

Pharmacological treatments for fatigue associated with palliative care: executive summary of a Cochrane Collaboration systematic review

Martin Mücke^{1,2,3*}, Mochamat^{1,4}, Henning Cuhls¹, Vera Peuckmann-Post⁵, Ollie Minton⁶, Patrick Stone⁷ & Lukas Radbruch^{1,8}

¹Department of Palliative Medicine, University Hospital Bonn, Bonn, Germany; ²Department of General Practice and Family Medicine, University Hospital Bonn, Bonn, Germany; ³Center for Rare Diseases Bonn (ZSEB), University Hospital of Bonn, Bonn, Germany; ⁴Department of Anesthesiology and Intensive Therapy, University of Diponegoro/Kariadi Hospital, Jawa Tengah, Indonesia; ⁵Medical Faculty RWTH Aachen, University Hospital of Aachen, Aachen, Germany; ⁶Division of Mental Health, St George's University of London, London, UK; ⁷Marie Curie Palliative Care Research Department, UCL Division of Psychiatry, London, UK; ⁸Centre for Palliative Care, Malteser Hospital Seliger Gerhard Bonn/Rhein-Sieg, Bonn, Germany

Abstract

Background In palliative care patients, fatigue can be severely debilitating and is often not counteracted with rest, thereby impacting daily activity and quality of life. Further complicating issues are the multidimensionality, subjective nature and lack of a consensus definition of fatigue. The review aimed to evaluate the efficacy of pharmacological treatments for fatigue in palliative care, with a focus on patients at an advanced stage of disease, including patients with cancer and other chronic diseases.

Methods We considered randomized controlled trials concerning adult palliative care with a focus on pharmacological treatment of fatigue compared with placebo, application of two drugs, usual care or a non-pharmacological intervention. The primary outcome had to be non-specific fatigue (or related terms such as asthenia). We searched the CENTRAL, MEDLINE, PsycINFO and EMBASE, and a selection of cancer journals up to 28 April 2014. Two review authors independently assessed trial quality and extracted the data.

Results We screened 1645 publications of which 45 met the inclusion criteria. In total, we analysed data from 18 drugs and 4696 participants. There was a very high degree of statistical and clinical heterogeneity in the trials. Meta-analysis of data was possible for modafinil, pemoline, and methylphenidate.

Conclusions Due to the limited evidence, we cannot recommend a specific drug for the treatment of fatigue in palliative care patients. Some drugs, which may be beneficial for the treatment of fatigue associated with palliative care such as amantadine, methylphenidate, and modafinil, should be further researched.

Keywords Pharmacological treatments; Fatigue; Palliative care; Advanced disease; Systematic review

Received: 18 October 2015; Accepted: 30 November 2015

*Correspondence to: Martin Mücke, Department of Palliative Medicine, University Hospital Bonn, Sigmund-Freud-Str. 25, 53127 Bonn, Germany; Phone: +49 228-28713591, Fax: +49 228-2879080024, Email: muecke@uni-bonn.de

Introduction

Fatigue is a common symptom in palliative care patients, and virtually, every intervention used to treat cancer, as well as the primary disease itself, may cause or contribute to fatigue. In a study of 1000 patients in an American palliative care programme, fatigue, weakness, and lack of energy were three of the five most frequently reported symptoms with a prevalence of 84%, 66%, and 61%, respectively.¹ Fatigue is also

commonly reported in non-cancer patients with progressive life-threatening diseases, such as multiple sclerosis and amyotrophic lateral sclerosis,² chronic obstructive pulmonary disease,³ heart failure,⁴ HIV,⁵ as well as chronic heart, kidney, or lung diseases.^{6,7} Several drugs, such as the new anti-neoplastic therapies, or drugs regularly used in palliative care have sedative properties, for example, opioid analgesics, benzodiazepines, antidepressants, or anticonvulsants can cause fatigue.⁸

The pathophysiology of fatigue in palliative care patients is not fully understood. 'Primary fatigue' has been said to be related to the high cytokine load. Disease-related symptoms, such as sleep disturbances, may also account for fatigue and may be termed 'secondary fatigue'. There are several definitions of fatigue. For this Cochrane review, we selected the definition of the European Association of Palliative Care: 'Fatigue is a subjective feeling of tiredness, weakness, or lack of energy'.⁸

Assessment of fatigue will depend on subjective self-assessment by the patient, substituted by caregiver or medical staff estimations only where self assessment is not possible. Single-item scales have been proposed, and a multitude of checklists and questionnaires with multiple dimensions have been validated.⁹ It is possible that a number of hindrances such as lack of consensus on the definition of fatigue or on significant cut-off levels of evaluation instruments limited structured approach with assessment and treatment steps have led to underestimation and undertreatment fatigue.

If possible, a causative treatment approach should be addressed. Most patients will require symptomatic treatment of fatigue with pharmacological and non-pharmacological therapies. Some studies^{10,11} have examined the role of non-drug treatments for cancer-related fatigue, such as patient education with provision of information on fatigue and its treatment, keeping a diary, energy expenditure planning, and physical exercise. On the other hand, there is a growing body of evidence that gives examples of effective pharmacological treatments for fatigue.^{12–14} Several recent systematic reviews^{15–17} have covered some drugs used to treat fatigue in cancer patients.

This paper provides an executive summary of a recent Cochrane Collaboration systematic review,¹⁸ which synthesizes evidence for the evaluation of the efficacy of pharmacological treatments for fatigue in palliative care, with a focus on patients at an advanced stage of disease, including patients with cancer and other chronic diseases. The review updated the original review,¹⁹ 'Pharmacological treatments for fatigue associated with palliative care' and also incorporated the review 'Drug therapy for the management of cancer-related fatigue'.¹⁶

Materials and methods

Eligibility criteria

Criteria for review entry were randomized controlled trials with focus on pharmacological treatment involving adults (≥ 18 years, both sexes), suffering fatigue in palliative care or in terminal illness. Participants could receive anti-cancer treatment.

Outcome measures

Patient-reported fatigue and the improvement of fatigue were the primary outcomes of this review, while the

secondary outcomes included asthenia, weakness, tiredness, exhaustion, and treatment-related burden.

Search strategy

We re-engineered the search strategy (filter) of the previous review by Peuckmann-Post *et al.*¹⁹ to facilitate the combination with another review by Minton *et al.*¹⁶ To identify studies for inclusion in this updated review, we developed a detailed search strategy for each electronic database and other resources. To validate the search strategy, we selected sentinel studies.^{20,21} The following electronic databases were searched from their inception until 28 April 2014 CENTRAL, MEDLINE (Ovid), PsycINFO (Ovid), and EMBASE. Additional information was obtained from standard textbooks on palliative medicine, unpublished literature through searches of conference proceedings and also from experts in the field of palliative care.

Data collection and analysis

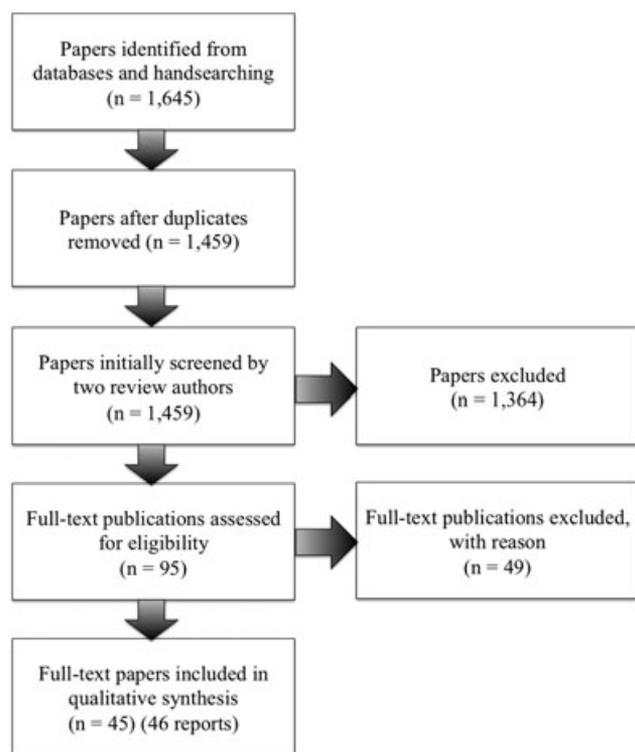
Two review authors extracted the data (M. M. and M. C.) using a standard data extraction form and reviewed the data from the included studies. Two other authors (L. R. and H. C.) cross-checked and sub-sampled the data. We contacted the original investigators when dealing with the missing data. Two authors (M. M. and M. C.) independently assessed risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion or by involving other review authors (L. R. and H. C.). Subgroup analysis was performed for dealing with following different criteria; type of drug, type of disease, and type of assessment tools.

Results

We identified 1645 publications in the search. After we removed 186 duplicate studies, we retrieved articles against the inclusion criteria and found 45 studies, which met the inclusion criteria (*Figure 1*). In total, we analysed data from 18 drugs, nine type of disease, and 4696 participants. Only two^{21,22} of the treatment groups in this review were large enough to give a low risk of bias (200 participants or more per treatment arm). Most studies reported some benefit of the active treatment. In general, adverse reactions were mild and had little or no impact.

We used studies investigating pemoline and modafinil in participants with multiple sclerosis-associated fatigue and methylphenidate in participants suffering from cancer and fatigue for meta-analysis. However, the US Food and Drug

Figure 1 Study flow diagram.¹⁸



Administration (FDA) has decided to withdraw pemoline products (marketed as Cylert) because of the risk of liver toxicity, which outweighs the benefits of the drug.

Methylphenidate in cancer

Meta-analysis was performed for two studies,^{23,24} which used the Functional Assessment for Chronic Illness Therapy - Fatigue as the assessment tool in fatigue, comparing

methylphenidate with placebo. The studies showed a slightly superior effect of methylphenidate compared with placebo (standardized mean difference 0.49, 95% confidence interval 0.15 to 0.83; Figure 2).

Modafinil in multiple sclerosis

Modafinil was tested in 115 patients with multiple sclerosis,²⁵ but failed to demonstrate the superiority of modafinil vs. placebo. Another recent study of 21 patients with multiple sclerosis showed positive effect of modafinil.² However, this result must be interpreted with caution because of the small participant numbers. Meta-analysis of these two studies also failed to demonstrate a significant effect, with a standardized mean difference of -0.14 (Figure 3).

Discussion

The aim of the Cochrane review¹⁸ was to evaluate the efficacy of pharmacological treatments for fatigue in palliative care, with a focus on patients at an advanced stage of disease, including patients with cancer and other chronic diseases.

Our search strategy allowed us to identify all relevant studies. We identified 45 studies for inclusion, with a wide range of underlying diseases and drug interventions. Treatment results pointed to weak and inconclusive evidence for the efficacy of amantadine, pemoline, and modafinil in multiple sclerosis and for carnitine and donepezil in cancer-related fatigue. Meta-analysis shows an estimated superior effect for methylphenidate in cancer-related fatigue, but not for modafinil in multiple sclerosis. Further studies about the efficacy and safety of potential medicines for fatigue treatment such as acetylsalicylic acid, mistletoe extract, megestrol acetate, and medroxyprogesterone acetate are needed.

Figure 2 Forest plot of comparison of methylphenidate vs. placebo in cancer: Functional Assessment for Chronic Illness Therapy - Fatigue score change.¹⁸

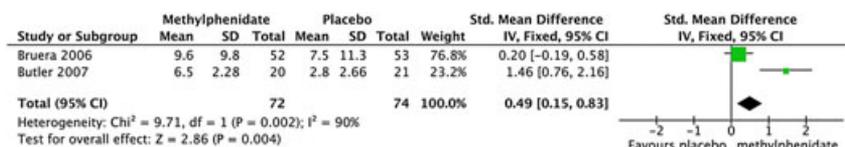
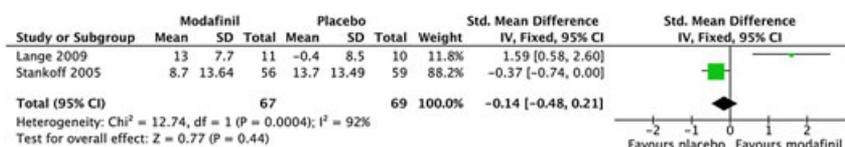


Figure 3 Forest plot of comparison of modafinil in cancer.¹⁸



Many of the included studies involved only a small number of participants and did not follow a consistent research methodology. In some cases, the investigated population was very heterogeneous, and any outcome may have been associated with depression, making it difficult to distinguish from primary fatigue. These limitations made it difficult to compare the methodological quality across the studies.

There are many possible causes of secondary fatigue. Unfortunately, little evidence from randomized trials is available on the efficacy of these treatments. In clinical practice, any potential cause for secondary fatigue should be treated.

The results of the literature search indicate that recent research interest focuses on modafinil, which seems a promising agent to diminish fatigue for palliative care patients. This may be an interesting perspective for the future.

Conclusions

There is insufficient evidence to support the use of a specific medicine to treat fatigue in palliative care patients. In this

regards, amantadine showed the promised benefit in patients with multiple sclerosis with fatigue and methylphenidate in patients with cancer-related fatigue. Further trials are needed for several medicines, which were used in some studies with positive results such as dexamethasone, methylprednisolone, acetylsalicylic acid, armodafinil, amantadine, and L-carnitine. To enhance the interpretation and generalization of findings from relevant study populations, randomized controlled trials with larger participant number are required. Consensus is needed regarding fatigue definition and outcome parameters for clinical trials.

Acknowledgements

The authors certify that they comply with the ethical guidelines for authorship and publishing of the *Journal of Cachexia, Sarcopenia and Muscle*.²⁶

Conflict of interest

The authors declare that they have no conflict of interest.

References

- Walsh D, Donnelly S, Rybicki L. The symptoms of advanced cancer: relationship to age, gender, and performance status in 1,000 patients. *Support Care Canc* 2000;**8**:175–179.
- Lange R, Volkmer M, Heesen C, Liepert J. Modafinil effects in multiple sclerosis patients with fatigue. *J Neurol* 2009;**256**: 645–650.
- Stridsman C, Lindberg A, Skär L. Fatigue in chronic obstructive pulmonary disease: a qualitative study of people's experiences. *Scand J Caring Sci* 2014;**28**:130–138.
- Goodlin SJ. Palliative care for end-stage heart failure. *Curr Heart Fail Rep* 2005;**2**:155–160.
- Norval DA. Symptoms and sites of pain experienced by AIDS patients. *S Afr Med J* 2004;**94**:450–454.
- Jhamb M, Liang K, Yabes J, Steel JL, Dew MA, Shah N, et al. Prevalence and correlates of fatigue in chronic kidney disease and end-stage renal disease: are sleep disorders a key to understanding fatigue? *Am J Nephrol* 2013;**38**:489–495.
- Tang W-R, Yu C-Y, Yeh S-J. Fatigue and its related factors in patients with chronic heart failure. *J Clin Nurs* 2010;**19**:69–78.
- Radbruch L, Strasser F, Elsner F, Gonçalves JF, Løge J, Kaasa S, et al. Fatigue in palliative care patients—an EAPC approach. *Palliat Med* 2008;**22**:13–32.
- Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. *J Psychosom Res* 2004;**56**:157–170.
- Schmitz KH, Holtzman J, Courneya KS, Mâsse LC, Duval S, Kane R. Controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *Canc Epidemiol Biomarkers Prev* 2005;**14**: 1588–1595.
- Mock V. Evidence-based treatment for cancer-related fatigue. *J Natl Cancer Inst Monogr* 2004;**32**:112–118.
- Barak Y, Magalashvili D, Dolgopiat MD, Ladkani D, Nitzani D, Mazor Z, et al. Effect of alfacalcidol on fatigue in MS patients: a randomized, double-blind study (S23.004). *Neurology* 2014;**82**:S23.004–S23.004.
- Morrow GR, Shelke AR, Roscoe JA, Hickok JT, Mustian K. Management of cancer-related fatigue. *Cancer Invest* 2005;**23**:229–239.
- Yennurajalingam S, Frisbee-Hume S, Palmer JL, Delgado-Guay MO, Bull J, Phan AT, et al. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. *J Clin Oncol* 2013;**31**:3076–3082.
- Pucci E, Branäs Tato P, D'Amico R, Giuliani G, Solari A, Taus C. A mantadine for fatigue in multiple sclerosis. *Cochrane Database of Systematic Reviews* 2007, Issue 1. Art. No.: CD002818. DOI: 10.1002/14651858.CD002818.pub2
- Minton O, Richardson A, Sharpe M, Hotopf M, Stone P. Drug therapy for the management of cancer-related fatigue. *Cochrane Database of Systematic Reviews* 2010, Issue 7. Art. No.: CD006704. DOI:10.1002/14651858.CD006704.pub3.
- Tejani AM, Wasdell M, Spiwak R, Rowell G, Nathwani S. Carnitine for fatigue in multiple sclerosis. *Cochrane Database Syst Rev* 2012;**5**:CD007280.
- Mücke M, Mochamat M, Cuhls H, Peuckmann-Post V, Minton O, Stone P, et al. Pharmacological treatments for fatigue associated with palliative care. *Cochrane Database Syst Rev* 2015;**5**:CD006788.
- Peuckmann-Post V, Elsner F, Krumm N, Trottenberg P, Radbruch L. Pharmacological treatments for fa-tigue associated with palliative care. *Cochrane Database of Systematic Reviews* 2010, Issue 11. Art. No.: CD006788. DOI:10.1002/14651858.CD006788.pub2
- Rabkin JG, Gordon PH, McElhiney M, Rabkin R, Chew S, Mitsumoto H. Modafinil treatment of fatigue in patients with ALS: a placebo-controlled study. *Muscle Nerve* 2009;**39**:297–303.
- Jean-Pierre P, Morrow GR, Roscoe JA, Heckler C, Mohile S, Janelsins M, 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.
22. Morrow GR, Hickok JT, Roscoe JA, Raubertas RF, Andrews PLR, Flynn PJ, *et al.* Differential effects of paroxetine on fatigue and depression: a randomized, double-blind trial from the University of Rochester Cancer Center Community Clinical Oncology Program. *J Clin Oncol* 2003;**21**:4635–4641.
 23. Bruera E, Valero V, Driver L, Shen L, Willey J, Zhang T, *et al.* Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. *J Clin Oncol* 2006;**24**:2073–2078.
 24. Butler JM, Case LD, Atkins J, Frizzell B, Sanders G, Griffin P, *et al.* A phase III, double-blind, placebo-controlled prospective randomized clinical trial of d-threo-methylphenidate HCl in brain tumor patients receiving radiation therapy. *Int J Radiat Oncol Biol Phys* 2007;**69**:1496–1501.
 25. Stankoff B, Waubant E, Confavreux C, Edan G, Debouverie M, Rumbach L, *et al.* Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study. *Neurology* 2005;**64**:1139–1143.
 26. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2015. *J Cachexia Sarcopenia Muscle* 2015;**6**:315–316.