A critical review of complementary therapies for cancer-related fatigue

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CRD summary
This review evaluated the effectiveness of complementary and alternative medicine for cancer-related fatigue. The authors concluded that there was insufficient evidence to recommend any specific intervention and that large randomised clinical trials are needed. Given some substantial methodological limitations in the review process and apparent discrepancies in the research recommendations, the reliability of the authors' conclusions is unclear.

Authors' objectives
To evaluate the use of complementary and alternative medicine (CAM) for cancer-related fatigue (CRF) and to determine the direction of future research.

Searching
PubMed (1966 to 2006), EMBASE (1988 to 2006), CINAHL (1982 to 2006), PsycINFO (1985 to 2006) and SPORTDiscus (1985 to 2004) were searched for relevant articles; the search terms were reported. The reference lists of key articles were handsearched.

Study selection
Study designs of evaluations included in the review
Prospective clinical trials were eligible for inclusion. A variety of study designs were included in the review.

Specific interventions included in the review
Studies of CAM interventions were eligible for inclusion. The National Centre for Complementary and Alternative Medicine's definition of CAM was adopted. The included studies reported on: acupuncture; combined aromatherapy, reflexology and foot soak; adenosine triphosphate infusion (ATP); energy conservation and activity management; healing touch; hypnosis; lectin standardised mistletoe extract; levocarnitine (L-carnitine) supplement; massage; mindfulness-based stress reduction; polarity therapy; relaxation and breathing exercise; sleep promotion; support group; Tibetan yoga; and psychosocial interventions.

Participants included in the review
Studies of patients with cancer were included. Details of the patients' characteristics, in terms of type of cancer, disease stage, age and gender, were not available for most studies. Patients with a variety of cancer conditions across a range of disease stages were included. Some participants had received, were undergoing, or were awaiting a range of other traditional treatments such as chemotherapy, radiation therapy, hormone therapy, bone marrow transplantation and stem cell transplant.

Outcomes assessed in the review
Studies of CRF either as a primary or secondary outcome were eligible for inclusion. The outcomes summarised in the review were fatigue, functional performance, mood disturbance, pain, hot flashes, quality of life, insomnia, nausea, gastrointestinal tract symptoms, depression, distress, state anxiety, sleep, confusion and vigour. Various outcome measures were used.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state how the validity assessment was performed. However, aspects of study quality were commented on in the review.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data
extraction. Generally, only descriptions of the direction of the main effect were reported; in a small number of studies, the size of effect and p-value were reported.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative.

How were differences between studies investigated?
There was no structured investigation of differences between the studies, which were grouped according to intervention type.

Results of the review
The authors reported that 21 studies were included in the review, but there seems to be some discrepancy within the text. Given the limitations in the reporting of the review, it was difficult to establish participant numbers for different types of study design. However, it appears that there were 8 randomised controlled trials (RCTs), two of which were pilot studies (n=658, based on 6 studies; participant numbers not available for 2 studies). Other study designs included in the review were clinical trials with no controls, retrospective cohort designs and single-arm feasibility studies.

The authors did not formally assess validity. However, they highlighted areas of methodological weaknesses in the ‘Results’ and ‘Discussion’ sections of the review. Many of the included studies were of less methodologically rigorous design. Where studies were controlled trials, there was often lack of randomisation or blinding. Other weaknesses affecting study validity were small sample sizes, high attrition rates, investigators leading the intervention group, insufficient baseline information to rule out the presence of confounding factors, the use of non-standardised outcome measures, and the lack of fatigue as an a priori end point.

Studies were often poorly reported and had significant methodological weaknesses. All studies included in the review reported positive effects for the intervention. However, many studies did not report the magnitude of the effect, whether the effect was significant, or the level of statistical significance of the effect, if present. The results of studies that provided levels of statistical significance or confidence intervals (CIs) are given below.

An RCT of ATP found that the treatment was associated with an improvement in lack of energy (p<0.001) and tiredness (p<0.0001). However, the reviewers concluded that the use of ATP would be limited by treatment constraints and possible side-effects. Acupuncture was reported to result in a mean improvement of fatigue by 31% (95% CI: 20.6, 40.5), 2 weeks after completion of treatment. Hypnosis was reported as improving current fatigue (p=0.017), but it is unclear whether this improvement was secondary to improvement in insomnia and hot flashes. L-carnitine was associated with an improvement of fatigue from 19.7 (standard deviation, SD=6.4) to 34.9 (SD=5.4) (p<0.001) on the Functional Assessment of Cancer Therapy-Fatigue Quality of Life Questionnaire. However, the patients were also receiving chemotherapy, which potentially confounds the results.

Authors' conclusions
There is insufficient evidence to recommend any CAM intervention as treatment for CRF.

CRD commentary
The inclusion criteria were well-defined, though broad for the intervention and participants. Study designs were restricted to prospective studies, although a retrospective study was included in the paper. Several relevant sources were searched, but it is unclear whether appropriate steps were taken to minimise language and publication bias, which may mean that relevant studies were missed. There was insufficient information on the study selection, validity assessment and data extraction processes to rule out the possibility of reviewer error and bias. Given the heterogeneity of the studies and the lack of statistical analysis, the decision to combine the results in a narrative was appropriate. There was insufficient reporting of study characteristics, study quality and statistical data to draw reliable conclusions from the review. Furthermore, the validity of the results from included studies was hampered by high attrition rate, absence of control groups, and failure to control for confounding variables such as exposure to other treatments. There were also discrepancies between the authors’ recommendations for research and the results of the review. Given methodological
limitations in both the included studies and the review, the reliability of the authors’ conclusions is unclear.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that large-scale randomised clinical trials of acupuncture, massage, L-carnitine and mistletoe should be conducted, although there appears to be some discrepancy between these recommendations and those arising from the results of the review. The use of CAM in clinical trials for conditions other than CRF should be examined for further intervention ideas.

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