Cancer-related fatigue: a systematic and meta-analytic review of non-pharmacological therapies for cancer patients
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CRD summary
The authors concluded that both psychosocial and exercise interventions are of clinically significant benefit for cancer-related fatigue, but that it was unclear which was most effective. In view of methodological problems in the review, especially the failure to adequately address statistical heterogeneity between the studies, these conclusions should be interpreted with caution.

Authors' objectives
To assess the effectiveness of psychosocial and physical exercise interventions for reducing fatigue and improving vigour and vitality in adult cancer patients.

Searching
The following databases were searched from inception to December 2006: CANCERLIT, CINAHL, EMBASE, MEDLINE and PsycINFO. Search terms were reported. The reference lists of retrieved articles and relevant reviews and commentaries were handsearched. The search was limited to studies published in peer-reviewed journals in English.

Study selection
Randomised controlled trials (RCTs), non-randomised controlled trials and before-and-after studies of adults (aged over 18 years) with any type or stage of cancer, and in any phase of treatment or recovery, were eligible for inclusion. In included studies, one study arm had to receive a non-pharmacological intervention, and fatigue or related symptoms (tiredness, lethargy, vigour, vitality or energy) had to be reported as a primary or secondary outcome. RCTs were required to include a non-active control arm.

Most studies included participants with a variety of cancer diagnoses or were restricted to women with breast cancer. Cancer stages varied. In about half the studies, participants were currently receiving conventional treatment. No studies restricted inclusion to participants with clinical symptoms of fatigue. The review included a wide range of psychosocial and exercise interventions, administered in a range of settings to individuals or groups. Several studies included more than one active intervention. Psychosocial interventions were usually multimodal including: psycho-education, coping strategies, stress management, counselling, and relaxation training. Exercise interventions included aerobics and strength or resistance training. Exercise interventions included aerobics and strength or resistance training. The duration of psychosocial interventions ranged from a single 25-minute session to weekly 90-minute sessions for one year. The duration of exercise interventions ranged from three weeks to six months, at varying frequencies. Controls received a placebo or no intervention, or were wait-listed.

One reviewer screened all abstracts for possible inclusion in the review and a second author independently checked 25% of them. Articles considered potentially eligible were checked independently by both reviewers.

Assessment of study quality
Randomised controlled trials (RCTs) were allocated one point for each of the following eight quality criteria: randomisation, allocation concealment, blinding of outcome assessment, comparability of groups at baseline, handling of withdrawals and drop-outs, use of intention-to-treat analysis and multiple follow-up assessments. RCTs scoring over 4 points were designated good quality.

The authors did not state how the assessment was performed.

Data extraction
Findings were classified by study design and type of intervention (psychosocial or physical exercise). Interventions incorporating both approaches were classified as psychosocial. Studies were classified as positive, negative or
equivocal, according to whether they reported a statistically significant treatment benefit for at least one outcome. For RCTs, effect sizes (Cohen's d) and 95% confidence intervals were calculated from the differences between group means divided by the standard deviation or, if necessary, estimated from other statistical values. Effect sizes of over 0.20 were considered clinically meaningful.

Two reviewers independently extracted data on standardised forms, settling disagreements by consensus.

**Methods of synthesis**

Findings of all studies were combined in a narrative synthesis organised by type of intervention (psychosocial or exercise), study design (RCT, CCT, or before-and-after) and outcome (fatigue or vigour/vitality). Where feasible, data from RCTs were pooled to obtain mean effect sizes and 95% confidence intervals, using a random-effects model, weighting trials by sample size. Subgroup analyses were conducted according to 14 sets of moderating variables including: study aim, study theory, type of outcome measure, treatment modality, quality characteristics, study design (prospective versus cross-sectional), type of cancer, treatment status, setting, duration of intervention, and specific interventional approach. Potential publication bias was assessed by meta-bias analyses.

**Results of the review**

The review included 108 studies: 68 randomised controlled trials (RCTs), eight non-randomised controlled trials (CCTs) and 32 before-and-after studies. Fifty-seven RCTs (n=4,621 patients) were meta-analysed. Sample sizes ranged from nine to 558 patients. Study quality scores for RCTs ranged from 1.5 to 7 points (out of a possible 8). The main limitations were failure to report adequate allocation concealment (72% of psychosocial RCTs, 41% of exercise-based RCTs) or blinded outcomes assessment (85% of psychosocial studies) and lack of intention-to-treat analysis (65% of psychosocial RCTs, 47% of exercise-based RCTs).

**Psychosocial intervention versus controls:** Overall 24% of 50 relevant randomised comparisons reported positive results for fatigue outcomes with psychosocial interventions; 30% reported positive results for vigour/vitality outcomes. Results for CCTs and before-and-after studies were inconsistent. When randomised comparisons of psychosocial interventions were pooled, a statistically significant small to moderate benefit was evident for both fatigue (effect size -0.31, p<0.001; 41 trials, n=3,620 patients) and vigour/vitality outcomes (effect size 0.3, p<0.001; 36 trials, n=3,460 patients).

Similarly, when randomised comparisons were pooled that reported outcomes at four to six month follow-up after a psychological intervention, a statistically significant small to moderate benefit was evident for both fatigue (effect size 0.32, p<0.001, 13 trials) and vigour/vitality outcomes (effect size 0.29, p<0.001, 13 trials).

**Exercise intervention versus controls:** Overall 35% of 17 relevant RCTs reported positive results for fatigue outcomes with exercise interventions; 30% reported positive results for vigour/vitality outcomes. Results for CCTs and before-and-after studies were inconsistent. When randomised comparisons of exercise interventions were pooled, a statistically significant benefit was evident for both fatigue (effect size -0.42, 95% CI: -0.60 to -0.23; 16 trials, n=1001 patients) and vigour/vitality outcomes (effect size 0.69, 95% CI: 0.44 to 0.95, seven trials, n=395). The effect size approached moderate size for fatigue and was in the moderate to strong range for vigour/vitality outcomes.

Meta-bias analyses showed no significant evidence of publication bias. All outcomes were heterogeneous.

Detailed results of subgroup analyses were also reported.

**Authors' conclusions**

Both psychosocial and exercise interventions were of clinically significant benefit in reducing cancer-related fatigue. It was unclear which was most effective.

**CRD commentary**

The objectives of the review were clear but the inclusion criteria were very broad, resulting in the inclusion of a very large volume of data. The authors conducted and reported well over 300 meta-analyses, which not only made the review...
hard to follow, but also increased the risk of statistically significant findings occurring by chance. Relevant sources were searched for studies, but the limitation to published studies in English meant that the review was prone to publication and language biases (as noted by the authors). However, assessment of the randomised controlled trials (RCTs) for publication bias showed no evidence of this. Steps were taken to minimise error and bias in data extraction by having two reviewers make decisions independently, but it was unclear whether this also applied to validity assessment. The process of initial study selection was performed largely by a single reviewer. Relevant criteria were used to assess the validity of RCTs, but the validity of studies with other designs was not assessed. The decision to combine studies of mixed design by narrative synthesis was appropriate. Suitable statistical techniques appear to have been used to pool the RCTs. However, although it was reported that all outcomes were heterogeneous, this problem was addressed solely by using random-effects models. Heterogeneity was not quantified, presented graphically (for example on forest plots) or explored. This made it difficult to evaluate the precision and reliability of the findings. Other potential sources of bias were discussed in the text, including the very wide variation in interventions and the small sample size for many subgroup analyses. The authors speculated about the relative efficacy of different interventions, but based much of their interpretation on indirect comparisons between subgroups. It is questionable whether study quality was given sufficient priority in this process. Variability in quality (where reported) and in sample size cast further doubt on the reliability of the results. In view of methodological problems in the review, in particular the failure to assess statistical heterogeneity between the studies, the authors' conclusions should interpreted with caution.

Implications of the review for practice and research

Practice: The authors stated that the best approach to cancer-related fatigue may be multimodal approach combining exercise and psychosocial interventions.

Research: The authors stated that large RCTs specifically designed to manage cancer-related fatigue in patients with clinical levels of fatigue are needed, to find out which components of multimodal approaches are most effective, and to determine the optimum timing and duration of treatment. Trials should integrate psychosocial, exercise and pharmacological components, and should have extended follow-up.

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