Clinical review

Extracts from "Clinical Evidence"

Chronic fatigue syndrome

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Interventions

Beneficial:
Exercise
Cognitive behavioural therapy

Unknown effectiveness:
Corticosteroids
Antidepressants
Dietary supplements
Oral nicotinamide adenine dinucleotide (NADH)

Unlikely to be beneficial:
Immunotherapy

Likely to be ineffective or harmful:
Prolonged rest

Background

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

Incidence/prevalence Community and primary care based studies have reported the prevalence of chronic fatigue syndrome to be 0.2-2.6%, depending on the criteria used.[3 4] Systematic population surveys have found similar rates of the syndrome in people of different socioeconomic status, and in all ethnic groups.[4 5] Female sex is the only demographic risk factor (relative risk 1.3 to 1.7 depending on diagnostic criteria used).[6]

Aetiology The cause of chronic fatigue syndrome is poorly understood.

Prognosis Studies of prognosis in chronic fatigue syndrome have focused on people attending specialist clinics, who are likely to have had the condition for longer and to have a poorer outlook. Children with

Diagnostic criteria for chronic fatigue syndrome

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

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the syndrome seem to have a notably better outcome: 54-94% of children show definite improvement (after up to six years' follow up); 20-50% of adults show some improvement in the medium term and only 6% return to premorbid levels of functioning.[7] Despite the considerable burden of morbidity associated with chronic fatigue syndrome, there is no evidence of increased mortality. Outcome is influenced by the presence of psychiatric disorders 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; effects on physical function and quality of life measured in several different ways by: the medical outcomes survey short form general health survey (SF-36), a rating scale measuring limitation of physical functioning caused by ill health[8]; the Karnofsky scale, a modified questionnaire originally developed for the rating of quality of life in people undergoing chemotherapy for malignancy[9]; the Beck depression inventory[10]; the sickness impact profile, a measure of the influence of symptoms on social and physical functioning[11]; and self reported severity of symptoms and levels of activity.

Methods

Clinical Evidence search and appraisal January 1999. All randomised controlled trials (RCTs) meeting *Clinical Evidence* criteria were reviewed. We found that the evidence on which to base clinical decisions was slender. Even where good evidence exists, there are likely to be large gaps in provision of services and expertise (for example, for cognitive behavioural therapies). Hence, for many practitioners it will be necessary to use clinical judgment linked with expertise derived from related areas, such as the management of chronic pain.

Question: What are the effects of treatments?

Option: Antidepressants

We found limited data from RCTs, providing insufficient evidence to support the use of antidepressants in people with chronic fatigue syndrome. However, research evidence suggests that antidepressants may be useful in treating associated depression, insomnia, or myalgia.

Benefits

We found no systematic reviews. ***Versus placebo:*** We found three RCTs. One that compared fluoxetine with placebo in 96 people found no significant benefit on outcomes used (the Beck depression inventory and the sickness impact profile).[12] Another allocated 136 people to four groups: exercise plus fluoxetine; exercise plus placebo; appointments to review activity diary with physiotherapist plus fluoxetine, and appointments to review activity diary with physiotherapist plus placebo. It found no significant difference in outcome (level of fatigue), although there was a trend indicating some benefit and there were modest improvements in measures of depression.[13] The first study used shorter treatment and studied people with a long duration of illness, which may explain the differing results. A third trial compared the monoamine oxidase inhibitor phenelzine versus placebo in 24 people with chronic fatigue syndrome, using a modified Karnofsky scale and other outcome measures.[14] This also found a non-significant trend toward improvement. ***Versus each other:*** We found one RCT comparing sertraline with clomipramine in people with chronic fatigue syndrome, but the lack of a placebo group makes it hard to draw useful conclusions.[15]

Harms

Up to 15% of participants withdrew from active treatment because of adverse drug effects.[12–15]

Comment

To date, clinical trials have taken place in specialist clinics, which may actively select for people whose condition is more resistant to treatment.

Option: Corticosteroids

Limited data from RCTs provide insufficient evidence about the effects of corticosteroids in people with chronic fatigue syndrome. Any benefit from low dose glucocorticoids seems to be short lived, and higher doses are associated with adverse effects.

Benefits

We found no systematic review. ***Versus placebo:*** We found three placebo controlled RCTs in people with chronic fatigue syndrome. One, a crossover RCT of fludrocortisone in 20 people, measured outcomes as change in symptom severity on a visual analogue scale, and functional status (using the SF-36).[16] It found no significant difference between active treatment and placebo, though the number of participants may have been too small to detect a difference. The two other trials evaluated hydrocortisone. One compared hydrocortisone 25-35 mg daily with placebo in 65 people and found a greater improvement in a self rated scale of "wellness" in the treatment group. However, other self rating scales did not show significant benefit.[17] The other study used a lower dose of hydrocortisone (5 or 10 mg daily) in 32 people and found short term improvement in fatigue. Nine people (28%) taking hydrocortisone improved, as measured by a self report fatigue scale, compared with three (9%) taking placebo. The benefit rapidly attenuated when treatment was stopped.[18]

Harms

The study using the higher doses of hydrocortisone found that 12 people (40%) receiving active treatment experienced adrenal suppression.[17] Minor adverse effects were reported in up to 10% of people in the other studies.[16 18]

Comment

The trials used different reasons for their choice of active treatment. The use of fludrocortisone, a mineralocorticoid, was based on the hypothesis that chronic fatigue syndrome is associated with neurally mediated hypotension.[19] The use of hydrocortisone in the other trials was based on evidence of underactivity of the hypothalamic-pituitary-adrenocortical axis in some people with the syndrome.[20]

Option: Exercise

Two RCTs have found that a graded exercise programme can substantially improve measures of

fatigue and physical functioning for people with chronic fatigue syndrome.

Benefits
We found no systematic review. We found two RCTs. The first compared aerobic exercise with flexibility training (control intervention) in 66 people.[21] The programmes involved individual weekly sessions over 12 weeks, with the exercise group building up their level of activity to 30 minutes exercise a day with a maximum energy expenditure of 60% of maximum oxygen consumption (VO_2 max). With the self rated clinical global impression scales used as an outcome measure, 55% of the aerobic exercise group reported feeling much better or very much better compared with 27% of the flexibility training group ($P = 0.05$). Significantly better outcomes were also reported as measured by physical fatigue and levels of physical functioning on the SF-36. The flexibility training group crossed over to aerobic exercise at the end of the trial, and significant improvements from baseline were found.

The second trial randomised 136 people with chronic fatigue syndrome to one of four groups: exercise plus fluoxetine; exercise plus placebo; appointments plus fluoxetine; and appointments plus placebo.[13] The exercise group undertook graded aerobic exercise for 20 minutes three times a week up to an energy expenditure of 75% of VO_2 max. Exercise was associated with significant improvements in fatigue and functional work capacity. This trial was complicated by a high withdrawal rate, particularly in the exercise groups (37% *v* 22% in the appointment groups), but the differences remained significant after intention to treat analysis.

Harms
Adverse effects of exercise were not reported in either trial, and we found no evidence that exercise is harmful in people with chronic fatigue syndrome. However, experience suggests that exacerbation of symptoms may result from overambitious or overhasty attempts at exercise. These can be reduced by cautious setting of targets and providing information about the cause of possible symptoms after exertion.

Comment
None.

Option: Prolonged rest

We found no evidence that prolonged rest is an effective treatment for chronic fatigue syndrome. We found considerable indirect evidence suggesting that prolonged rest may be harmful.

Benefits
We found no systematic reviews or RCTs.

Harms
We found no direct evidence of harmful effects of rest in people with chronic fatigue syndrome. However, we found observational evidence suggesting that prolonged inactivity may perpetuate or worsen fatigue and its associated symptoms in both healthy volunteers[22] and in people recovering from viral illness.[23]

Comment
None.

Option: Dietary supplements

One small RCT found limited evidence of benefit from magnesium injections. Two small RCTs of oral evening primrose oil found mixed results.

Benefits
We found no systematic review. ***Magnesium:*** We found one RCT comparing intramuscular injections of magnesium with placebo in people with chronic fatigue syndrome over a six week period.[24] This trial found important benefits with magnesium: 12/15 of the treatment group improved compared with 3/17 of the placebo group. ***Evening primrose oil:*** We found two RCTs comparing evening primrose oil with placebo in people with a diagnosis of postviral fatigue syndrome or chronic fatigue syndrome, only one of which found significant benefit. One RCT compared evening primrose oil (4 g orally per day) with placebo in 63 people with a diagnosis of postviral fatigue syndrome.[25] At three months, 85% of the people receiving active treatment had improved compared with 17% on placebo. However, a further three month trial found no significant difference between evening primrose oil (4 g orally per day) and placebo in 50 people with chronic fatigue syndrome (using the Oxford diagnostic criteria).[26]

Harms
These trials reported no adverse effects.

Comment
Subsequent studies have failed to find a deficiency of magnesium in people with chronic fatigue syndrome.[27–29] The difference in outcome for the studies of evening primrose oil may be partly explained by participant selection; the second study used currently accepted diagnostic criteria.[26] Also, whereas the first study used liquid paraffin as a placebo,[25] the second study used sunflower oil, which is better tolerated and less likely to affect the placebo response adversely.[26]

Option: Immunotherapy

Four small RCTs of IgG in people with chronic fatigue syndrome found only limited benefit and considerable adverse effects. RCTs of other forms of immunotherapy have found no evidence of a benefit over placebo.

Benefits
We found no systematic review. ***IgG:*** We found four RCTs comparing IgG with placebo. In the first, 30 patients were given either intravenous IgG (1 g/kg) or albumin (placebo) every 30 days.[30] After six months no differences were found in measures of fatigue or physical and social functioning. A similar study randomised 49 patients to three infusions of either intravenous IgG (2 g/kg) or placebo (a maltose solution).[31] Treatment was given monthly. Ten of the 23 immunoglobulin recipients improved in terms of a physician rated assessment of symptoms and disability, compared with three of 26 placebo recipients. The studies differed in that the second study used twice the dose of IgG, did not require that participants fulfilled the operational criteria for chronic fatigue syndrome, and made no assessments of them during the study, waiting until three months after completion.[31] A subsequent attempt by the same group to replicate the results was unsuccessful.[32] A further trial compared IgG (1 g/kg)

with placebo in 71 adolescents (age 11-18 years).[33] Three infusions were given one month apart. There was a significant difference between the active treatment and control groups in mean functional outcome determined by taking the mean of clinician ratings from four areas of the participants' activities. However, both groups showed significant improvements from baseline, continuing to the six month post-treatment assessment. ***Other immunotherapies:*** We found one RCT comparing interferon alfa with placebo (n=30).[34] In this study, improvement was found only on subgroup analysis. Other RCTs have found no significant advantage over controls from dialysable leucocyte extract (in a factorial design with cognitive behavioural therapy)[35] or terfenadine.[36]

Harms

Considerable adverse effects (gastrointestinal complaints, headaches, arthralgia, and worsening fatigue) were reported with IgG in up to 82% of trial participants.[30] Adverse effects were also notable with alpha interferon, and two of 13 participants on active treatment developed neutropenia.[34]

Comment

None.

Option: Cognitive behavioural therapy

A systematic review of RCTs has found that cognitive behavioural therapy administered by highly skilled therapists in specialist centres is an effective intervention for people with chronic fatigue syndrome, with a number needed to treat (NNT) of 2. The generalisability of this finding to less specialised settings is likely to be limited.

Benefits

We found one systematic review, updated in August 1998, which identified 13 RCTs of cognitive behavioural therapy in people with chronic fatigue syndrome.[37] Three trials met the reviewers' inclusion criteria (all participants fulfilled diagnostic criteria for chronic fatigue syndrome, use of adequate randomisation, and use of controls).[35 38 39] The earliest study in 90 people used the Australian diagnostic criteria and evaluated cognitive behavioural therapy and immunotherapy, using a factorial design.[35] The comparison group received standard medical care. Cognitive behavioural therapy was given every two weeks for six sessions lasting 30-60 minutes each. Treatment involved encouraging participants to exercise at home and feel less helpless. There was no significant difference in outcomes between cognitive behavioural therapy and standard care when the Karnofsky scale and symptom report on a visual analogue scale were used. The second study used the Oxford diagnostic criteria and compared cognitive behavioural therapy with normal general practice care in 60 people attending a secondary care centre.[38] 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. At 12 months, on the Karnofsky scale, 73% of those receiving cognitive behavioural therapy were improved compared with 27% receiving standard care. The relative benefit increase was 175% (95% confidence interval 54% to 432%), with two people needing to be treated with cognitive behavioural therapy for one patient to achieve normal functioning (NNT 2; 2 to 5). This study was replicated in the third study in 60 people attending a different secondary care centre.[39] The cognitive behavioural therapy was given in 13 weekly sessions, and the control patients received relaxation therapy. Outcome was assessed by using the medical outcomes survey short form. A good outcome was found in 63% of those treated with cognitive behavioural therapy compared with 17% receiving relaxation therapy. The relative benefit increase was 270% (137% to 531%) with a NNT of 2 (1 to 7). In both the second and third studies, improvement continued over 6-12 months' follow up.[38 39]

Harms

No harmful effects were reported.

Comment

The disappointing results of the Australian study may have been because the therapy was less intense and no attempts at cognitive reappraisal were offered, and because routine care was itself reasonably effective.[35] The conflict between the differing illness models for the two active treatments being evaluated, cognitive behavioural therapy and immunotherapy, may also have had an impact on effectiveness. The Australian diagnostic criteria are no longer widely used. The other two studies took place in centres with highly skilled cognitive behavioural therapists.[38 39] The generalisability of their positive results to settings outside specialist centres remains uncertain. A large Dutch RCT (G Bleijenberg, personal communication) and a British RCT based in primary

Summary points

Though we found limited data from RCTs providing insufficient evidence to support the use of antidepressants in people with chronic fatigue syndrome, antidepressants may be useful in treating associated depression, insomnia, or myalgia

We found limited data from RCTs providing insufficient evidence to support the use of corticosteroids in people with chronic fatigue syndrome; any benefit from low dose glucocorticoid treatment seems to be short lived, and higher doses are associated with adverse effects

Two RCTs have found that a graded exercise programme can produce substantial improvements in measures of fatigue and physical functioning for people with chronic fatigue syndrome

We found no evidence that prolonged rest is an effective treatment for chronic fatigue syndrome, and indirect evidence that prolonged rest may be harmful

Limited data from small RCTs provide no clear evidence of benefit from magnesium injections or oral evening primrose oil in people with chronic fatigue syndrome

Four small RCTs of IgG in people with chronic fatigue syndrome found only limited benefit and adverse effects; other forms of immunotherapy have no advantage over placebo

A systematic review of RCTs has found that cognitive behavioural therapy administered by highly skilled therapists in specialist centres is effective in people with chronic fatigue syndrome

care (L Ridsdale et al, personal communication) are due to report shortly.

Option: Oral nicotinamide adenine dinucleotide

One small RCT found evidence of limited benefit from oral nicotinamide adenine dinucleotide.

Benefits

We found no systematic review. We found one RCT using a crossover design, which compared nicotinamide adenine dinucleotide (NADH) 10 mg a day and placebo over four weeks.[40] Of the 33 people with chronic fatigue syndrome who completed the study, 26 were included in the analysis. On a symptom rating scale, 8/26 receiving the study drug attained a 10% improvement, compared with 2/26 receiving placebo.

Harms

Minor adverse effects (loss of appetite, dyspepsia, flatulence) were reported with the study drug but did not lead to stopping treatment.

Comment

The rationale for this treatment is that NADH facilitates generation of ATP, which may be depleted in chronic fatigure syndrome.[40] The authors plan to conduct a further study using greater numbers.

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Corrections and clarifications

ABC of complementary medicine: Unconventional approaches to nutritional medicine
In this article by Andrew Vickers and Catherine Zollman (27 November, pp 1419-22) the box "Examples of dietary interventions claimed to help in specific conditions" (p 1420) should have stated that the Gerson diet for cancer consisted of a vegetarian diet with "coffee enemas and various supplements" (not "coffee, enemas, and various supplements").

National electronic Library for Health (NeLH)
In this article by J A Muir Gray and Simon de Lusignan (4 December, pp 1476-9) Sir Edward Wayne's name was misspelt (p 1476).

Obituaries
In the obituary of Dr Douglas Arthur Longmore Ashforth (4 December 1999, p 1503), Dr Ashforth's surname was misspelt.

Reviews
In Stuart Brooks's review of the CD Rom *The Virtual Surgeon: ACL Reconstruction* (27 November, p 1442), the price quoted for the CD was £363. In fact, it is available for £150 from TVF Multimedia (tel 020 7837 3000).