Chronic fatigue syndrome

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ABSTRACT

INTRODUCTION: Chronic fatigue syndrome affects between 0.006% and 3% of the population depending on the criteria of definition used, with women being at higher risk than men. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of selected treatments for chronic fatigue syndrome? We searched: Medline, Embase, The Cochrane Library, and other important databases up to November 2013 (BMJ Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). RESULTS: At this update, searching of electronic databases retrieved 169 studies. After deduplication and removal of conference abstracts, 86 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 71 studies and the further review of 15 full publications. Of the 15 full articles evaluated, two systematic reviews, one RCT, and one further follow-up report of an RCT were added at this update. We performed a GRADE evaluation for 23 PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the effectiveness of four interventions based on information relating to the effectiveness and safety of antidepressants, cognitive behavioural therapy, corticosteroids, and graded exercise therapy.

Key points

- Chronic fatigue syndrome (CFS) is characterised by severe, disabling fatigue, and other symptoms, including musculoskeletal pain, sleep disturbance, impaired concentration, and headaches.

  CFS affects between 0.006% and 3% of the population depending on the criteria used, with women being at higher risk than men.

- Previous editions of *BMJ Clinical Evidence* have covered a wide range of interventions, but many have retained an evaluation of 'likely to be ineffective' or 'unknown effectiveness' for several editions with no new published research available. In the current edition, we decided to focus on describing those interventions with the best evidence of effectiveness, in widespread clinical use or with recent trial data.

  Other treatments previously considered include dietary supplements, evening primrose oil, galantamine, homeopathy, immunotherapy, intramuscular magnesium, oral nicotinamine adenine dinucleotide, and prolonged rest.

- Graded exercise therapy has been shown to effectively improve measures of fatigue and physical functioning.

  Educational interventions with encouragement of graded exercise (treatment sessions, telephone follow-ups, and an educational package explaining symptoms and encouraging home-based exercise) improve symptoms more effectively than written information alone.

- Cognitive behavioural therapy (CBT) is effective in treating chronic fatigue syndrome in adults.

  CBT may also be beneficial when administered by therapists with no specific experience of chronic fatigue syndrome, but who are adequately supervised.

  In adolescents, CBT can reduce fatigue severity and improve school attendance compared with no treatment.

- We don't know how effective antidepressants and corticosteroids are in treating chronic fatigue syndrome.

  Antidepressants should be considered in people with depressive disorders. Tricyclics, in particular, have potential therapeutic value because of their analgesic properties and the high prevalence of muscle and joint pain in CFS.

Clinical context

GENERAL BACKGROUND

Chronic fatigue syndrome (CFS) is characterised by severe, disabling fatigue and other symptoms, including musculoskeletal pain, sleep disturbance, impaired concentration, and headaches. The two most widely used definitions of CFS are from the Centers for Disease Control and Prevention (CDC) and the Oxford criteria. The principal difference between these definitions is the number and severity of symptoms, other than fatigue, that must be present.

FOCUS OF THE REVIEW

There are a wide range of treatments that have been proposed for CFS, most of which have little or poor evidence base and which have been extensively considered in the previous version of this *BMJ Clinical Evidence* systematic overview. For this update, the focus was on treatments that had the best evidential support in previous editions, that are in widespread clinical use, and/or have recent trial data.

COMMENTS ON EVIDENCE

There is good-quality evidence that both cognitive behavioural therapy (CBT) and graded exercise therapy are effective treatments for reducing fatigue and increasing functional capacity in people with CFS. There is less evidence for the drug treatments considered in this overview (antidepressants and corticosteroids); in particular, the evidence for corticosteroid use in people with CFS is limited. Several different instruments were used across studies to measure our outcomes of interest. Some of these involved self-rating by the person with CFS, whereas others report clinician-rated outcomes (in which case the assessor should be blinded). We have not reported school attendance as a main outcome in this overview, however, if available, we have added this data to the relevant Further information on studies section. Most studies were quite short-term; we only found one study with follow-up beyond 12 months.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this overview was carried out from the date of the last search, March 2010, to November 2013. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 169 studies. After deduplication and removal of conference abstracts, 86 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 71 studies and the further review of 15 full publications. Of the 15 full articles evaluated, two systematic reviews, one RCT, and one further follow-up report of an RCT were added at this update.

ADDITIONAL INFORMATION

The largest RCT to date found that CBT and graded exercise therapy are more effective than adaptive pacing therapy or specialised medical care. While antidepressants may not be effective for CFS per se, they should be considered for patients with depressive disorders. Tricyclic antidepressants, in particular, should be considered in patients with chronic joint and/or muscle pain given their additional analgesic properties.

DEFINITION

Chronic fatigue syndrome (CFS) is characterised by severe, disabling fatigue, and other symptoms, including musculoskeletal pain, sleep disturbance, impaired concentration, and headaches. The two most widely used definitions of CFS, from the US Centers for Disease Control and Prevention (CDC) (the current criteria were issued in 1994, which superseded the 1988 CDC criteria) [1] and from Oxford, UK, [2] were developed as operational criteria for research (see table 1, p 38). The principal difference between these definitions is the number and severity of symptoms, other than fatigue, that must be present. A third operational definition, the Australian criteria, is similar to the CDC diagnostic criteria and has also been used in treatment trials. [3] The 1994 CDC criteria were reviewed with the aim of improving case ascertainment for research. [4] The exclusion criteria were clarified, and the use of specific instruments for the assessment of symptoms was recommended. [4] Another suggested definition from Canada [5] includes a large number of non-specific features, potentially includes medical disorders that could be excluded under other definitions, and mixes signs, symptoms, and presumed aetiology. The authors of the Canadian guidelines state that they are based on a lesser level of evidence and are intended more as clinical practice guidelines; [6] this definition is not widely used.

INCIDENCE/ PREVALENCE

Community-based and primary-care-based studies have reported the prevalence of CFS to be from 0.007% to 2.8% in the general adult population, and from 0.006% to 3.0% in primary care, depending on the criteria used. [7]

AETIOLOGY/ RISK FACTORS

Despite considerable research effort and several hypotheses, the cause of CFS remains poorly understood. Endocrine and immunological abnormalities have been found in many people, although it is unclear whether these changes are causal or are part of the course of the syndrome. [8] Certain infectious illnesses, such as Epstein-Barr virus, Q fever, and viral meningitis, are associated with a greater risk of developing CFS, but many people have no evidence of viral infection, and there is no evidence of persistent infection. [9] Family and twin studies suggest a significant genetic component to the tendency to develop chronic fatigue. [7] People with prior psychiatric disorders are more likely to report CFS later in life (OR 2.7, 95% CI 1.3 to 5.6). [10] A history of childhood trauma/abuse increases the later risk of developing CFS (OR 3.4, 95% CI 1.4 to 7.9). [11] There is also a likely role for psychological factors such as perfectionism, attributions, perceptions, and coping. [7] While some prospective cohort studies have suggested that a pre-morbid tendency to

undertake high levels of exercise is a risk factor, [12] others have not replicated this. [13] Women are at higher risk than men (RR 1.3–1.7, depending on diagnostic criteria used; CIs not reported). [14] Population surveys in the US have found that Caucasians have a lower risk of CFS compared with Latin Americans, African-Americans, and Native Americans. [15] [16] Contrary to popular misconceptions of the illness, there is no link with higher social class [17] and rates may be higher in those with lower socioeconomic status. [15]

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% to 94% of children showed definite improvement in symptoms (after up to 6 years' follow-up), whereas 20% to 50% of adults showed some improvement in the medium term (12–39 months) and only 6% returned to premorbid levels of functioning. [18] Nevertheless, one prospective follow-up study suggests that, even after long illness periods, around 50% of patients can return to part- or full-time work. [19] Despite the considerable burden of morbidity associated with CFS, we found no evidence of increased mortality. The systematic review found that a longer duration of illness, fatigue severity, comorbid depression and anxiety, and a physical attribution for CFS are factors associated with a poorer prognosis. [18] Another review found a median full recovery rate of 5% (range 0–31%), and the median proportion of patients who improved during follow-up to be 39.5% (range 8–63%). Good outcome was associated with less fatigue severity at baseline, a sense of control over symptoms, and not attributing the illness to a physical cause. [20]

AIMS OF INTERVENTION

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

OUTCOMES

Severity of symptoms (including **fatigue** and **overall improvement**) and their effects on **functional status** (includes physical function, physical health, and functional impairment); **quality of life**; and **adverse effects**. There are several different instruments used to measure these outcomes, including: the medical outcomes survey short-form general health survey (SF-36, [21] a rating scale measuring quality of life, including 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], pain, energy levels, and mood); the Karnofsky scale, [22] a modified questionnaire originally developed for the rating of quality of life in people having chemotherapy for malignancy (where 0 = death and 100 = no evidence of disease); the Beck Depression Inventory, [23] a self-rated checklist for quantifying depressive symptoms (score range 0–63, where a score of 20 or more is usually considered clinically significant depression); the Hospital Anxiety and Depression scale (HADS, [24] which consists of 2 self-rated subscales, each with score range 0–21, where a score of 11 or more is considered clinically significant); the Sickness Impact Profile, [25] a measure of the influence of symptoms on social and physical functioning; the Chalder Fatigue Scale, [26] a rating scale measuring subjective fatigue (score range 0–11, where scores 4 or more = excessive fatigue); the Abbreviated Fatigue Questionnaire, [27] a rating scale of subjective bodily fatigue (score range 4–28, where a lower score indicates a higher degree of fatigue); the Clinical Global Impression scale, [28] a validated clinician-rated measure of overall change compared with baseline at study onset (7 possible scores from 'very much worse' [score 7] to 'very much better' [score 1]); the Checklist Individual Strength fatigue subscale (score range 8 [no fatigue at all] to 56 [maximally fatigued]); [29] the Nottingham Health Profile, [30] with questions in 6 self-report categories: energy, pain perception, sleep patterns, sense of social isolation, emotional reactions, and physical mobility (maximum weighted score 100 [all listed complaints present], and minimum 0 [none of listed complaints present]); the Multidimensional Fatigue Inventory (MFI), [31] with 5 subscales: general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation (each with a score range of 4–20, higher scores indicate higher degree of fatigue); and self-reported severity of symptoms and levels of activity; and the Fatigue Severity Scale, [32] with nine self-rated 7-point subscales assessing behavioural consequences of fatigue.

METHODS

Search strategy *Clinical Evidence* search and appraisal November 2013. Databases used to identify studies for this systematic review include: Medline 1966 to November 2013, Embase 1980 to November 2013, The Cochrane Database of Systematic Reviews 2013, Issue 10 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this review were systematic reviews and RCTs published in English. RCTs had to be at least single blinded for drug interventions, but non-blinded studies were included for non-drug interventions. For drug interventions we excluded all studies described as 'open', 'open label', or not blinded. RCTs had to contain 20 or more individuals, of whom 80% or more were followed up. There was no minimum length of follow-up required to include studies. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant and comprehensive studies identified through an agreed process involving our evidence team, editorial

team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed a priori with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our predefined criteria for inclusion in the benefits and harms section, may have been reported in the 'Further information on studies' or 'Comment' section. **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update, we have removed the following interventions: immunotherapy, dietary supplements, evening primrose oil, magnesium (intramuscular), oral nicotinamide adenine dinucleotide (NADH), homeopathy, prolonged rest, and galantamine. **Data and quality** To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue which may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 39). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of selected treatments for chronic fatigue syndrome?

OPTION COGNITIVE BEHAVIOURAL THERAPY

- For GRADE evaluation of interventions for Chronic fatigue syndrome, see table, p 39 .
- Cognitive behavioural therapy (CBT) is effective in treating chronic fatigue syndrome in adults.
- CBT may also be beneficial when administered by therapists with no specific experience of chronic fatigue syndrome, but who are adequately supervised.
- In children and adolescents, CBT can reduce fatigue severity and improve school attendance compared with no treatment.

Benefits and harms

CBT versus control interventions:

We found three systematic reviews (search dates 2008; [33] 1987 to 2012; [34] and search date not specified [35]). The first systematic review included 15 RCTs in adults. [33] The review included results from unpublished RCTs and studies that did not meet *BMJ Clinical Evidence* quality criteria in its meta-analyses, and so we have reported the results of each of the six published RCTs identified by the review that did meet *BMJ Clinical Evidence* inclusion criteria individually. [36] [37] [38] [39] [40] [41] We found one additional RCT [42] in children and adolescents that reported on the effects of CBT on school attendance; [42] see Further information on studies for full details. The second systematic review, [34] a narrative review of interventions in children and adolescents, found one additional RCT [43] and one subsequent RCT. [44] The subsequent RCT used an internet-based CBT intervention in adolescents and also reported on school attendance [44] (see Further information on studies). Long-term follow-up of this study was reported separately. [45] The third systematic review was also a narrative review and all the relevant RCTs were already reported individually here. [35] We also found one additional RCT. [46]

Fatigue

CBT compared with control interventions CBT may be more effective at improving fatigue than control interventions (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fatigue severity					
[39] RCT **3-armed trial**	278 adults with CFS (CDC criteria) In review [33]	**Improvement in fatigue severity (Checklist Individual Strength [CIS-fatigue]) , 8 months** 27/83 (33%) with CBT 10/80 (13%) with guided support The remaining arm evaluated no intervention See Further information on studies for description of CBT and guided support	RR 2.6 for CBT *v* guided support 95% CI 1.3 to 5.0 RCT had high withdrawal rate; see Further information on studies for full details	●●○	CBT
[39] RCT **3-armed trial**	278 adults with CFS (CDC criteria) In review [33]	**Improvement in fatigue severity (self-reported) , 8 months** 42/74 (57%) with CBT 12/71 (17%) with guided support The remaining arm evaluated no intervention See Further information on studies for description of CBT and guided support	RR 3.4 for CBT *v* guided support 95% 1.9 to 5.8 RCT had high withdrawal rate; see Further information on studies for full details	●●○	CBT
[39] RCT **3-armed trial**	278 adults with CFS (CDC criteria) In review [33]	**Improvement in fatigue severity (CIS-fatigue) , 8 months** 27/83 (33%) with CBT 8/62 (13%) with no intervention The remaining arm evaluated guided support See Further information on studies for description of CBT and guided support	RR 2.5 for CBT *v* no intervention 95% CI 1.2 to 5.2 RCT had high withdrawal rate; see Further information on studies for full details	●●○	CBT
[39] RCT **3-armed trial**	278 adults with CFS (CDC criteria) In review [33]	**Improvement in fatigue severity (self-reported) , 8 months** 42/74 (57%) with CBT 23/78 (30%) with no intervention The remaining arm evaluated guided support See Further information on studies for description of CBT and guided support	RR 1.9 for CBT *v* no intervention 95% CI 1.3 to 2.9 RCT had high withdrawal rate; see Further information on studies for full details	●○○	CBT
[40] RCT **3-armed trial**	153 adults with CFS (CDC criteria) In review [33]	**Change in fatigue severity (Chalder Fatigue Score)** with group CBT with usual care Absolute results not reported 103 people in this analysis Treatment effects at 6 and 12 months were pooled for analysis The remaining arm evaluated education and support	Difference –2.61 for group CBT *v* usual care 95% CI –4.92 to –0.30 P = 0.03	○○○	CBT

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		See Further information on studies for description of CBT and usual care			
[40] RCT **3-armed trial**	153 adults with CFS, CDC criteria In review [33]	**Change in fatigue severity (Chalder Fatigue Score)** with group CBT with education and support Absolute results not reported 102 people in this analysis Treatment effects at 6 and 12 months were pooled for analysis The remaining arm evaluated usual care See Further information on studies for description of CBT and education and support interventions	Difference –3.16 for group CBT *v* education and support 95% CI –5.59 to –0.74 P = 0.011	○○○	CBT
[36] RCT **4-armed trial**	90 adults with a mean age of 39.6 years who fulfilled diagnostic criteria for CFS (not further defined) In review [33]	**Mean fatigue score (profile of mood states subscale) , 7 months (3 months after completion of treatment)** 16.8 with CBT plus placebo 17.3 with usual care plus placebo 43 people in the analysis The remaining 2 arms reported on CBT plus dialysable leukocyte extract (DLE) and DLE alone CBT consisted of 6 sessions of CBT lasting 30 to 60 minutes every 2 weeks and placebo consisted of 8 biweekly injections of lyophilised normal saline	Significance not assessed		
[41] RCT **4-armed trial**	114 adults with CFS (as defined by CDC criteria); baseline fatigue severity scale (FSS) scores 6.05 in people having CBT, 5.82 in people having relaxation therapy In review [33]	**Mean score on FSS , 12 months** 5.37 with CBT 5.62 with relaxation therapy 57 people in this analysis The population in this RCT may have been less impaired than in other similar RCTs The remaining 2 arms assessed anaerobic activity therapy and cognitive therapy See Further information on studies for further details on study population and interventions	Significance not assessed		
[42] RCT	69 children and adolescents aged 10 to 17 years with CFS (CDC criteria)	**Change in fatigue severity score (Checklist Individual Strength [CIS-fatigue]) , 5 months** –22.3 with CBT –7.6 with no intervention CBT consisted of 10 sessions over 5 months	Absolute difference 14.5 95% CI 7.4 to 21.6	○○○	CBT

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[43] RCT	63 adolescents aged 11–18 years with CFS (CDC or Oxford criteria) In review [34]	**Mean fatigue score (Chalder Fatigue Scale) , 6 months post treatment** 13.3 with family-focused CBT 14.2 with psycho-education 56 people in this analysis Treatment duration was 6 months	Treatment effect +0.24 95% CI –3.61 to +4.10 P = 0.9	⟷	Not significant
[44] RCT	131 adolescents aged 12–18 years with CFS (CDC criteria) In review [34]	**Fatigue severity (CIS-20) , 6 months** 24.0 with internet CBT 42.3 with usual care See Further information on studies for details on interventions	Mean difference –18.3 95% CI –22.9 to –13.7 P <0.0001	○○○	CBT
[46] RCT **4-armed trial**	641 adults with CFS (Oxford criteria)	**Chalder Fatigue Questionnaire , 24 weeks** 21.5 with CBT 24.0 with specialist medical care 321 people in this analysis The remaining 2 arms assessed adaptive pacing therapy and graded exercise therapy; see Further information on studies for details on interventions	Significance not assessed		
[46] RCT **4-armed trial**	641 adults with CFS (Oxford criteria)	**Chalder Fatigue Questionnaire , 52 weeks** 20.3 with CBT 23.8 with specialist medical care 321 people in this analysis The remaining 2 arms assessed adaptive pacing therapy and graded exercise therapy	Mean difference –3.4 95% CI –5.0 to –1.8 P = 0.0001	○○○	CBT

No data from the following reference on this outcome. [37] [38] [45]

Overall improvement

CBT compared with control interventions CBT seems more effective than control interventions at increasing recovery at 6 months to 5 years (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recovery					
[47] RCT	53 adults with CFS (CDC criteria) Further report of reference [38]	**Complete recovery , 5 years** 17/31 (55%) with CBT 7/22 (32%) with relaxation therapy	RR 1.7 95% CI 0.9 to 3.4	⟷	Not significant
[47] RCT	53 adults with CFS (CDC criteria) Further report of reference [38]	**Proportion of people rating themselves as 'much improved' or 'very much improved' , 5 years** 17/25 (68%) with CBT 10/28 (36%) with relaxation therapy	RR 1.9 95% CI 1.1 to 3.4	●○○	CBT

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[43] RCT	63 adolescents aged 11–18 years with CFS (CDC or Oxford criteria) In review [34]	**Child-reported Global Improvement , 6 months post treatment** 24/27 (89%) with family-focused CBT 26/29 (90%) with psycho-education Treatment duration was 6 months Mother-reported Global Improvement and Independent Global Improvement were also reported, both also not significant	OR 1.08 95% CI 0.20 to 5.89 P = 0.93	⟷	Not significant
[44] RCT	131 adolescents aged 12–18 years with CFS (CDC criteria) In review [34]	**Proportion of people rating themselves as 'completely recovered' or 'much better' , 6 months** 52/67 (78%) with internet CBT 17/64 (27%) with usual care	RR 2.9 95% CI 1.9 to 4.5 P <0.0001	○○○	CBT
[45] RCT	131 adolescents aged 12–18 years with CFS (CDC criteria)	**Complete recovery , 2.7 years** 64% with internet CBT 53% with usual care Absolute numbers not reported See Further information on studies	P = 0.251	⟷	Not significant
[46] RCT **4-armed trial**	641 adults with CFS (Oxford criteria)	**Proportion of people rating themselves as 'much better' or 'very much better' , 52 weeks** 61/161 (41%) with CBT 38/160 (25%) with specialist medical care The remaining 2 arms assessed adaptive pacing therapy and graded exercise therapy	OR 2.2 95% CI 1.2 to 3.9 P = 0.011	●●○	CBT

No data from the following reference on this outcome. [36] [37] [39] [40] [41] [42]

Functional status

CBT compared with control interventions CBT may be more effective than control interventions at improving physical functioning (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Physical functioning					
[38] RCT	60 adults with CFS (CDC criteria) attending a secondary-care centre In review [33]	**Predefined increase in functional score (assessed by SF-36 questionnaire) , 13 weeks** 19/30 (63%) with CBT 5/30 (17%) with relaxation CBT was given in 13 weekly sessions	RR 3.70 95% CI 2.37 to 6.31 NNT 3 95% CI 1 to 7	●●○	CBT
[40] RCT **3-armed trial**	153 adults with CFS (CDC criteria) In review [33]	**Change in functional score (assessed by SF-36 questionnaire)** with group CBT with usual care	Absolute difference –1.63 for group CBT *v* usual care 95% CI –4.05 to +0.78	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported 103 people in this analysis Treatment effects at 6 and 12 months were pooled for analysis The remaining arm evaluated education and support See Further information on studies for description of CBT and usual care			
[40] RCT **3-armed trial**	153 people with CFS (CDC criteria) In review [33]	**Change in functional score (assessed by SF-36 questionnaire)** with group CBT with education and support Absolute results not reported 102 people in this analysis Treatment effects at 6 and 12 months were pooled for analysis The remaining arm evaluated usual care See Further information on studies for description of CBT and educational and support interventions	Absolute difference –1.23 for group CBT *v* education and support 95% CI –3.52 to +1.05	⟷	Not significant
[36] RCT **4-armed trial**	90 adults with a mean age of 39.6 years who fulfilled diagnostic criteria for CFS (not further defined) In review [33]	**Mean number of non-sedentary hours , 7 months (3 months after completion of treatment)** 5.2 with CBT plus placebo 5.2 with usual care plus placebo 43 people in the analysis The remaining 2 arms reported on CBT plus dialysable leukocyte extract (DLE) and DLE alone CBT consisted of 6 sessions of CBT lasting 30 to 60 minutes every 2 weeks and placebo consisted of 8 biweekly injections of lyophilised normal saline	Significance not assessed		
[36] RCT **4-armed trial**	90 adults with a mean age of 39.6 years who fulfilled diagnostic criteria for CFS (not further defined) In review [33]	**Mean score for ability to participate in daily activities (Karnofsky performance score) , 7 months (3 months after completion of treatment)** 72.1 with CBT plus placebo 73.4 with usual care plus placebo 43 people in the analysis The remaining 2 arms reported on CBT plus DLE and DLE alone CBT consisted of 6 sessions of CBT lasting 30 to 60 minutes every 2 weeks and placebo consisted of 8 biweekly injections of lyophilised normal saline	Significance not assessed		
[41] RCT **4-armed trial**	114 adults with CFS (defined by CDC criteria); baseline physical functioning scores	**Mean score on SF-36 for physical functioning , 12 months** 58.64 with CBT 61.20 with relaxation therapy	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	46.36 in people receiving CBT, 53.77 in people receiving relaxation In review [33]	57 people in this analysis The population in this RCT may have been less impaired than in other similar RCTs The remaining 2 arms evaluated anaerobic activity therapy and cognitive therapy See Further information on studies for further details on study population and interventions			
[42] RCT	69 children and adolescents aged 10 to 17 years with CFS (CDC criteria)	**Change in functional score (assessed by short-form [SF]-36 questionnaire) , 5 months** 27.3 with CBT 10.0 with no treatment CBT consisted of 10 sessions over 5 months	Absolute difference 17.3 95% CI 6.2 to 28.4	○○○	CBT
[43] RCT	63 adolescents aged 11–18 years with CFS (CDC or Oxford criteria) In review [34]	**Mean score on SF-36 for physical functioning , 6 months post treatment** 80.4 with family-focused CBT 64.0 with psycho-education 53 people in this analysis Treatment duration was 6 months	Adjusted mean difference +13.42 95% CI –2.14 to +29.00 P = 0.09 Mean difference adjusted for associated baseline values	⟷	Not significant
[44] RCT	131 adolescents aged 12–18 years with CFS (CDC criteria) In review [34]	**Physical functioning (assessed by CHQ-CF87) , 6 months** 88.5 with internet CBT 70.1 with usual care See Further information on studies for details on interventions	Mean difference 18.4 95% CI 12.9 to 23.9 P <0.0001	○○○	CBT
[46] RCT **4-armed trial**	641 adults with CFS (Oxford criteria)	**Mean score on SF-36 for physical functioning , 52 weeks** 58.2 with CBT 50.8 with specialist medical care 321 people in this analysis The remaining 2 arms assessed adaptive pacing therapy and graded exercise therapy	Mean difference 7.1 95% CI 2.0 to 12.1 P = 0.0068	○○○	CBT

No data from the following reference on this outcome. [37] [39] [45]

Quality of life

CBT compared with control interventions CBT may be more effective than usual care at improving measures of mental health; however, we don't know about overall quality of life, as results are inconsistent (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[37] RCT	60 adults with CFS (Oxford criteria) In review [33]	**Proportion of people with a final score on Karnofsky quality-of-life scale of >80 , 12 months** 22/30 (73%) with CBT 8/30 (27%) with usual care	RR 2.75 95% CI 1.54 to 5.32 NNT 3 95% CI 2 to 5	●●○	CBT

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		See Further information on studies for description of CBT and usual care			
[40] RCT **3-armed trial**	153 adults with CFS (CDC criteria) In review [33]	**Change in quality-of-life score (assessed by short-form [SF]-36 questionnaire) , 12 months** with group CBT with usual care Absolute results not reported 103 people in this analysis The remaining arm evaluated education and support See Further information on studies for description of CBT and usual care	Absolute difference 4.36 for group CBT *v* usual care 95% CI 0.72 to 7.97 P = 0.019	○○○	CBT
[40] RCT **3-armed trial**	153 adults with CFS (CDC criteria) In review [33]	**Change in quality-of-life score (assessed by SF-36 questionnaire) , 12 months** with group CBT with education and support Absolute results not reported 102 people in this analysis The remaining arm evaluated usual care See Further information on studies for description of CBT and usual care	Absolute difference +3.16 for group CBT *v* education and support 95% CI –0.05 to +6.38 P = 0.5	⟷	Not significant
[36] RCT **4-armed trial**	90 adults with a mean age of 39.6 years who fulfilled diagnostic criteria for CFS (not further defined) In review [33]	**Mean visual analogue score , 7 months (3 months after completion of treatment)** 469 with CBT plus placebo 477 with usual care plus placebo 43 people in the analysis The remaining 2 arms reported on CBT plus dialysable leukocyte extract (DLE) and DLE alone CBT consisted of 6 sessions of CBT lasting 30 to 60 minutes every 2 weeks and placebo consisted of 8 biweekly injections of lyophilised normal saline	Significance not assessed		
[43] RCT	63 adolescents aged 11–18 years with CFS (CDC or Oxford criteria) In review [34]	**Mean work and social adjustment score , 6 months post treatment** 2.5 with family-focused CBT 3.3 with psycho-education Treatment duration was 6 months	Adjusted mean difference –0.48 95% CI –1.55 to +0.59 P = 0.37 Mean difference adjusted for associated baseline values	⟷	Not significant
Mental health					
[40] RCT **3-armed trial**	153 adults with CFS (CDC criteria) In review [33]	**Change in mental health score (assessed by SF-36 questionnaire)** with group CBT with usual care Absolute results not reported	Absolute difference 4.35 for group CBT *v* usual care 95% CI 0.72 to 7.97 P = 0.019	○○○	CBT

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		103 people in this analysis Treatment effects at 6 and 12 months were pooled for analysis The remaining arm evaluated education and support See Further information on studies for description of CBT and usual care			
[40] RCT **3-armed trial**	153 adults with CFS (CDC criteria) In review [33]	**Change in mental health score (assessed by SF-36 questionnaire)** with group CBT with education and support Absolute results not reported 102 people in this analysis Treatment effects at 6 and 12 months were pooled for analysis The remaining arm evaluated usual care See Further information on studies for description of CBT and educational and support interventions	Absolute difference +3.16 for group CBT *v* education and support 95% CI –0.05 to +6.38 P = 0.5	⟷	Not significant
[40] RCT **3-armed trial**	153 adults with CFS (CDC criteria) In review [33]	**Anxiety (assessed by Hospital Anxiety and Depression scale [HADS] score)** with group CBT with usual care Absolute results not reported 103 people in this analysis Treatment effects at 6 and 12 months were pooled for analysis The remaining arm evaluated education and support See Further information on studies for description of CBT and usual care	Absolute difference –1.27 for group CBT *v* usual care 95% CI –2.52 to –0.02 P = 0.045 Result is of borderline significance	○○○	CBT
[40] RCT **3-armed trial**	153 adults with CFS (CDC criteria) In review [33]	**Anxiety (assessed by HADS score)** with group CBT with education and support Absolute results not reported 102 people in this analysis Treatment effects at 6 and 12 months were pooled for analysis The remaining arm evaluated usual care See further information on studies for description of CBT and educational and support interventions	Absolute difference –0.51 for group CBT *v* education and support 95% CI –1.70 to +0.68	⟷	Not significant
[40] RCT **3-armed trial**	153 adults with CFS (CDC criteria) In review [33]	**Depression (assessed by HADS score)** with group CBT with usual care Absolute results not reported	Absolute difference –0.56 for group CBT *v* usual care 95% CI –1.69 to +0.58	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		103 people in this analysis Treatment effects at 6 and 12 months were pooled for analysis The remaining arm evaluated education and support See Further information on studies for description of CBT and usual care			
[40] RCT **3-armed trial**	153 adults with CFS (CDC criteria) In review [33]	**Depression (assessed by HADS score)** with group CBT with education and support Absolute results not reported 102 people in this analysis Treatment effects at 6 and 12 months were pooled for analysis The remaining arm evaluated usual care See Further information on studies for description of CBT and educational and support interventions	Absolute difference –0.13 for group CBT *v* education and support 95% CI –1.13 to +0.87	⟷	Not significant
[46] RCT **4-armed trial**	641 adults with CFS (Oxford criteria)	**Depression (assessed by HADS score) , 52 weeks** 6.2 with CBT 7.2 with specialist medical care 321 people in this analysis The remaining 2 arms assessed adaptive pacing therapy and graded exercise therapy	P = 0.0003	○○○	CBT
[46] RCT **4-armed trial**	641 adults with CFS (Oxford criteria)	**Anxiety (assessed by HADS score) , 52 weeks** 6.8 with CBT 8.0 with specialist medical care 321 people in this analysis The remaining 2 arms assessed adaptive pacing therapy and graded exercise therapy	P = 0.0003	○○○	CBT

No data from the following reference on this outcome. [38] [39] [42] [44] [45]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[43] RCT	63 adolescents aged 11–18 years with CFS (CDC or Oxford criteria) In review [34]	**Serious adverse events** with family-focused CBT with psycho-education 1 participant in the CBT group was admitted to hospital with de-			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		pression during the follow-up phase			
[46] RCT **4-armed trial**	641 adults with CFS (Oxford criteria)	**Serious adverse events** 7/161 (4%) with CBT 7/160 (4%) with specialist medical care Unclear if these were related to the treatment The remaining 2 arms assessed adaptive pacing therapy and graded exercise therapy	Significance not assessed		

No data from the following reference on this outcome. [36] [37] [38] [39] [42] [40] [41] [44] [45]

Further information on studies

[37] 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 that inhibited a return to normal functioning. The control was usual general practice care in people attending a secondary-care centre.

[39] *Interventions* 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 people receiving non-directive support from a social worker. *Loss to follow-up* This multicentre RCT 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 commented that the results were similar after intention-to-treat analysis, but these results were not presented.

[40] CBT (52 people) consisted of eight sessions over 16 weeks administered by experienced therapists. The education and support group (50 people) met the same therapists as those with CBT, in the same setting, for the same duration, and were taught a different relaxation exercise each week. The usual-care group (51 people) was managed in primary care and only attended the hospital for assessment at baseline and at 6 and 12 months. No adjustments were made for the multiple number of statistical tests carried out.

[41] CBT (29 people) consisted of 13 45-minute sessions over 26 weeks administered by experienced therapists. Relaxation treatment (28 people) comprised a combination of progressive muscle relaxation, stretching, autogenic training, and breathing focus techniques over 26 weeks and each biweekly session also lasted 45 minutes. Both of the interventions were individualised for different participants (not further defined). The RCT also reported that the study population at baseline was less physically impaired, more likely to be employed, and less likely to have psychiatric co-morbidities than some of the previous similar RCTs in this area, and this may explain the difference in the results between RCTs.

[42] The RCT found that CBT significantly improved school attendance at 5 months (% change in school attendance: 28% with CBT *v* 10% with no treatment; difference 18%, 95% CI 0.8% to 35.5%). A follow-up study (mean duration 2.1 years) of the RCT assessed 66/69 (96%) of the original trial participants. At the end of the trial, all participants were offered CBT: of the 34 people originally assigned waiting-list control, 18 received CBT. The analysis, therefore, compared outcomes in 50 people treated with CBT (32 people initially randomised to CBT plus 18 people initially randomised to waiting-list control who subsequently received CBT) with outcomes in the 16 people who refused CBT and thus received no treatment. The follow-up study found that, irrespective of the group to which they were randomised in the initial RCT, people receiving CBT were significantly less fatigued (P = 0.009), had significantly higher physical functioning as measured on the short-form (SF)-36 physical functioning subscale (P = 0.07), and had significantly improved school/work attendance (P = 0.002) at a mean 2 years than people given no intervention. [48]

[43] Family-focused CBT (32 people) consisted of 13 1-hour sessions offered every 2 weeks. The psycho-education consisted of four sessions over 6 months, the content was similar to that for the CBT, however, the delivery was didactic. Both interventions were provided by the same two experienced therapists with independent assessors for subjective outcomes. The RCT found that school attendance improved faster in the CBT group (dichotomised school attendance of at least 70%: 7/32 [22%] with family-focused CBT *v* 3/31 [10%] with psycho-

education, P value not reported). However, this improvement was not maintained over time, and by the 6-month follow-up there was no significant difference between the groups (dichotomised school attendance of at least 70%: 21/32 [66%] with family-focused CBT *v* 18/31 [67%] with psycho-education, OR 0.95 [95% CI 0.32 to 2.82], P = 0.93). This was one of the few studies that found CBT may be no better than a control, though it is worth noting that the control, psycho-education, had some active ingredients.

[44] The internet-based programme consisted of a psycho-educational section and a CBT section with 21 interactive modules. Support was also given by trained cognitive behavioural psychotherapists through e-consults alone. People could email therapists at anytime; emails were answered on a set day, once per week, unless it was an emergency email. Parents participated in a parallel program on a separate account with the same frequency of email contact to offer support and encouragement to their child as required. Usual multidisciplinary care consisted of individual or group-based rehabilitation, face-to-face CBT, or graded exercise treatment with a physical therapist; however, it was unclear how many got what treatment or how long for in the control arm. The authors state it was pragmatic, and that they were unable to state what was given, as treatments varied by region. The RCT (131 adolescents, aged 12–18 years) found that CBT significantly improved school attendance at 6 months (84% with internet CBT *v* 52% with usual care; mean difference 36%, 95% CI 21.5 to 43.6, P <0.0001) and full school attendance (defined as absence of 10% or less) at 6 months (50/67 [75%] with internet CBT *v* 10/64 [16%] with usual care; RR 4.8, 95% CI 2.7 to 8.9, P <0.0001). After 6 months, people could switch groups: 32/67 (48%) went from usual care to the internet intervention and 11/68 (16%) of the internet group changed to usual care.

[45] The RCT reported that 112/135 (83%) adolescents completed long-term follow-up (mean 2.7 years, range 1.7–3.8 years). Only recovery was reported based on original randomisation. Other outcomes, such as fatigue and school attendance, were reported as recovered versus not recovered and are, therefore, not reported here.

[46] CBT included planned gradual increases in both physical and mental activity and problem-solving to help address social and emotional obstacles. It was delivered by clinical psychologists and nurse therapists with up to 14 sessions in the first 23 weeks (initially once-weekly, decreasing to once every 2 weeks after the first four sessions). An additional booster session was offered at 36 weeks. The control group received specialist medical care delivered by doctors with specialist experience in CFS. Treatment consisted of an explanation of CFS, generic advice (e.g., to avoid extremes of activity and rest), specific self-help advice, and drug therapy if required (especially for insomnia, pain, and mood). At least three sessions were offered during the 12 months, increasing in number if clinically indicated.

Comment:

A randomised trial comparing CBT and non-directive counselling found that both interventions were of benefit in the management of people who consulted their family doctor because of fatigue symptoms. [49] In this study, 28% of the sample conformed to CDC criteria for CFS.

We found one RCT (171 people, CDC criteria) comparing a minimal intervention based on CBT (comprising a self-instruction booklet with information about CFS and weekly assignments) with a waiting-list control. [50] The intervention lasted at least 16 weeks and included email or phone contact with an experienced therapist every 2 weeks. The RCT found that guided self-instructions significantly reduced fatigue as measured by the Checklist Individual Strength (CIS) fatigue severity subscale compared with waiting list control at 6 to 12 months. The RCT also found that a greater proportion of those receiving self-instructions had a clinically significant improvement (CIS fatigue severity <35) compared with waiting list controls and the self-instruction group also scored significantly higher on the SF-36 physical function subscale compared with the control group at 6 to 12 months.

Clinical guide

There is moderate evidence of benefit of CBT in CFS. The effectiveness of CBT for CFS outside specialist settings has been questioned. The results of the multicentre RCT [39] suggest that CBT may be effective when administered by less-experienced therapists with adequate supervision. The largest trial to date (PACE) found that CBT is more effective than adaptive pacing and equally effective to graded exercise. [46]

OPTION GRADED EXERCISE THERAPY

- For GRADE evaluation of interventions for Chronic fatigue syndrome, see table, p 39 .
- Graded exercise therapy has been shown to effectively improve measures of fatigue and physical functioning.
- Educational interventions with encouragement of graded exercise (treatment sessions, telephone follow-ups, and an educational package explaining symptoms and encouraging home-based exercise) improve symptoms more effectively than written information alone.

Benefits and harms

Graded exercise therapy versus control interventions:

We found four systematic reviews (search dates 2004; [51] 2005; [52] 1987 to 2012; [34] and search date not specified [35]). The first systematic review [51] included the results of an unpublished RCT in its meta-analyses, and so we have reported the results of the three published RCTs identified by the review individually. [53] [54] [55] The second systematic review [52] did not perform a meta-analysis or report quantified results from each study, and identified one additional RCT not included in the first systematic review. [56] The third systematic review, [34] a narrative review of interventions in children and adolescents, included one RCT that met *BMJ Clinical Evidence* inclusion criteria. [57] The fourth systematic review was a narrative review, and all the relevant RCTs were already reported individually here. [35] We also found one additional RCT. [46]

Fatigue

Graded exercise therapy compared with control intervention Graded aerobic exercise programmes seem more effective at improving measures of fatigue compared with control interventions (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fatigue					
[53] RCT	66 people with CFS (Oxford criteria) In review [51]	**Mean change in Chalder Fatigue Score , 12 weeks** –8.4 with graded exercise therapy –3.1 with control intervention (flexibility and relaxation training) See Further information on studies for description of exercise intervention and relaxation training	P = 0.004	○○○	graded exercise therapy
[54] RCT **4-armed trial**	136 people with CFS (Oxford criteria) In review [51]	**Proportion of people with Chalder Fatigue Score <4 , 26 weeks** 12/67 (18%) with graded exercise therapy, with or without fluoxetine 4/69 (6%) with general advice, with or without fluoxetine Data pooled for graded exercise groups and for general advice groups Interventions compared were graded aerobic exercise plus placebo, graded aerobic exercise plus fluoxetine, general advice plus placebo, and general advice plus fluoxetine See Further information on studies for description of graded exercise and general advice	RR 3.10 95% CI 1.05 to 9.10 NNT 9 95% CI 5 to 91	●●○	graded exercise therapy
[55] RCT	61 people with CFS (CDC criteria) In review [51]	**Mean change in Chalder Fatigue Score for physical fatigue (8 items for physical fatigue [0–8]) , 12 weeks** 3.5 with graded exercise therapy 1.8 with control intervention (flexibility and relaxation training) See Further information on studies for description of exercise intervention and relaxation training	P = 0.07	⟷	Not significant
[57] RCT	22 adolescents with CFS (Fuduka critera) In review [34]	**Fatigue severity (on Fatigue Severity Scale [FSS]) , change from baseline to 4 weeks** –0.42 with graded exercise therapy	P = 0.16	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		–0.12 with control intervention (progressive resistance training)			
[46] RCT **4-armed trial**	641 adults with CFS (Oxford criteria)	**Chalder Fatigue Questionnaire , 52 weeks** 20.6 with graded exercise therapy 23.8 with specialist medical care 320 people in this analysis The remaining 2 arms assessed adaptive pacing therapy and CBT	Mean difference –3.2 95% CI –4.8 to –1.7 P = 0.0003	○○○	graded exercise therapy
Mental fatigue					
[55] RCT	61 people with CFS (CDC criteria) In review [51]	**Mean change in Chalder Fatigue Score for mental fatigue (6 items for mental fatigue [0–6]) , 12 weeks** 1.8 with graded exercise therapy 0.8 with control intervention (flexibility and relaxation training) See Further information on studies for description of exercise intervention and relaxation training	P = 0.02	○○○	graded exercise therapy

No data from the following reference on this outcome. [56]

Overall improvement

Graded exercise therapy compared with control interventions Graded exercise therapy seems to lead to greater overall improvement in symptoms compared with control interventions (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall improvement					
[53] RCT	66 people with CFS (Oxford criteria) In review [51]	**Proportion of people who reported feeling 'much better' or 'very much better' on Clinical Global Impression Scale , 12 weeks** 52% with graded aerobic exercise therapy 27% with control intervention (flexibility and relaxation training) Absolute numbers not reported See Further information on studies for description of exercise intervention and relaxation training	P = 0.04	○○○	graded exercise therapy
[55] RCT	61 people with CFS (CDC criteria) In review [51]	**Proportion of people with self-rated improvement with Clinical Global Impression Scale , 12 weeks** 29/32 (91%) with graded exercise therapy 22/29 (76%) with control intervention (flexibility and relaxation training) See Further information on studies for description of exercise intervention and relaxation training	P = 0.23	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[56] RCT	49 people with CFS (CDC criteria) In review [52]	**Proportion of people who reported feeling 'much better' or 'very much better' in a self-reported rating of improvement , 12 weeks** 48% with graded exercise therapy 21% with standard medical care Absolute numbers not reported Graded exercise was defined as increased activity to 30 minutes of exercise 5 times a week up to an energy expenditure of 70% of VO_2 max	P = 0.05	○○○	graded exercise therapy
[46] RCT **4-armed trial**	641 adults with CFS (Oxford criteria)	**Proportion of people rating themselves as 'much better' or 'very much better' , 52 weeks** 62/160 (41%) with graded exercise therapy 38/160 (25%) with specialist medical care The remaining 2 arms assessed adaptive pacing therapy and CBT	OR 2.0 95% CI 1.2 to 3.5 P = 0.013	○○○	graded exercise therapy

No data from the following reference on this outcome. [54]

Functional status

Graded exercise therapy compared with control intervention Graded aerobic exercise programmes seem to be more effective at improving measures of physical functioning compared with control interventions (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Physical functioning					
[53] RCT	66 people with CFS (Oxford criteria) In review [51]	**Mean change in short-form (SF)-36 physical function score , 12 weeks** 20.5 with graded exercise therapy 8.0 with control intervention (flexibility and relaxation training) See Further information on studies for description of exercise intervention and relaxation training	P = 0.01	○○○	graded exercise therapy
[57] RCT	22 adolescents wit CFS (Fuduka criteria) In review [34]	**Physical function (SF-36 physical function score) , change from baseline to 4 weeks** 5.7 with graded exercise therapy 6.4 with control intervention (progressive resistance training)	P = 0.83	⟷	Not significant
[46] RCT **4-armed trial**	641 adults with CFS (Oxford criteria)	**Physical function (SF-36 physical) , 52 weeks** 57.7 with graded exercise therapy 50.8 with specialist medical care 320 people in this analysis The remaining 2 arms assessed adaptive pacing therapy and CBT	Mean difference 9.4 95% CI 4.4 to 14.4 P = 0.0005	○○○	graded exercise therapy

No data from the following reference on this outcome. [54] [55] [56]

Quality of life

Graded exercise therapy compared with control interventions Graded exercise therapy may be more effective than control interventions at improving depressive symptoms and anxiety symptoms at up to 1 year (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mental health					
[55] RCT	61 people with CFS (CDC criteria) In review [51]	**Self-reported anxiety symptoms (mean change in Hospital Anxiety and Depression scale [HADS] anxiety score) , 12 weeks** 1.6 with graded exercise therapy 0.9 with control intervention (flexibility and relaxation training) See Further information on studies for description of exercise intervention and relaxation training	P = 0.2	⟷	Not significant
[55] RCT	61 people with CFS (CDC criteria) In review [51]	**Self-reported depressive symptoms (mean change in HADS depression score) , 12 weeks** 1.7 with graded exercise therapy 0.6 with control intervention (flexibility and relaxation training) See Further information on studies for description of exercise intervention and relaxation training	P = 0.04	○○○	graded exercise therapy
[57] RCT	22 adolescents wit CFS (Fuduka criteria) In review [34]	**Depression (assessed by Becks Depression Index) , change from baseline to 4 weeks** –4.2 with graded exercise therapy –6.7 with control intervention (progressive resistance training)	P = 0.40	⟷	Not significant
[46] RCT **4-armed trial**	641 adults with CFS (Oxford criteria)	**Depression (assessed by HADS score) , 52 weeks** 6.1 with graded exercise therapy 7.2 with specialist medical care 320 people in this analysis The remaining 2 arms assessed adaptive pacing therapy and CBT	P = 0.0035	○○○	graded exercise therapy
[46] RCT **4-armed trial**	641 adults with CFS (Oxford criteria)	**Anxiety (assessed by HADS score) , 52 weeks** 7.1 with graded exercise therapy 8.0 with specialist medical care 320 people in this analysis The remaining 2 arms assessed adaptive pacing therapy and CBT	P = 0.0142	○○○	graded exercise therapy

No data from the following reference on this outcome. [53] [54] [56]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal rates					
[54] RCT **4-armed trial**	136 people with CFS, Oxford criteria In review [51]	**Withdrawal rates** 25/68 (37%) with graded exercise therapy, with or without fluoxetine 15/69 (22%) with general advice, with or without fluoxetine Reasons for withdrawal were not reported Data pooled for graded exercise groups and for general advice groups Interventions compared were graded aerobic exercise plus placebo, graded aerobic exercise plus fluoxetine, general advice plus placebo, and general advice plus fluoxetine See Further information on studies for description of graded exercise and general advice	RR 1.70 95% CI 0.98 to 2.90	⟷	Not significant
[46] RCT **4-armed trial**	641 adults with CFS (Oxford criteria)	**Serious adverse events** 13/160 (8%) with graded exercise therapy 7/160 (4%) with specialist medical care Unclear if these were related to the treatment The remaining 2 arms assessed adaptive pacing therapy and CBT	P = 0.0142	○○○	specialist medical care

No data from the following reference on this outcome. [53] [55] [56] [57]

Graded exercise therapy plus education versus written information alone:

We found one systematic review (search date 2004). [51] The review identified one RCT comparing three types of educational intervention plus encouragement of graded exercise with only written information (control group). [58]

Fatigue

Graded exercise therapy plus education compared with written information alone An educational package to encourage graded exercise is more effective at improving measures of fatigue at 1 year than written information alone (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fatigue					
[58] RCT **4-armed trial**	148 people with CFS, Oxford criteria In review [51]	**Mean Chalder Fatigue Score (scale range: 0–11; a score >3 indicates excessive fatigue) , 1 year** 3.2 with minimum intervention graded exercise 10.6 with written information	P <0.001 for minimum intervention graded exercise *v* control	○○○	graded exercise therapy plus education

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The remaining arms evaluated telephone intervention graded exercise and maximum intervention graded exercise See Further information on studies for description of the 3 educational interventions			
[58] RCT **4-armed trial**	148 people with CFS, Oxford criteria In review [51]	**Mean Chalder Fatigue Score (scale range: 0–11; a score >3 indicates excessive fatigue) , 1 year** 3.5 with telephone intervention graded exercise 10.6 with written information The remaining arms evaluated minimum intervention graded exercise and maximum intervention graded exercise See Further information on studies for description of the 3 educational interventions	P <0.001 for telephone intervention graded exercise *v* control	○○○	graded exercise therapy plus education
[58] RCT **4-armed trial**	148 people with CFS, Oxford criteria In review [51]	**Mean Chalder Fatigue Score (scale range: 0–11; a score >3 indicates excessive fatigue) , 1 year** 3.1 with maximum intervention graded exercise 10.6 with written information The remaining arms evaluated minimum intervention graded exercise and telephone intervention graded exercise See Further information on studies for description of the 3 educational interventions	P <0.001 for maximum intervention graded exercise *v* control	○○○	graded exercise therapy plus education

Overall improvement

No data from the following reference on this outcome. [58]

Functional status

Graded exercise therapy plus education compared with written information alone An educational package to encourage graded exercise is more effective at improving measures of physical functioning at 1 year than written information alone (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Physical functioning					
[58] RCT **4-armed trial**	148 people with CFS, Oxford criteria In review [51]	**Mean short-form (SF)-36 physical functioning score (score range: 10–30, where 10 = maximum impairment and 30 = no impairment) , 1 year** 25.1 with minimum intervention graded exercise 16.9 with written information	P <0.001 for minimum intervention graded exercise *v* control	○○○	graded exercise therapy plus education

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The remaining arms evaluated telephone intervention graded exercise and maximum intervention graded exercise See further information on studies for description of the 3 educational interventions			
[58] RCT **4-armed trial**	148 people with CFS, Oxford criteria In review [51]	**Mean SF-36 physical functioning score (score range: 10–30, where 10 = maximum impairment and 30 = no impairment), 1 year** 24.3 with telephone intervention graded exercise 16.9 with written information The remaining arms evaluated minimum intervention graded exercise and maximum intervention graded exercise See Further information on studies for description of the 3 educational interventions	P <0.001 for telephone intervention graded exercise *v* control	○○○	graded exercise therapy plus education
[58] RCT **4-armed trial**	148 people with CFS, Oxford criteria In review [51]	**Mean SF-36 physical functioning score (score range: 10–30, where 10 = maximum impairment and 30 = no impairment), 1 year** 24.9 with maximum intervention graded exercise 16.9 with written information The remaining arms evaluated minimum intervention graded exercise and telephone intervention graded exercise See Further information on studies for description of the 3 educational interventions	P <0.001 for maximum intervention graded exercise *v* control	○○○	graded exercise therapy plus education

Quality of life

No data from the following reference on this outcome. [58]

Adverse effects

No data from the following reference on this outcome. [58]

Further information on studies

[53] Everyone had individual weekly sessions supervised by an exercise physiologist. People in 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 60% of VO_2 max). People in the flexibility and relaxation training group were taught

stretching and relaxation techniques (maximum 30 minutes daily, 5 days/week) and were specifically told to avoid any extra physical activities.

[54] The graded-exercise groups were given specific advice to do 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_2 max. People in the general-advice groups were not given any specific advice on frequency, intensity, or duration of aerobic activity.

[55] Graded activity consisted of aerobic exercise (walking, swimming, or cycling) for up to 15 minutes every second day. Intensity of activity was determined by mean heart rate during exercise. If there was a worsening of symptoms, the next exercise session was shortened or cancelled, and subsequent sessions reduced to a length considered by the participant to be manageable. People in the relaxation and flexibility group listened to a relaxation tape and performed stretching exercises every second day.

[58] People in the three educational-intervention groups received a minimum intervention consisting of 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 the minimum intervention; one group received seven additional follow-up telephone calls (telephone intervention); and another received seven additional face-to-face sessions over 4 months (maximum intervention). People in the written-information group received advice and an information booklet that encouraged graded activity, but gave no explanation for the symptoms.

[57] Graded aerobic exercise training consisted of 20 to 40 minutes of stationary cycling and treadmill at 40% to 60% of heart rate reserve. The progressive resistance training involved 16 exercises combining upper and lower body strength and core stability performed with single set, light to moderate load, and high (10-15) repetitions. In addition, exercise programmes (aerobic or resistance-based, according to group) were set for weekends and bank holidays. Both were for 5 days per week for a total of 4 weeks. All exercise was supervised by an experienced physiologist. The outcomes assessor was blinded.

[46] Graded exercise therapy was aimed at 30 minutes of light exercise, five times per week. The intensity and aerobic nature of the exercise was gradually increased as target heart rates were reached. The most commonly chosen exercise was walking. The therapy delivered by physiotherapists and an exercise physiologist with up to 14 sessions in the first 23 weeks (initially once-weekly, decreasing to once every 2 weeks after the first four sessions). An additional booster session was offered at 36 weeks. The control group received specialist medical care delivered by doctors with specialist experience in CFS. Treatment consisted of an explanation of CFS, generic advice (e.g., to avoid extremes of activity and rest), specific self-help advice, and drug therapy if required (especially for insomnia, pain, and mood). At least three sessions were offered during the 12 months, increasing in number if clinically indicated.

Comment: **Clinical guide**

There is good evidence of benefit for graded exercise therapy in CFS. However, experience suggests that CFS symptoms may be exacerbated by overly ambitious or overly hasty attempts at exercise. The largest RCT to date (PACE) suggested that graded exercise therapy is more effective than adaptive pacing, and equally effective to CBT. [46]

OPTION ANTIDEPRESSANTS

- For GRADE evaluation of interventions for Chronic fatigue syndrome, see table, p 39 .
- We don't know how effective antidepressants are in treating chronic fatigue syndrome (CFS).
- Antidepressants should be considered in people with depressive disorders. Tricyclics, in particular, have potential therapeutic value because of their analgesic properties, given the high prevalence of muscle and joint pain in CFS.

Benefits and harms

Fluoxetine versus placebo:

We found one systematic review (search date 2005), [52] which did not conduct a meta-analysis or report quantified results from each study. The systematic review [52] identified two RCTs. [59] [54]

Fatigue

Fluoxetine compared with placebo Fluoxetine may be no more effective at improving fatigue than placebo at 8 to 12 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fatigue					
[59] RCT	107 depressed and non-depressed people with CFS (Oxford criteria) In review [52]	**Mean scores on subscale of Checklist Individual Strength , 8 weeks** with fluoxetine with placebo Absolute results not reported	Mean difference –0.16 95% CI –0.64 to +0.31	⟷	Not significant
[54] **4-armed trial**	136 people with CFS (Oxford criteria) In review [52]	**Fatigue severity , 12 weeks** with fluoxetine with placebo Absolute results not reported Combined analysis: results pooled for fluoxetine groups and for placebo groups Interventions compared were graded aerobic exercise plus placebo, graded aerobic exercise plus fluoxetine, general advice plus placebo, and general advice plus fluoxetine	Reported as not significant P value not reported	⟷	Not significant

Overall improvement

No data from the following reference on this outcome. [54] [59]

Functional status

No data from the following reference on this outcome. [54] [59]

Quality of life

Fluoxetine compared with placebo Fluoxetine may be more effective than placebo at improving symptoms of anxiety and depression (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Depression					
[59] RCT	107 depressed and non-depressed people with CFS (Oxford criteria) In review [52]	**Improvement in the Beck Depression Inventory , 8 weeks** with fluoxetine with placebo Absolute results not reported	Mean difference –0.19 95% CI –0.35 to –0.02 The difference is small, and possibly not clinically important	◌◌◌	fluoxetine
[54] **4-armed trial**	136 people with CFS (Oxford criteria) In review [52]	**Mean change in Hospital Anxiety and Depression scale (HADS) score , 12 weeks** with fluoxetine with placebo Absolute results not reported	Mean difference 1.10 95% CI 0.03 to 2.20	◌◌◌	fluoxetine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Combined analysis: results pooled for fluoxetine groups and for placebo groups Interventions compared were graded aerobic exercise plus placebo, graded aerobic exercise plus fluoxetine, general advice plus placebo, and general advice plus fluoxetine			

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal					
[59] RCT	107 depressed and non-depressed people with CFS (Oxford criteria) In review [52]	**Withdrawal rates owing to adverse effects** 9/54 (17%) with fluoxetine 2/53 (4%) with placebo	Reported as not significant P value not reported	⟷	Not significant
[54] RCT **4-armed trial**	136 people with CFS (Oxford criteria) In review [52]	**Withdrawal rates** 24/68 (36%) with fluoxetine 16/69 (24%) with placebo Combined analysis: results pooled for fluoxetine groups and for placebo groups Interventions compared were graded aerobic exercise plus placebo, graded aerobic exercise plus fluoxetine, general advice plus placebo, and general advice plus fluoxetine	Significance not assessed		
Adverse effects					
[59] RCT	107 depressed and non-depressed people with CFS (Oxford criteria) In review [52]	**Tremor , 8 weeks** with fluoxetine with placebo	P = 0.006	○○○	placebo
[59] RCT	107 depressed and non-depressed people with CFS (Oxford criteria) In review [52]	**Perspiration , 8 weeks** with fluoxetine with placebo	P = 0.008	○○○	placebo

Phenelzine versus placebo:

We found one systematic review (search date 2005), [52] which identified one RCT. [60]

Fatigue

No data from the following reference on this outcome. [60]

Overall improvement

Phenelzine compared with placebo Phenelzine may be more effective than placebo at improving symptoms of chronic fatigue syndrome at 6 weeks. However, evidence was very weak and limited to one small RCT of 30 people (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall improvement					
[60] RCT	30 people with CFS (CDC 1988 criteria) In review [52]	**Overall improvement , 6 weeks** with phenelzine with placebo Absolute results not reported The RCT assessed various outcomes 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) The RCT concluded that there was a pattern of improvement across several measures with phenelzine compared with placebo	Significance not assessed for individual measures reported		

Functional status

No data from the following reference on this outcome. [60]

Quality of life

No data from the following reference on this outcome. [60]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal because of adverse effects					
[60] RCT	30 people with CFS (CDC 1988 criteria) In review [52]	**Withdrawal because of adverse effects , 6 weeks** 3/15 (20%) with phenelzine 0/15 (0%) with placebo	Significance not assessed		

Moclobemide versus placebo:

We found one systematic review (search date 2005), [52] which identified one RCT. [61]

Fatigue

No data from the following reference on this outcome. [61]

Overall improvement

Moclobemide compared with placebo Moclobemide seems to be no more effective than placebo at improving symptoms of chronic fatigue at 6 weeks. However, evidence was limited to one small RCT of 90 people (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall improvement					
[61] RCT	90 people with CFS (Australian criteria) In review [52]	**Proportion of people reporting improvement on self-reported global improvement scale , 6 weeks** 24/47 (51%) with moclobemide (450–600 mg/day) 14/43 (33%) with placebo	OR 2.16 95% CI 0.90 to 5.10	⟷	Not significant
[61] RCT	90 people with CFS (Australian criteria) In review [52]	**Standardised improvement on Karnofsky scale , 6 weeks** 0.86 with moclobemide (450–600 mg/day) 0.58 with placebo	Mean difference +0.28 95% CI –0.2 to +0.8	⟷	Not significant

Functional status

No data from the following reference on this outcome. [61]

Quality of life

No data from the following reference on this outcome. [61]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal because of adverse effects					
[61] RCT	90 people with CFS (Australian criteria) In review [52]	**Withdrawal because of adverse effects , 6 weeks** 7/47 (15%) with moclobemide (450–600 mg/day) 6/43 (14%) with placebo	Significance not assessed		
Adverse effects					
[61] RCT	90 people with CFS (Australian criteria) In review [52]	**Adverse effects , 6 weeks** with moclobemide (450–600 mg/day) with placebo			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Reported adverse effects were agitation (5 people), headache (2 people), insomnia (6 people), gastrointestinal problems (5 people), malaise (4 people), and anxiety (3 people) Individual adverse effects according to treatment group not reported			

Sertraline versus clomipramine:

We found one RCT. [62]

Fatigue

No data from the following reference on this outcome. [62]

Overall improvement

Sertraline compared with clomipramine Sertraline may be no more effective than clomipramine at improving symptoms of chronic fatigue. However, evidence was limited to one small RCT of 40 people (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall improvement					
[62] RCT	40 people with CFS	**Mean % improvement from baseline in the Clinical Global Impression scale** 31.8% with sertraline 20.7% with clomipramine	P = 0.28	⟷	Not significant

Functional status

No data from the following reference on this outcome. [62]

Quality of life

No data from the following reference on this outcome. [62]

Adverse effects

No data from the following reference on this outcome. [62]

Comment:

Fluoxetine versus placebo
The first RCT [59] used a shorter duration of treatment and studied people with a longer duration of illness compared with the second RCT. [54]

Adverse effects
The FDA and other regulatory bodies have issued a number of alerts and revised prescribing information regarding the use of antidepressants — in particular, relating to the increased risk of self-harm and suicide. [63]

Clinical guide
Although antidepressants have not been shown in RCTs to be of significant benefit, their use should be considered in people with depressive disorders. Tricyclic antidepressants have analgesic properties and may be of benefit to patients experiencing muscle and/or joint pain; they may also be of benefit in people complaining of persistent insomnia.

OPTION CORTICOSTEROIDS

- For GRADE evaluation of interventions for Chronic fatigue syndrome, see table, p 39 .
- We don't know how effective corticosteroids are in the treatment of chronic fatigue syndrome.

Benefits and harms

Fludrocortisone versus placebo:

We found one systematic review (search date 2005), [52] which did not conduct a meta-analysis or report quantified results from each study. The review [52] identified two RCTs. [64] [65]

Fatigue

Fludrocortisone compared with placebo Fludrocortisone may be no more effective than placebo at improving measures of fatigue at 6 weeks. However, evidence was limited to one small RCT of 25 people (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fatigue					
[65] RCT **Crossover design**	25 people with CFS, CDC criteria In review [52]	**Mean change in fatigue severity visual analogue scale (VAS) score , 6 weeks** 0.1 with fludrocortisone 0.4 with placebo	P = 0.37 Results should be interpreted with caution, as it is possible that treatment effects may persist after crossover	⟷	Not significant

No data from the following reference on this outcome. [64]

Overall improvement

Fludrocortisone compared with placebo Fludrocortisone may be no more effective than placebo at improving symptoms of chronic fatigue syndrome at 9 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall improvement					
[64] RCT	100 people with neurally mediated hypotension and CFS (CDC criteria) In review [52]	**Proportion of people with an improvement of at least 15 points on a self-reported global scale of 'wellness' (scale of 1–100) , 9 weeks** 14% with fludrocortisone (titrated to 0.1 mg/day) 10% with placebo	P = 0.76	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute numbers not reported The RCT determined *a priori* that an improvement of at least 5 points on a self-rated 100-point global scale of 'wellness' was a meaningful change			

No data from the following reference on this outcome. [65]

Functional status

Fludrocortisone compared with placebo Fludrocortisone may be no more effective than placebo at improving measures of physical functioning at 6 weeks. However, evidence was limited to one small RCT of 25 people (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Physical functioning					
[65] RCT **Crossover design**	25 people with CFS (CDC criteria) In review [52]	**Mean change in short-form (SF)-36 physical functioning score , 6 weeks** +6.5 with fludrocortisone –1.6 with placebo	P = 0.15 Results should be interpreted with caution, as it is possible that treatment effects may persist after crossover	⟷	Not significant

No data from the following reference on this outcome. [64]

Quality of life

No data from the following reference on this outcome. [64] [65]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal					
[64] RCT	100 people with neurally mediated hypotension and CFS (CDC criteria) In review [52]	**Withdrawal because of adverse effects , 9 weeks** 12/50 (24%) with fludrocortisone (titrated to 0.1 mg/day) 4/50 (8%) with placebo	RR 3.00 95% CI 1.04 to 8.67 NNH 6 95% CI 3 to 8	●●○	placebo
[65] RCT **Crossover design**	25 people with CFS (CDC criteria) In review [52]	**Withdrawal rate** 3 people with fludrocortisone 1 person with placebo People receiving fludrocortisone withdrew because of worsening CFS symptoms (fatigue, headache, or insomnia) The person withdrew from the placebo group to have scheduled ovarian surgery	Results should be interpreted with caution, as it is possible that treatment effects may persist after crossover		

Hydrocortisone versus placebo:

We found one systematic review (search date 2005), [52] which did not conduct a meta-analysis or report quantified results from each study. The review [52] identified two RCTs. [66] [67]

Fatigue

Hydrocortisone compared with placebo Hydrocortisone may be more effective than placebo at improving fatigue scores at 1 month. However, the RCT did not test the significance of differences between groups, and evidence was limited to one small RCT of 32 people (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fatigue					
[67] RCT **Crossover design**	32 people with CFS In review [52]	**Mean change in fatigue score from baseline (patient-assessed 11-item scale, overall score 0–33, higher score indicates greater fatigue) , 1 month** –6.7 with hydrocortisone (5 or 10 mg/day) –2.4 with placebo Absolute numbers not reported Allocated treatments were given for 4 weeks Pre-crossover results	Significance not assessed Benefit from hydrocortisone may be short-term; see Further information on studies for full details		

No data from the following reference on this outcome. [66]

Overall improvement

Hydrocortisone compared with placebo Hydrocortisone may be more effective than placebo at improving overall symptoms of chronic fatigue at 12 weeks. However, the clinical significance of the result was unclear (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall improvement					
[66] RCT	65 people with CFS (CDC 1998 criteria) In review [52]	**Proportion of people with improvement of at least 5 points on self-rated 100-point scale , 12 weeks** 53% with hydrocortisone (25–35 mg/day) 29% with placebo Absolute numbers not reported Allocated treatments were given for 12 weeks	P = 0.04 Clinical significance of this difference is unclear	○○○	hydrocortisone

No data from the following reference on this outcome. [67]

Functional status

Hydrocortisone compared with placebo Hydrocortisone seems no more effective than placebo at improving functional status (as assessed by activity scale and Sickness Impact Profile) at 12 weeks. However, evidence was limited to one small RCT of 65 people (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Functional status					
[66] RCT	65 people with CFS (CDC 1998 criteria) In review [52]	**Change in activity scale (change from baseline) , 12 weeks** 0.3 with hydrocortisone (25–35 mg/day) 0.7 with placebo Allocated treatments were given for 12 weeks	P = 0.32	⟷	Not significant
[66] RCT	65 people with CFS (CDC 1998 criteria) In review [52]	**Change in Sickness Impact Profile (change from baseline) , 12 weeks** –2.5 with hydrocortisone (25–35 mg/day) –2.2 with placebo Allocated treatments were given for 12 weeks	P = 0.85	⟷	Not significant

No data from the following reference on this outcome. [67]

Quality of life

Hydrocortisone compared with placebo Hydrocortisone seems no more effective than placebo at improving depressive symptoms at 12 weeks. However, evidence was limited to one small RCT of 65 people (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Depression					
[66] RCT	65 people with CFS (CDC 1998 criteria) In review [52]	**Change in Beck Depression Inventory (change from baseline) , 12 weeks** –2.1 with hydrocortisone (25–35 mg/day) –0.4 with placebo Allocated treatments were given for 12 weeks	P = 0.17	⟷	Not significant

No data from the following reference on this outcome. [67]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[66] RCT	65 people with CFS (CDC 1998 criteria) In review [52]	**Adverse effects** with hydrocortisone (25–35 mg/day) with placebo 12 people (40%) taking hydrocortisone experienced adrenal suppression (assessed by measuring cortisol levels)			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Allocated treatments were given for 12 weeks			
[67] RCT **Crossover design**	32 people with CFS In review [52]	**Adverse effects** with hydrocortisone (5 or 10 mg/day) with placebo The RCT reported minor adverse effects in up to 10% of people taking hydrocortisone: 3 people taking hydrocortisone had exacerbation of acne and nervousness 1 person taking placebo had an episode of fainting Allocated treatments were given for 4 weeks Pre-crossover results			

Hydrocortisone plus fludrocortisone versus placebo:

We found one systematic review (search date 2005), [52] which identified one RCT. [68]

Fatigue

Hydrocortisone plus fludrocortisone compared with placebo Combined treatment with hydrocortisone plus fludrocortisone may be no more effective than placebo at improving fatigue at 3 months (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fatigue					
[68] RCT **Crossover design**	100 people with CFS (CDC criteria) In review [52]	**Mean visual analogue scale (VAS) fatigue score (0 = no fatigue to 10 = severe fatigue) , 3 months** 6.6 with hydrocortisone 5 mg daily plus fludrocortisone 50 micrograms daily 6.7 with placebo Pre-crossover results not reported No washout period between treatments; see Comment section Treatments were given for 3 months	P = 0.76 Results should be interpreted with caution, as it is possible that treatment effects may persist after crossover	⟷	Not significant
[68] RCT **Crossover design**	100 people with CFS (CDC criteria) In review [52]	**Mean score on Abbreviated Fatigue Questionnaire , 3 months** 8 with hydrocortisone 5 mg daily plus fludrocortisone 50 micrograms daily 7 with placebo Pre-crossover results not presented No washout period between treatments; see Comment Treatments were given for 3 months	P = 0.69 Results should be interpreted with caution, as it is possible that treatment effects may persist after crossover	⟷	Not significant

Overall improvement

No data from the following reference on this outcome. [68]

Functional status

No data from the following reference on this outcome. [68]

Quality of life

No data from the following reference on this outcome. [68]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[68] RCT **Crossover design**	100 people with CFS (CDC criteria) In review [52]	**Adverse effects** with hydrocortisone 5 mg daily plus fludrocortisone 50 micrograms daily with placebo 2 people withdrew because of concerns about the effect of corticosteroids 1 person withdrew because of adverse effects (acne and weight gain) of hydrocortisone plus fludrocortisone treatment Pre-crossover results not presented No washout period between treatments; see Comment Treatments were given for 3 months			

Further information on studies

[65] The RCT found no significant difference between fludrocortisone and placebo in change in myalgia score (assessed using a visual analogue scale [VAS] from 0 [no problem] to 10 [could not be worse]: –0.3 with fludrocortisone *v* +1.1 with placebo; P = 0.53); concentration (change in concentration score: –0.9 with fludrocortisone *v* –0.3 with placebo; P = 0.4); joint pain (change in joint pain score: –0.3 with fludrocortisone *v* 0.8 with placebo; P = 0.15); or social functioning (change in social functioning: 6.5 with fludrocortisone *v* 0.0 with placebo; P = 0.3).

[67] The crossover RCT found that, although fatigue decreased with low-dose hydrocortisone, fatigue increased within 28 days of crossover into the placebo group. [67] Therefore, any benefit from low-dose hydrocortisone may be short-lived, whereas higher doses are associated with adverse effects.

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. [69] The use of hydrocortisone, a glucocorticoid, in the other RCTs was based on evidence of under-activity of the hypothalamic-pituitary-adrenocortical axis in some people with CFS. [70]

Clinical guide
There is weak evidence of benefit for low-dose hydrocortisone; however, benefit may be short-lived, there are no longer-term or follow-up studies, and higher doses are associated with adverse effects.

GLOSSARY

Beck Depression Inventory Standardised scale to assess depression. This instrument consists of 21 items to assess the intensity of depression. Each item is a list of 4 statements (rated 0, 1, 2, or 3), arranged in increasing severity, about a particular symptom of depression. The range of scores possible are 0 = least severe depression to 63 = most severe depression. It is recommended for people aged 13 to 80 years. Scores of more than 12 or 13 indicate the presence of depression.

Chronic fatigue syndrome, Australian definition (1) Chronic persisting or relapsing fatigue of a generalised nature, exacerbated by minor exercise, causing significant disruption of usual daily activities, and present for more than 6 months; (2) Neuropsychiatric dysfunction including impairment of concentration evidenced by difficulty in completing mental tasks that were easily accomplished before the onset of the syndrome; new onset of short-term memory impairment; (3) No alternative diagnosis reached by history, physical examination, or investigations over a 6-month period. [3]

Clinical Global Impression Scale A one-item, observer-rated scale for measuring the severity of a condition. It has been investigated for validity and reliability. The scale is scored from 0 (not ill at all) to 7 (severely ill).

Karnofsky score Is a measure of performance status based on physical ability (scale 0–100). 100: normal, no complaints or evidence of disease; 90: able to perform normal activity, minor signs and symptoms of disease; 80: able to perform normal activity with effort, some signs and symptoms of disease; 70: cares for self, unable to perform normal activity or to do active work; 60: requires occasional assistance but is able to care for most of own needs; 50: requires considerable assistance and frequent medical care; 40: requires special care and assistance, disabled; 30: hospital admission indicated, although death not imminent, severely disabled; 20: hospital admission necessary, active supportive treatment required, very sick; 10: fatal processes progressing rapidly, moribund; 0: death.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Cognitive behavioural therapy Two systematic reviews, [34] [35] one RCT, [46] and a further longer term follow-up report added. [45] Categorisation unchanged (beneficial).

Graded exercise therapy Two systematic reviews [34] [35] and one RCT added. [46] Categorisation unchanged (beneficial).

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Competing interests: AJC has received honoraria for unrestricted educational lectures from an educational organisation supported by Pfizer (who make Sertraline) and from Astra Zeneca, and has been a co-investigator on one research grant from Lundbeck. TC has received occasional payments from universities and conference organisers for conducting workshops on the treatment of chronic fatigue syndrome. MH and SW have given talks at a meeting organised by Janssen Pharmaceuticals. AJC, TC, MH, and SW are authors of references cited in this overview. SR declares he has no competing interests.

Disclaimer

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

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 4 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 (greater than 24 hours)	
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 or other substance misuse	
– severe obesity	

CDC, US Centers for Disease Control and Prevention.

GRADE **Evaluation of interventions for Chronic fatigue syndrome.**

Important outcomes			Fatigue, Functional status, Overall improvement, Quality of life						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consis-tency**	**Direct-ness**	**Effect size**	**GRADE**	**Comment**
What are the effects of selected treatments for chronic fatigue syndrome?									
8 (1279) [33] [36] [39] [40] [41] [42] [43] [44] [46]	Fatigue	CBT versus control interventions	4	–2	0	0	0	Low	Quality points deducted for flaws in analysis and incomplete reporting of results
4 (561) [47] [43] [44] [45] [46]	Overall improve-ment	CBT versus control interventions	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results; consistency point deducted for con-flicting results
8 (991) [33] [36] [38] [40] [41] [42] [43] [44] [46]	Functional status	CBT versus control interventions	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for inclusion of multiple compar-isons with no statistical adjustment
5 (680) [36] [37] [40] [43] [46]	Quality of life	CBT versus control interventions	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for con-flicting results
5 (599) [53] [54] [55] [57] [46]	Fatigue	Graded exercise therapy versus control interventions	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting re-sults
4 (496) [53] [55] [56] [46]	Overall improve-ment	Graded exercise therapy versus control interventions	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (408) [53] [57] [46]	Functional status	Graded exercise therapy versus control interventions	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (403) [55] [57] [46]	Quality of life	Graded exercise therapy versus control interventions	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results; directness point deducted for control including active relaxation
1 (148) [58]	Fatigue	Graded exercise therapy plus education versus written informa-tion alone	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (148) [58]	Functional status	Graded exercise therapy plus education versus written informa-tion alone	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (243) [54] [59]	Fatigue	Fluoxetine versus placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results; directness point deducted for com-bined analysis
2 (243) [54] [59]	Quality of life	Fluoxetine versus placebo	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting of results; directness points deducted for uncer-tainty of clinical importance of result in 1 RCT and for combined analysis (includes an active intervention; graded aerobic exercise) in 1 RCT
1 (30) [60]	Overall improve-ment	Phenelzine versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incom-plete reporting of results, and unclear statistical analysis

Important outcomes			Fatigue, Functional status, Overall improvement, Quality of life						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consis-tency**	**Direct-ness**	**Effect size**	**GRADE**	**Comment**
1 (90) [61]	Overall improve-ment	Moclobemide versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (40) [62]	Overall improve-ment	Sertraline versus clomipramine	4	–2	0	0	0	Low	Quality points deducted for sparse data and in-complete reporting of results
1 (25) [65]	Fatigue	Fludrocortisone versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and possible crossover effect
1 (100) [64]	Overall improve-ment	Fludrocortisone versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and in-complete reporting of results
1 (25) [65]	Functional status	Fludrocortisone versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and possible crossover effects
1 (32) [67]	Fatigue	Hydrocortisone versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and in-complete reporting of results; directness point deducted for no statistical analysis between groups
1 (65) [66]	Overall improve-ment	Hydrocortisone versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and in-complete reporting of results
1 (65) [66]	Functional status	Hydrocortisone versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (65) [66]	Quality of life	Hydrocortisone versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (100) [68]	Fatigue	Hydrocortisone plus fludrocorti-sone versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, methodological flaws, and incomplete reporting of results

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.