Defining and managing chronic fatigue syndrome
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Authors' objectives
The review covered four research objectives: (1) to find the existing case definitions of chronic fatigue syndrome (CFS) in adults; (2) what case definitions have been substantiated and/or validated in adults; (3) the prevalence and natural history of CFS in adults; and (4) whether there is evidence to show that particular treatments improve clinical symptoms of CFS when compared to placebo, no therapy, or each other. Only the fourth objective is addressed in this abstract of the review.

Searching
MEDLINE, the Cochrane Library, PsycINFO (from 1980 to July 2000), EMBASE (from 1988 to 1993 and 1998 to 2000) and the Journal of Chronic Fatigue Syndrome (from 1996 to 2000) were searched using an extensive list of search terms, which were listed in full in the report. In addition, Internet sites addressing clinical guidelines and CFS, bibliographies of pertinent articles, and textbooks were scanned, and experts were consulted. An updated search (through October 2000) was conducted using PubMed. Technical panel members and peer reviewers were asked to identify pertinent unpublished literature up to January 2001. Studies reported in any language were considered.

Study selection
Study designs of evaluations included in the review
The inclusion criteria for the review included case-control studies or controlled trials (defined as any prospective study that compares participants given an active therapy to participants given placebo, no therapy, or other active therapy). The included studies had to have 10 or more participants.

Specific interventions included in the review
The inclusion criteria for the review included interventions of active therapy for CFS compared with placebo or other active therapy. The included immunological therapies were antiviral, antihistamine, immunomodulator (immunoglobulin, interferon, and a transfer factor using dialysable extract from immune lymphocytes), immunomodulator/antiviral, or a vaccine (staphylococcus toxoid). The pharmacological therapies were steroids (fludrocortisone and hydrocortisone), anticholinergic (galanthamine), growth hormone, nicotinamide adenine dinucleotide, or antidepressants (phenelzine, fluoxetine, moclobemide and selegiline). Supplement therapies were magnesium, essential fatty acid, and liver extract. Physical therapies were graded exercise versus flexibility and relation, educational intervention about the importance of exercise versus standard medical care, massage therapy versus sham transcutaneous electrical nerve stimulation, and osteopathy versus normal care. Other types of included therapy were homeopathic, complex multidimensional therapies including cognitive behavioural therapy (CBT), social support and therapy described as ‘comprehensive’.

Participants included in the review
The inclusion criteria for the review included adult participants with CFS. The included studies had to state one of four specified definitions of CFS: Centers for Disease Control (CDC) 1988, Australia 1990, Oxford 1991, or CDC 1994. The participants took part in studies from the USA (42%), the UK (34%), Australia (16%), The Netherlands (5%) and other countries (Belgium, Canada, Iceland and Sweden; 11%).

Outcomes assessed in the review
The inclusion criteria for the review were not pre-specified. The outcomes stated in the report were a variety of measures covering wellness, health improvement and health perception, quality of life, physical symptoms, cognitive functions, return to work, pain, energy and emotional well-being.

How were decisions on the relevance of primary studies made?
Two authors independently screened the titles and abstracts for inclusion.
Assessment of study quality
The authors assessed the studies for quality by assessing randomisation, the adequacy of randomisation, whether the trial was single- or double-blind, the number of drop-outs, and the appropriateness of the analysis used. The authors do not state how the papers were assessed for quality, or how many of the reviewers performed the quality assessment.

Data extraction
Two reviewers independently extracted the data from the included studies. None of the abstractors were blinded either to the study title or to the authors’ names. Disagreements were uncommon (less than 1%) and were resolved by consensus. The authors state that no formal reliability testing was done. The authors calculated standardised mean differences between treatment and comparison group scores as a measure of effect size (ES) for each study. These ESs were adjusted for between-group differences at baseline and for small sample size.

Methods of synthesis
How were the studies combined?
The outcomes were grouped according to a list that had been developed specifically to assess symptoms in patients with CFS. The studies were synthesised in a narrative with regard to the methodological characteristics of the studies: for example, sources of populations enrolled, CFS case definitions used to select the study participants, sample sizes, adequacy of randomisation process, interventions and comparisons. In addition to the narrative synthesis, pooled standardised mean differences were also calculated.

How were differences between studies investigated?
The authors examined relationships between the clinical outcomes, participant characteristics and methodological characteristics in evidence tables and graphical summaries, such as forest plots.

Results of the review
Thirty-eight controlled trials met the inclusion criteria.

The results of the controlled trials evaluating multiple interventions had mixed results.

Immunologic therapy (n=515; 9 placebo-controlled trials, 1 trial with no-treatment control group, and one 4-arm trial): the review reported mixed results for this group.

Corticosteroids: evidence from these trials was scant and insufficient to conclude whether corticosteroids were effective or ineffective for CFS, but there was some evidence of harm from glucocorticoid therapy.

Antidepressants (n=382; 5 placebo-controlled trials): antidepressants alone and antidepressants plus exercise showed no consistent patterns of improvement, though occasional improvements were found in some symptoms, such as increased vigour and less anxiety.

Behavioural interventions (n=597; 6 controlled trials, of which 5 were randomised): behavioural therapies that emphasise increasing activity and physical exercise have generally resulted in decreased symptoms of fatigue and improvements in functional status and quality of life. Whether formal and comprehensive CBT delivered by experienced therapists is superior to graded exercise programmes alone is not clear. Also, it is unlikely that the beneficial effects of such general treatments are specific or limited only to patients with CFS. These therapies may help some people with CFS, but their effectiveness does not help establish an underlying etiology or cause of CFS.

Other pharmacological agents or supplements: the results were either mixed or provided insufficient evidence to conclude whether these therapies were or were not effective in improving symptoms or functional outcomes.

Complementary therapies (n=164; 3 trials): the review reported mixed results for these interventions.

Authors’ conclusions
Existing case definitions for CFS appear to characterise a group of people with prolonged fatigue and impaired ability to function. The validity and superiority of any particular case definition are not well established. Surveys suggest that the prevalence of CFS in community populations is less than 1%. Precise estimates of rates of recovery, improvement and/or relapse from CFS are not available. Although several therapies have been studied, the potential benefits as well as harms of most therapies are not well established. Behavioural interventions that emphasise increasing activity levels may improve quality of life and function in some people with CFS.

**CRD commentary**

The authors have clearly stated the research questions and the inclusion and exclusion criteria for each of the questions in the review. The literature search was extensive and covered several databases and although three of the research questions used searches limited to English language publications, the question abstracted for this review did not use any language restrictions. The search terms were stated, and there were attempts to find unpublished or grey literature and possible publication bias. The quality of the included studies was formally assessed and the authors used the quality assessment results in the discussion of the methodological strengths and weaknesses of the grouped studies. The reporting of the conduct of the review was good with some details of who performed the quality assessment and data extraction, and the selection of studies.

The data extraction was reported in tables in the review, along with the definitions and outcomes used. A narrative synthesis of the data was presented, which was appropriate given the format and variety of the individual study results. The authors’ conclusions and recommendations appear to follow from the results presented. However, the output of this review was very mixed regarding the results, so there is not a lot of information to guide practice.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors make three statements regarding implications for future research. First, there is a need to determine effective treatments for CFS using replicable randomised controlled trials with adequate numbers of participants and measurement of appropriate outcomes and adequate follow-up, and to investigate whether therapies from other treatment areas would benefit CFS patients. Second, the comparative efficacy of CBT versus exercise therapy for CFS patients needs to be investigated. Third, future research should address the development of standardised outcome measures that assess degree of severity and a comprehensive range of symptoms and that are sensitive to changes in illness status, along with the development of standardised definitions of outcomes such as recovery and improvement.

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