on hydrocortisone had exacerbation of acne and nervousness, and one person on placebo had an episode of fainting.[26]

Comment: The RCTs used different reasons for their choice of active treatment. The use of fludrocortisone, a mineralocorticoid, was based on the hypothesis that CFS is associated with neurally mediated hypotension.[27] The use of hydrocortisone, a glucocorticoid, in the other RCTs was based on evidence of underactivity of the hypothalamic–pituitary–adrenocortical axis in some people with CFS.[28] Any benefit from low dose glucocorticoids seems to be short lived, and higher doses are associated with adverse effects.

OPTION ORAL NICOTINAMIDE ADENINE DINUCLEOTIDE

One small RCT found insufficient evidence about the effects of oral nicotinamide adenine dinucleotide versus placebo in people with chronic fatigue syndrome.

Benefits: We found one systematic review (search date 2000), which did not report quantified results.[15] It identified one poor quality randomised crossover trial (35 people) comparing nicotinamide adenine dinucleotide (10 mg daily) versus placebo for 4 weeks.[29] Of the 35 people, two were excluded for non-compliance and seven were excluded for using psychotropic drugs. It found a significant improvement on a self devised 50 item symptom rating scale with nicotinamide adenine dinucleotide (8/26 people [30%] attained a 10% improvement with nicotinamide adenine dinucleotide *v* 2/26 people [8%] with placebo; $P < 0.05$, calculated by authors).

Harms: Minor adverse effects (loss of appetite, dyspepsia, flatulence) were reported on active treatment but did not lead to cessation of treatment.[29]

Comment: The RCT had a number of problems with its methods, including the use of inappropriate statistical analyses, the inappropriate exclusion of people from the analysis, and lack of numerical data preventing independent re-analysis of the published results.[30]

OPTION EXERCISE

RCTs have found that a graded aerobic exercise programme versus flexibity and relaxation training or general advice significantly improves measures of fatigue and physical functioning. One RCT has found a significant improvement in measures of physical functioning, fatigue, mood, and sleep at 1 year with an educational package to encourage graded exercise versus written information only.

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Benefits: We found one systematic review (search date 2000), which did not report quantified results.[15] **Graded aerobic exercise:** The review identified two RCTs.[15,17,31] One RCT (66 people) compared graded aerobic exercise (active intervention) versus flexibility and relaxation training (control intervention) over 12 weeks.[31] All participants undertook individual weekly sessions supervised by an exercise physiologist. The aerobic exercise group built up their level of activity to 30 minutes of exercise a day (walking, cycling, swimming up to a maximum oxygen consumption of VO_2max 60%). People in the flexibility and relaxation training group were taught stretching and relaxation techniques (maximum 30 min daily, 5 days/wk) and were specifically told to avoid any extra physical activities. It found that more people from the aerobic exercise group reported feeling "better" or "very much better", and an improvement in physical fatigue and physical functioning versus the control group (clinical global impression scale: 52% *v* 27%, P = 0.04; Chalder fatigue scale: –8.4 *v* –3.1, P = 0.004; SF-36 scale: 20.5 *v* 8.0, P = 0.01). The flexibility training group crossed over to aerobic exercise at the end of the trial and significant improvements from baseline were found (peak oxygen consumption; P < 0.0001: physical function; P = 0.002 compared with baseline). The second RCT (136 people) compared four groups (graded aerobic exercise plus fluoxetine; graded aerobic exercise plus drug placebo; general advice plus fluoxetine; general advice plus drug placebo) over 24 weeks.[17] The graded exercise groups were given specific advice to undertake preferred aerobic exercise (such as walking, jogging, swimming, or cycling) for 20 minutes three times a week up to an energy expenditure of 75% of VO_2max. The general advice (exercise placebo) groups were not given any specific advice on frequency, intensity, or duration of aerobic activity they should be undertaking. It found that, at week 26, there were fewer cases of fatigue in the graded exercise groups versus people receiving general advice (Chalder fatigue scale < 4: 12/67 [18%] *v* 4/69 [6%]; RR 3.1, 95% CI 1.05 to 9.10; NNT 9, 95% CI 5 to 91). **Educational intervention:** The review identified one RCT (148 people) but did not report quantified results.[15,32] The RCT compared three types of educational interventions to encourage graded exercise versus only providing written information (control group).[32] The participants in the three educational intervention groups received two treatment sessions, two telephone follow ups, and an educational package that provided an explanation of symptoms and encouraged home based exercise. One group received seven additional follow up telephone calls and another received seven additional face to face sessions over 4 months. People in the written information group received advice and an information booklet that encouraged graded activity but gave no explanation for the symptoms. The RCT found that, in people who had received an educational intervention, there was improvement in physical functioning, fatigue, mood, sleep, and disability (self reported) compared with the people who had only received written information. No significant differences were found

between the educational intervention groups (mean for 3 educational intervention groups versus written information, SF-36 subscale: ≥ 25 or an increase of ≥ 10, 1 year after randomisation, 69% *v* 6%, P < 0.001; Chalder fatigue scale: 3 *v* 10, P < 0.001; Hospital Anxiety and Depression scale: depression 4 *v* 10, P < 0.001; anxiety 7 *v* 10, P < 0.01).

Harms: None of the RCTs reported data on adverse effects, and we found no evidence that exercise is harmful in people with chronic fatigue syndrome. In the second aerobic exercise RCT, more people withdrew with exercise than without exercise but the difference was not significant (25/68 [37%] with exercise *v* 15/69 [22%] without exercise; RR 1.7, 95% CI 0.98 to 2.9).[17] The reasons for the withdrawals from the graded exercise groups were not stated.

Comment: Experience suggests that symptoms of chronic fatigue syndrome may be exacerbated by overly ambitious or overly hasty attempts at exercise.

OPTION PROLONGED REST

We found no RCTs on the effects of prolonged rest. Indirect observational evidence in healthy volunteers and in people recovering from a viral illness suggests that prolonged rest may perpetuate or worsen fatigue and symptoms.

Benefits: We found no systematic review or RCTs of prolonged rest in people with chronic fatigue syndrome.

Harms: We found no direct evidence of harmful effects of rest in people with chronic fatigue syndrome. We found observational evidence suggesting that prolonged inactivity may perpetuate or worsen fatigue and is associated with symptoms in both healthy volunteers[33] and in people recovering from viral illness.[34]

Comment: It is not clear that evidence from people recovering from viral illness can be extrapolated to people with chronic fatigue syndrome.

OPTION MAGNESIUM

One small RCT found that intramuscular magnesium injections versus placebo significantly improved symptoms at 6 weeks.

Benefits: We found one systematic review (search date 2000), which did not report quantified results.[15] The review identified one RCT (32 people with chronic fatigue syndrome), which compared weekly intramuscular injections of magnesium sulphate 50% versus placebo (water for injection) for 6 weeks.[35] It found that magnesium improved overall benefit (12/15 [80%] *v* 3/17 [18%]; RR 4.5, 95% CI 1.6 to 13.1; NNT 2, 95% CI 2 to 4), energy (P = 0.002), pain (P = 0.001), and emotional reactions (P = 0.013).

Harms: The RCT reported no adverse effects.

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Comment: Subsequent studies have not found a deficiency of magnesium in people with chronic fatigue syndrome.[36–38] In the RCT, only red blood cell magnesium was slightly lower than the normal range. In the three subsequent studies, magnesium was in the normal range and no different from controls. However, none of the studies state where the normal range comes from so it is difficult to say if they are equivalent.

OPTION EVENING PRIMROSE OIL

One small RCT found no significant difference with evening primrose oil versus placebo in depression scores at 3 months.

Benefits: We found one systematic review (search date 2000), which did not report quantified results.[15] The review identified one RCT (50 people with chronic fatigue syndrome according to Oxford, UK, diagnostic criteria), which compared evening primrose oil (4 g daily) versus placebo for 3 months.[39] It found no significant difference between groups in depression scores (Beck Depression Inventory), physical symptoms, or participant assessment (at 3 months 46% were improved with placebo *v* 29% with evening primrose oil; P = 0.09; figures were not presented in a manner that allowed RR with CI to be calculated).

Harms: The RCT reported no adverse effects.

Comment: One RCT (63 people) compared evening primrose oil (4 g daily) versus placebo in people with a diagnosis of postviral fatigue syndrome.[40] This diagnosis was made on the basis of overwhelming fatigue, myalgia, and depression, which had been present for at least 1 year and all had been preceded by a febrile illness. At 3 months, 33/39 (85%) of the people on active treatment had improved compared with 4/24 (17%) on placebo — a significant benefit (P < 0.0001). The difference in outcome may be partly explained by participant selection; the study in people with chronic fatigue syndrome used currently accepted diagnostic criteria.[39] Also, whereas this RCT used liquid paraffin as a placebo,[40] the chronic fatigue syndrome RCT used sunflower oil, which is better tolerated and less likely to affect the placebo response adversely.[39]

OPTION IMMUNOTHERAPY

Small RCTs found that immunoglobulin G versus placebo modestly improved physical functioning and fatigue at 3–6 months, but was associated with considerable adverse effects. Small RCTs found insufficient evidence on the effects of interferon alfa versus placebo.

Benefits: We found one systematic review (search date 2000), which did not report quantified results.[15] **Immunoglobulin G:** The review identified four relevant RCTs comparing immunoglobulin G versus placebo for 6 months.[41–44] The first RCT (30 people) compared monthly intravenous injections of immunoglobulin G (1 g/kg) versus placebo (albumin).[41] After 6 months, no large differences were found in measures of fatigue (self reported symptom severity) or in physical and social functioning (SF-36). There was a significant improvement in social function with placebo versus immunoglobulin G

(dichotomous figures not provided). The second RCT (49 people) compared monthly intravenous immunoglobulin G (2 g/kg) versus intravenous placebo (a maltose solution) for 3 months.[42] More people receiving immunoglobulin G versus placebo improved in terms of a physician rated assessment of symptoms and disability (10/23 [44%] *v* 3/26 [11%]; P = 0.03). The third RCT (99 adults) compared placebo versus three doses of immunoglobulin G (0.5, 1, or 2 g/kg).[43] It found no significant difference in quality of life, scores on visual analogue scales, or in changes in hours spent in non-sedentary activities. The fourth RCT (71 adolescents aged 11–18 years) compared immunoglobulin G (1 g/kg) versus placebo.[44] Three infusions were given 1 month apart. There was a significant difference between the active treatment and control groups in mean functional outcome, which was determined by taking the mean of clinician ratings from four areas of the participants' activities (number of people achieving improvement of ≥ 25% at 6 months: 26/36 [52%] with immunoglobin *v* 15/34 [31%] with placebo, RR 1.6, 95% CI 1.1 to 2.5). However, both groups showed significant improvements from baseline, continuing to the 6 month assessment after treatment. **Other treatments:** The review identified two RCTs (30 people) comparing interferon alfa versus placebo.[45,46] The first RCT only found treatment benefit on subgroup analysis of people with isolated natural killer cell dysfunction.[45] The second randomised crossover trial did not present results in a manner that allowed clear interpretation of treatment effect.[46] Other RCTs found no significant advantage over placebo from aciclovir,[47] dialysable leucocyte extract (in a factorial design with cognitive behavioural therapy),[48] or terfenadine.[49]

Harms: **Immunoglobulin G:** In the first RCT, adverse effects judged to be worse than pretreatment symptoms in either group included gastrointestinal complaints (18 people), headaches (23 people), arthralgia (6 people), and worsening fatigue. Of these symptoms, only headaches differed significantly between the groups (immunoglobulin G 14/15 [93%] *v* placebo 9/15 [60%]). Six participants (3 immunoglobulin G, 3 placebo) were considered to have major adverse effects. Adverse events by treatment group were only reported for headache.[41] **Other treatments:** In the RCT comparing interferon alfa 2/13 (15%) people taking active treatment developed neutropenia.[45]

Comment: **Immunoglobulin G:** The first two RCTs differed in that the second used twice the dose of immunoglobulin G, did not require that participants fulfil the operational criteria (similar but not identical to US Centers for Disease Control and Prevention criteria) for chronic fatigue syndrome, and made no assessments of them during the study, waiting until 3 months after completion.[42] **Other treatments:** Terfenadine, particularly at high blood concentrations, is associated with rare hazardous cardiac arrhythmias.[50]

OPTION COGNITIVE BEHAVIOURAL THERAPY

One systematic review has found that cognitive behavioural therapy versus standard medical care or relaxation therapy administered by highly skilled therapists in specialist centres improves quality of life and

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physical functioning. One additional multicentre RCT has found that cognitive behavioural therapy administered by less experienced therapists versus guided support groups or no interventions may also be effective.

Benefits: We found two systematic reviews (search dates 1998[51] and 2000[15]). The first review[51] identified three RCTs that met the reviewers' inclusion criteria (all participants fulfilled accepted diagnostic criteria for chronic fatigue syndrome [CFS], use of adequate randomisation, and use of controls).[48,52,53] The second review identified one additional RCT that met inclusion criteria but the review did not report quantified results.[16,54] The first RCT (90 people with CFS according to Australian diagnostic criteria that are similar to US Centers for Disease Control and Prevention [CDC] criteria) identified by the reviews evaluated cognitive behavioural therapy (CBT) and immunological therapy (dialysable leucocyte extract) using a factorial design.[48] The comparison group received standard medical care. It found no significant difference in quality of life measures (Karnofsky scale and symptom report on a visual analogue scale) between CBT and standard medical care. CBT was given every 2 weeks for six sessions lasting 30–60 minutes each. Treatment involved encouraging participants to exercise at home and feel less helpless. The second RCT (60 people with CFS according to Oxford, UK, diagnostic criteria) identified by the reviews compared CBT versus normal general practice care in people attending a secondary care centre.[53] It found that, at 12 months, CBT improved quality of life (Karnofsky scale) compared with those receiving standard medical care (final score > 80: 22/30 [73%] with CBT *v* 8/30 [27%] with placebo; RR 2.75, 95% CI 1.54 to 5.32; NNT 3, 95% CI 2 to 5). The active treatment consisted of a cognitive behavioural assessment, followed by 16 weekly sessions of behavioural experiments, problem solving activity, and re-evaluation of thoughts and beliefs inhibiting return to normal functioning. The third RCT (60 people with CFS according to CDC diagnostic criteria in people attending a secondary care centre) identified by the reviews compared CBT with relaxation therapy.[52] It found substantial improvement in physical functioning (based on predefined absolute or relative increases in the SF-36 score) with CBT compared with relaxation therapy (19/30 [63%] with CBT *v* 5/30 [17%] with relaxation; RR 3.7, 95% CI 2.37 to 6.31; NNT 3, 95% CI 1 to 7). Improvement continued over 6–12 months' follow up. CBT was given in 13 weekly sessions. A 5 year follow up study of 53 (88%) of the original participants found that more people rated themselves as "much improved" or "very much improved" with CBT compared with relaxation therapy (17/25 [68%] with CBT *v* 10/28 [36%] with relaxation therapy; RR 1.9, 95% CI 1.1 to 3.4; NNT 4, 95% CI 2 to 19).[55] More people treated with CBT met the authors' criteria for complete recovery at 5 years but the difference was not significant (17/31 [55%] with CBT *v* 7/22 [32%] with relaxation therapy; RR 1.7, 95% CI 0.9 to 3.4). The additional multicentre RCT identified by the second review (278 people with CFS according to CDC criteria) compared CBT, guided support groups, or no intervention.[54] The CBT consisted of 16 sessions over 8 months administered by 13 therapists with no previous experience of treating CFS. The guided support groups were similar to CBT in terms of treatment

schedule, with the participants receiving non-directive support from a social worker. At 8 months' follow up it found that more people in the CBT group met the criteria for clinical improvement for fatigue severity (checklist individual strength) and self reported improvement in fatigue compared with the guided support and no treatment groups (fatigue severity: CBT *v* support group, 27/83 [33%] *v* 10/80 [13%], RR 2.6, 95% CI 1.3 to 5.0; CBT *v* no intervention 27/83 [33%] *v* 8/62 [13%], RR 2.5, 95% CI 1.2 to 5.2; self reported improvement: CBT *v* support group 42/74 [57%] *v* 12/71 [17%], RR 3.4, 95% CI 1.9 to 5.8; CBT *v* no intervention 42/74 [57%] *v* 23/78 [30%], RR 1.9, 95% CI 1.3 to 2.9). The results were not corrected for multiple comparisons.

Harms: No harmful effects were reported.

Comment: The effectiveness of CBT for CFS outside of specialist settings has been questioned. The results of the multicentre RCT suggest that cognitive behavioural therapy may be effective when administered by less experienced therapists given adequate supervision. The trial had a high withdrawal rate (25% after 8 months), especially in the CBT and guided support groups. Although the presented confidence intervals are not adjusted for multiple comparisons the results would remain significant after any reasonable adjustment. The authors comment that the results were similar following intention to treat analysis but these results were not presented.[54] A randomised trial comparing CBT and non-directive counselling found that both interventions were of benefit in the management of people consulting their family doctor because of fatigue symptoms. In this study, 28% of the sample conformed to CDC criteria for CFS.[56]

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Competing interests: None declared.

Chronic fatigue syndrome

TABLE 1 **Diagnostic criteria for chronic fatigue syndrome (see text, p 1).**

CDC 1994[1]	**Oxford, UK[2]**
Clinically evaluated, medically unexplained fatigue of at least 6 months' duration that is:	Severe, disabling fatigue of at least 6 months' duration that:
– of new onset	– affects both physical and mental functioning
– not a result of ongoing exertion	– was present for more than 50% of the time
– not substantially alleviated by rest	
– a substantial reduction in previous levels of activity	
The occurrence of four or more of the following symptoms:	Other symptoms, particularly myalgia, sleep, and mood disturbance, may be present.
– subjective memory impairment	
– tender lymph nodes	
– muscle pain	
– joint pain	
– headache	
– unrefreshing sleep	
– postexertional malaise (> 24 h)	
Exclusion criteria	
– Active, unresolved, or suspected disease likely to cause fatigue	– Active, unresolved, or suspect disease likely to cause fatigue
– Psychotic, melancholic, or bipolar depression (but not uncomplicated major depression)	– Psychotic, melacholic, or bipolar depression (but not uncomplicated major depression)
– Psychotic disorders	– Psychotic disorders
– Dementia	– Dementia
– Anorexia or bulimia nervosa	– Anorexia or bulimia nervosa
– Alcohol or other substance misuse	
– Severe obesity	

CDC, US Centers for Disease Control and Prevention