

Cancer-related fatigue: an updated systematic review of its management

Has there been any progress on how to relieve fatigue in cancer patients? The current evidence is mixed at best, say **Ollie Minton, Bee Wee** and **Paddy Stone**, who regret that hardly any research can be translated into clear guidance for clinical practice

Fatigue is a consistent problem for most, if not all, patients with advanced cancer.¹ Its exact mechanisms are unclear and this means that available treatments are non-specific.¹ In this article, we will discuss the role of drug and non-drug interventions and the evidence from meta-analyses regarding their effectiveness and potential use in clinical practice.

Method

For this article, we conducted an updated review of management for fatigue which uses data from three relevant Cochrane systematic reviews.²⁻⁴ Two of them specifically looked at cancer-related fatigue,^{2,4} while the authors of the other one examined fatigue in palliative care patients regardless of diagnosis.³

We also conducted a Medline search using the key search terms 'fatigue', 'neoplasms' and 'palliative care'. This was conducted up to the beginning of May 2013. The detailed search terms and methods can be found in the relevant reviews²⁻⁴ on the Cochrane Library

website (www.thecochranelibrary.com).

It is worth noting that there have been over 170 clinical trials conducted in the area of cancer-related fatigue. However, the heterogeneous populations and variety of outcome measures used have meant that synthesising the data has not always been possible. It is equally fair to say that a meta-analysis cannot necessarily provide guidance on individual patient management.

In this article, we will separately discuss the role of drugs and exercise in the management of cancer-related fatigue, before making overall recommendations for clinical practice.

The role of drugs

Recent drug research has focused on psychostimulants, namely methylphenidate and modafinil. There has also been some further examination of antidepressants but, while these drugs were found to improve mood, they showed no effect on fatigue.² The role of corticosteroids was examined by the authors of the review investigating fatigue in palliative care patients.³ However, despite the widespread clinical use and anecdotal benefit, there are no corresponding studies to support the effectiveness of these drugs.

We examined the increased evidence supporting the use of methylphenidate. There are now eight randomised controlled trials (RCTs) published.⁵ These trials are mainly in patients with advanced disease and mixed tumour types but also include patients receiving chemotherapy.

The picture is mixed, with only two trials out of eight demonstrating superiority of methylphenidate over placebo. These two trials include the one with the largest sample size and longest follow-up. The limitations of

Key points

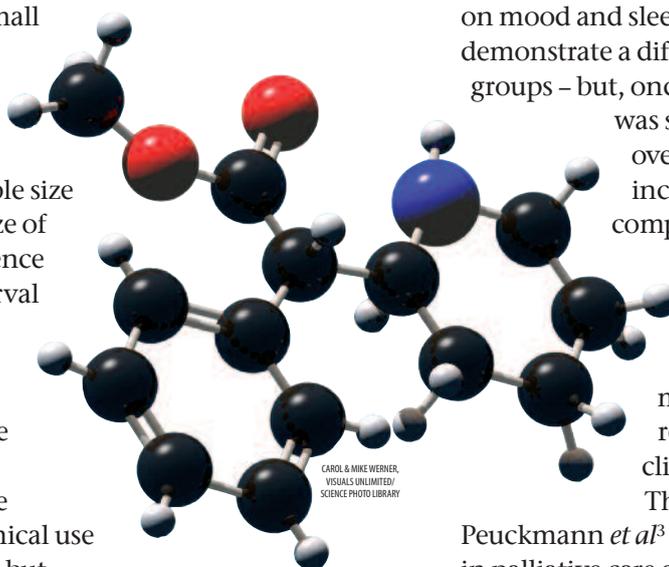
- The mechanisms of fatigue in advanced cancer are still unclear and there is no recommended treatment for relieving it.
- Psychostimulants may have a role in relieving fatigue, but the evidence supporting their use is mixed; while there is some evidence of benefits with methylphenidate, modafinil has been shown to be no better than placebo in a range of cancers.
- Exercise to maintain function may improve symptoms of fatigue, but there is no clear regimen for advanced cancer patients.
- A greater understanding of the biology of cancer fatigue as well as further, appropriately powered research are needed.

many of the other trials are small sample sizes and a short follow-up duration (two weeks or less).

In the combined meta-analysis,⁵ the total sample size is 710 and the overall effect size of the standardised mean difference is -0.22 (95% confidence interval [CI] -0.38 to -0.06; $p=0.007$); 710 is a reasonable number of patients, but a variety of dosing regimens and outcome measures were used.

Methylphenidate cannot be recommended for routine clinical use without further positive trials but equally, based on the current evidence, we cannot dismiss its role. A larger trial with a longer follow-up (four weeks or more) and a minimum dosage of 20 mg is required to make more definitive conclusions. Four weeks and 20 mg are the mean duration of treatment and dose from the eight trials; the positive trials had both a longer treatment duration and higher dose. It is worth noting that methylphenidate trials did not demonstrate an overall statistically significant increase in adverse events over placebo. This suggests that methylphenidate use should not be limited because of a fear of side effects.

On the other hand, based on two RCTs,^{6,7} it appears that there is little or no evidence supporting the role of modafinil in cancer fatigue. One trial was conducted in a mixed tumour group with patients on chemotherapy,⁶ the other in advanced lung cancer with patients off treatment.⁷ The total sample size is 790, the overall effect size is -0.06 (95% CI -0.20 to -0.08; $p=0.73$). This indicates no statistically significant effect over placebo. There was a subgroup analysis from the first trial⁶ that indicated a positive effect of modafinil in severe fatigue (based on a score of 8 or more on a 0–10 numerical rating scale). It is difficult to translate this isolated finding into a recommendation for practice. The authors of the advanced lung cancer study⁷ demonstrated no change in outcomes based on a subanalysis of baseline fatigue and performance status. They did demonstrate a clinically significant improvement in fatigue scores in both patient groups (who had received either placebo or modafinil after unblinding). A number of secondary analyses



■ Molecular model of methylphenidate. There is some evidence that the drug alleviates cancer fatigue, but further trials are needed before it can be recommended for routine clinical use

on mood and sleepiness ratings failed to demonstrate a difference between the two groups – but, once again, an improvement was seen in both. There was no overall statistically significant increase in adverse events compared with placebo.

However, despite these results and the use of appropriately powered trials, the lack of effect means modafinil cannot be recommended for routine clinical use.

The Cochrane review by Peuckmann *et al*³ focused on drugs for fatigue in palliative care generally. There is little data from any conditions other than cancer that could influence practice. The absolute numbers were very small and the quality of the trials was poor. It was not possible to produce any meta-analysis. The authors concluded there was no evidence supporting the use of modafinil in multiple sclerosis, but that there was possibly a role for amantadine (an antiretroviral drug). However, this was based on low-quality evidence and has not been adopted in practice. Overall, no recommendations for practice can be made from these findings.

The role of exercise

The role of exercise in relieving cancer fatigue has recently been evaluated in a Cochrane systematic review.⁴ The meta-analysis involving nearly 3,000 participants found evidence in favour of exercise with an overall effect size of -0.27 (95% CI -0.37 to -0.17).

This is an impressive overall size, but it does mask specific problems related to trial quality and contamination between groups undergoing interventions. There are also some specific exclusions to these observed benefits. The research has mainly been carried out in patients with breast and prostate cancer and in those receiving treatment. There has been little or no examination in patients with advanced disease. It is also important to note that only aerobic exercise had an effect – resistance training did not.

Once again, it is difficult to translate the effect size into recommendations for practice. There are no suggestions from the review authors about the optimum frequency, duration or intensity of the exercise regimen

to be used. There may also be a resource issue if the exercise programme needs to be supervised. It is, however, interesting to note that the overall effect size is larger than that demonstrated in the methylphenidate studies. In a research setting, it may be worth exploring a combined regimen of drug and exercise. There were non-specific benefits noted from many of the secondary trial outcomes in terms of reduced pain, improved mood and reduced sleep disturbance. There were no adverse outcomes specifically reported in the populations studied.

Discussion

While it is encouraging to see an increase in the volume of trials, there is no clear agreement on recommendations for clinical practice from the research. This may be partly because the interventions used in the studies – for example, the exercise interventions – are not standardised.

It is worth identifying the clinical phenotype of patients who might benefit and when. There is a suggestion that pharmacological interventions result in a greater response in patients with more severe fatigue, but the evidence is not sufficiently solid to draw any conclusion. Screening patients regularly would help to identify those who may benefit from treatment.

A better understanding of the underlying pathophysiology of fatigue would help to generate directions for future clinical trials.⁸

There is sufficient evidence to encourage exercise to alleviate fatigue in cancer patients

If we had a more detailed understanding of the mechanism for cancer fatigue, we might be able to design more targeted treatments. Our current understanding is that fatigue is driven by a pro-inflammatory cytokine response.¹ These cytokines may cause diverse effects, including alterations in muscle function and the blood–brain barrier. Modulation of these pathways may result in improvement. Numerous monoclonal antibodies are now commercially available and could form the basis of future clinical trials. These trials also ought to include a mechanistic component with storing of serum for subsequent analysis. This is a routine approach undertaken in the vast majority of cancer treatment trials.

Finally, it is also worth noting that in advanced cancer, fatigue rarely occurs in

isolation.⁹ A subset analysis of a large European study of patients with advanced cancer demonstrated fatigue associated with mood and sleep disturbances and increased pain. However, there was no link to cachexia or non-specific inflammatory markers such as C-reactive protein.

Conclusions

There is sufficient evidence to encourage exercise to alleviate fatigue in cancer patients, particularly in those with earlier disease or on active treatment, but no recommendation can be made about frequency, duration or intensity. Further clinical trials are needed to investigate the potential benefits of methylphenidate. An agreement on the clinical characteristics and severity of cancer fatigue would allow clinicians to determine which patients are most likely to respond. A greater understanding of the biology of cancer fatigue would allow researchers to develop more targeted treatments. At the moment, we are in a somewhat disappointing position, given the increasing number of clinical trials and the impact of fatigue in advanced cancer.

Declaration of interest

The authors declare that there is no conflict of interest.

References

1. Stone P, Minton O. Cancer-related fatigue. *Eur J Cancer* 2008; **44**: 1097–1104.
2. Minton O, Richardson A, Sharpe M, Hotopf M, Stone P. Drug therapy for the management of cancer-related fatigue. *Cochrane Database Syst Rev* 2010; **7**: CD006704.
3. Peuckmann V, Elsner F, Krumm N, Trottenberg P, Radbruch L. Pharmacological treatments for fatigue associated with palliative care. *Cochrane Database Syst Rev* 2010; **10**: CD006788.
4. Cramp F, Daniel J. Exercise for the management of cancer-related fatigue in adults. *Cochrane Database Syst Rev* 2008; **16**: CD006145.
5. Minton O, Richardson A, Sharpe M, Hotopf M, Stone PC. Psychostimulants for the management of cancer-related fatigue: a systematic review and meta-analysis. *J Pain Symptom Manage* 2011; **41**: 761–767.
6. Jean-Pierre P, Morrow GR, Roscoe JA *et al*. A phase 3 randomized, placebo-controlled, double-blind, clinical trial of the effect of modafinil on cancer-related fatigue among 631 patients receiving chemotherapy: a University of Rochester Cancer Center Community Clinical Oncology Program Research base study. *Cancer* 2010; **116**: 3513–3520.
7. Wee B, Dutton S, Fife K *et al*. Modafinil for the treatment of lung cancer: a multicentre, randomised, double-blinded, placebo-controlled trial. Poster presented at the 8th National Cancer Research Institute Cancer Conference, Liverpool, 4–7 November 2012.
8. Minton O, Stone PC. Review: the use of proteomics as a research methodology for studying cancer-related fatigue: a review. *Palliat Med* 2010; **24**: 310–316.
9. Minton O, Strasser F, Radbruch L, Stone P. Identification of factors associated with fatigue in advanced cancer: a subset analysis of the European palliative care research collaborative computerized symptom assessment data set. *J Pain Symptom Manage* 2012; **43**: 226–235.

Ollie Minton, Honorary Senior Lecturer in Palliative Medicine, Population Health Sciences & Education, St Georges University of London; Bee Wee, Senior Lecturer in Palliative Medicine, Sir Michael Sobell House and University of Oxford; Paddy Stone, Professor of Palliative Medicine, St George's University of London, UK