

[Intervention Review]

# Pharmacological treatments for fatigue associated with palliative care

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## ABSTRACT

### Background

This review updates the original review, 'Pharmacological treatments for fatigue associated with palliative care' and also incorporates the review 'Drug therapy for the management of cancer-related fatigue'.

In healthy individuals, fatigue is a protective response to physical or mental stress, often relieved by rest. By contrast, in palliative care patients' fatigue can be severely debilitating and is often not counteracted with rest, thereby impacting daily activity and quality of life. Fatigue frequently occurs in patients with advanced disease (e.g. cancer-related fatigue) and modalities used to treat cancer can often contribute. Further complicating issues are the multidimensionality, subjective nature and lack of a consensus definition of fatigue. The pathophysiology is not fully understood and evidence-based treatment approaches are needed.

### Objectives

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.

### Search methods

For this update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PsycINFO and EMBASE, and a selection of cancer journals up to 28 April 2014. We searched the references of identified articles and contacted authors to obtain unreported data. To validate the search strategy we selected sentinel references.

### Selection criteria

We considered randomised controlled trials (RCTs) concerning adult palliative care with a focus on pharmacological treatment of fatigue compared to 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 did not include studies on fatigue related to antineoplastic treatment (e.g. chemotherapy, radiotherapy, surgical intervention). We also included secondary outcomes that were assessed in fatigue-related studies (e.g. exhaustion, tiredness).

## Data collection and analysis

Two review authors (MM and MC) independently assessed trial quality and extracted data. We screened the search results and included studies if they met the selection criteria. If we identified two or more studies that investigated a specific drug with the same dose in a population with the same disease and using the same assessment instrument or scale, we conducted meta-analysis. In addition, we compared the type of drug investigated in specific populations, as well as the frequent adverse effects of fatigue treatment, by creating overview tables.

## Main results

For this update, we screened 1645 publications of which 45 met the inclusion criteria (20 additional studies to the previous reviews). 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 and we discuss the reasons for this in the review. There were some sources of potential bias in the included studies, including a lack of description of the methods of blinding and allocation concealment, and the small size of the study populations. We included studies investigating pemoline and modafinil in participants with multiple sclerosis (MS)-associated fatigue and methylphenidate in patients suffering from advanced cancer and fatigue in meta-analysis. 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. Methylphenidate and pemoline seem to be effective in patients with HIV, but this is based only on one study per intervention, with only a moderate number of participants in each study. Meta-analysis shows an estimated superior effect for methylphenidate in cancer-related fatigue (standardised mean difference (SMD) 0.49, 95% confidence interval (CI) 0.15 to 0.83). Therapeutic effects could not be described for dexamphetamine, paroxetine or testosterone. There were a variety of results for the secondary outcomes in some studies. Most studies had low participant numbers and were heterogeneous. In general, adverse reactions were mild and had little or no impact.

## Authors' conclusions

Based on limited evidence, we cannot recommend a specific drug for the treatment of fatigue in palliative care patients. Fatigue research in palliative care seems to focus on modafinil and methylphenidate, which may be beneficial for the treatment of fatigue associated with palliative care although further research about their efficacy is needed. Dexamethasone, methylprednisolone, acetylsalicylic acid, armodafinil, amantadine and L-carnitine should be further examined. Consensus is needed regarding fatigue outcome parameters for clinical trials.

## PLAIN LANGUAGE SUMMARY

### *Pharmacological treatments for fatigue associated with advanced disease*

In an advanced disease such as cancer, fatigue can be described as tiredness, weakness or lack of energy. Fatigue can affect daily activity and quality of life, and it is frequently reported by palliative care patients. The underlying causes of fatigue are not very well understood and fatigue is difficult to treat.

We searched the literature in April 2014 and found 45 randomised controlled trials for this update of the review. We analysed data from 4696 participants who received treatment for their fatigue. The trials dealt with neurological diseases (such as multiple sclerosis (753 participants), post-polio syndrome (58) and Parkinson's disease (19)), different types of cancer (3223), HIV/AIDS (514), end-stage renal disease (56), multi-type advanced disease in hospice patients (30), amyotrophic lateral sclerosis (28) and end-stage chronic lung disease (15).

There was weak evidence for the efficacy of amantadine, pemoline and modafinil in reducing fatigue in patients with multiple sclerosis. There was also weak evidence for the efficacy of carnitine and donepezil for cancer-related fatigue. One small trial showed that people with HIV/AIDS and fatigue seemed to benefit from treatment with methylphenidate or pemoline. There was some low-quality evidence from small trials that methylphenidate, a stimulant drug that improves concentration, is effective for the management of cancer-related fatigue. There was no information about dexamphetamine, paroxetine or testosterone.

Previous studies have shown that erythropoietin and darbepoetin, drugs that improve anaemia (a shortage of red cells or haemoglobin in the blood), are also effective for cancer-related fatigue. However, due to safety concerns and side effects shown by more recent studies, erythropoietin and darbepoetin should no longer be used. Therefore, we excluded these drugs from this review update.

Overall, most side effects of the investigated drugs seemed to be mild.

Based on limited evidence from small studies, the evidence does not support the use of a specific drug for the treatment of fatigue in palliative care. Future trials should measure fatigue in advanced disease using comparable and standardised measures.

## BACKGROUND

This review is not only an update of a previously published review in the Cochrane Database of Systematic Reviews (Peuckmann-Post 2011). We have also conducted it with a new search strategy to incorporate another review on drug therapy for the management of cancer-related fatigue (Minton 2010), in order to increase its scope.

In healthy individuals, fatigue serves as a protective response to physical or mental stress. By contrast, in patients with chronic disease, fatigue can be severely debilitating and thereby have an impact on quality of life and daily activities (Morrow 2005). 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 (Walsh 2000). Fatigue is also commonly reported in non-cancer patients with progressive life-threatening diseases, such as multiple sclerosis and amyotrophic lateral sclerosis (progressive degeneration of motor neurons leading to cumulative paralysis), as well as chronic heart, kidney or lung diseases (Jhamb 2013; Tang 2010). More than half of patients with multiple sclerosis describe fatigue as one of their most troubling symptoms (Bakshi 2003; Krupp 2003; NMSS 2002). Fatigue has also been reported by the majority of patients with chronic obstructive pulmonary disease (COPD) (Elkington 2005; Stridsman 2014; Trendall 2001) and heart failure (Goodlin 2005). Approximately half of HIV patients suffer from fatigue (Breitbart 1998; Norval 2004). High levels of tumour necrosis factor (TNF) and interleukin-1 from HIV infections may cause fatigue (Darko 1995). Cancer-related fatigue is one of the most common symptoms experienced by cancer patients (Cuhls 2014; Morrow 2003). It can be problematic at the time of diagnosis, during and after treatment and in patients with advanced disease (Cuhls 2014; Morrow 2003). Most studies have reported prevalence figures in excess of 60% (Stone 2002). The subjective sensations attributed to cancer-related fatigue are characterised by a pervasive and persistent sense of tiredness, which is not relieved by sleep or rest. Several drugs, such as the new anti-neoplastic therapies, may be associated with novel causes of secondary fatigue. Drugs regularly used in palliative care have sedative properties, for example opioid analgesics, benzodiazepines, antidepressants or anticonvulsants can cause fatigue load (EAPC 2008).

## Description of the condition

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 (release of high amounts of cytokines from the tumour or antineoplastic therapy). Associated disease-related symptoms, such as sleep disturbances, infections, malnutrition, hypothyroidism and anaemia, may also account for fatigue and may be termed 'secondary fatigue'. Synonyms for fatigue are asthenia, neuromuscular weakness and tiredness. There seems to be a considerable overlap between fatigue and depression. Weakness and tiredness are among the predominant symptoms of depression and feeling depressed is often part of the affective dimension of fatigue. However, there are some symptoms that are associated with depression (such as sustained feelings of worthlessness, recurrent thoughts of death) and some symptoms that are considered specific to fatigue (such as post-exertional malaise).

Different definitions have been proposed for fatigue. In partnership with the American Cancer Society, the National Comprehensive Cancer Network (NCCN) defines cancer-related fatigue as "a distressing persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" (NCCN 2014). A similar definition has been used for multiple sclerosis: "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities" (NMSS 2002). The Fatigue Coalition has suggested the use of the International Classification of Diseases - 10 (ICD-10) criteria for the definition of cancer-related fatigue, which is "significant fatigue, diminished energy or an increased need to rest, disproportionate to any recent change in activity level" and has to be present every day or nearly every day for two consecutive weeks out of the last month (Cella 2001). Five out of 10 additional symptoms, such as generalised weakness, diminished concentration or unrestorative sleep, are required for the diagnosis. However, the symptom thresholds and time span have been chosen arbitrarily (Cella 1998), and this has been criticised. Considering the lack of an internationally acknowledged definition, we identified and chose the following working definition for this review: "Fatigue is a subjective feeling of tiredness, weakness, or lack of energy"; this definition has been suggested by an expert working group of the European Association of Palliative Care (EAPC 2008).

## Description of the intervention

Assessment of fatigue will depend on subjective self evaluation by the patient, substituted by caregiver or medical staff estimations only where self assessment is not possible. Single-item scales (e.g. 'do you get tired for no reason?') have been proposed and a multitude of checklists and questionnaires with multiple dimensions (such as physical, affective and cognitive) have been validated (Dittner 2004).

Lack of consensus on the definition of fatigue and its subjective and multidimensional nature, as well as culture and language differences, have challenged research approaches to fatigue. Further, standard research studies, such as double-blinded randomised controlled trials (RCTs), can often not be performed in this debilitated patient population due to fluctuating symptom intensity, declining performance status, rapid disease trajectories and short prognosis, resulting in weak evidence for treatment strategies. Several instruments exist to evaluate fatigue, but no consensus on significant cut-off levels has yet been achieved to establish a model of clinically meaningful improvement of fatigue. Only a few scales and instruments have been evaluated for different languages (Cantarero-Villanueva 2014; Kummer 2011). A structured approach with assessment and treatment steps is lacking. As a result, fatigue continues to be underestimated and undertreated. Consequently, a structured approach, including treatment options, is needed.

Treatment options for fatigue should address the causal mechanism if possible. However, the underlying mechanism of action is often not known and may be complex. Most patients will require symptomatic treatment of fatigue with pharmacological and non-pharmacological therapies. Non-pharmacological treatment options include patient education with provision of information on fatigue and its treatment, keeping a diary, energy expenditure planning and physical exercise (review in Mock 2004; NCCN 2014; Schmitz 2005). Recent studies support the use of resistance training or 'anabolic' exercise (Galvao 2005). Most patients will try to counteract exhaustion and fatigue with prolonged periods of rest (Richardson 1997). However, rest will often not restore energy and persistent reduction of physical activity may even promote fatigue (Evans 2007).

Pharmacological treatment of fatigue may work through interaction with cytokine load and the patient's host reaction to the underlying disease, restoring peripheral energy depletion, or by treating metabolic disorders and supplementing other apparent physiological deficiencies such as decreased haemoglobin concentration (Morrow 2005). There is a growing body of evidence that gives examples of effective pharmacological treatments for fatigue (Barak 2014; Lawrence 2004; Morrow 2005; Patrick 2004; Rao 2004; Rosenberg 2005; Wagner 2004; Yennurajalingam 2013; Zifko 2004). Drug treatment for non-specific fatigue will be required by many patients in addition to specific measures against deficiencies or comorbid conditions. Concerning drug-induced fatigue, for example with opioid treatment, symptomatic phar-

macological treatment of fatigue may functionally counteract this adverse effect, probably by enhancing excitatory mechanisms as observed following treatment with amphetamines (Sood 2006).

## Why it is important to do this review

The latest systematic review about pharmacological treatments for fatigue associated with palliative care was published several years ago (Peuckmann-Post 2011). Other systematic reviews have covered the use of particular drugs for fatigue in multiple sclerosis, such as amantadine (Pucci 2007), and carnitine (Tejani 2012). Treatment of fatigue in cancer patients, including erythropoietic agents, was the subject of another Cochrane review with meta-analysis (Minton 2010). In contrast to this meta-analysis our review aims to cover a broader scope of palliative care patients with cancer and non-cancer diseases, but it is restricted to advanced-stage diseases. We have incorporated the main topic of Minton 2010 into this review, so that cancer-related fatigue will be reflected.

## OBJECTIVES

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

### Criteria for considering studies for this review

#### Types of studies

We only included randomised controlled trials (RCTs). We considered full reports concerning fatigue in palliative care with a focus on pharmacological treatment. The primary outcome of these studies had to be fatigue (or related terms such as asthenia). We searched for diseases requiring palliative care or diseases at an advanced, life-threatening stage.

#### Types of participants

- Age 18 years or more.
- Participants of both sexes.
- Palliative care patients with fatigue, i.e. patients with an incurable disease (terminal illness) such as advanced cancer, HIV/AIDS, multiple sclerosis, amyotrophic lateral sclerosis, or cardiac, lung or kidney failure. Participants could receive

anticancer treatment. We considered terminal illness to be when the estimated life expectancy is six months or less, under the assumption that the disease will run its normal course.

### Types of interventions

- Identified studies had to evaluate and report the effect of pharmacological treatment on fatigue with the following drugs: psychostimulants (amphetamines, modafinil, armodafinil, methylphenidate, pemoline), amantadine, corticosteroids (dexamethasone, prednisone, methylprednisolone), donepezil, antidepressants such as selective serotonin reuptake inhibitors (SSRIs; paroxetine), acetylsalicylic acid, megestrol acetate, alfalcaldidol and acetyl-L-carnitine.
- If we identified further agents used for the treatment of unspecific fatigue, we added these studies.
- Studies should compare fatigue with drug treatment versus no drug treatment or versus alternative drug treatment, or both.
- We did not include studies on the pharmacological treatment of fatigue with a primary target of clinical conditions such as depression or anxiety.
- We included antidepressants only if used for the treatment of fatigue as the primary outcome.
- We did not focus on physiological deficiencies such as lack of haemoglobin (erythropoietic agents, blood transfusion), nor did we focus on drugs targeting specific cytokines, e.g. for reduction of tumour necrosis factor alpha, as these treatments target specific aetiologies of fatigue. Erythropoietic agents have been covered in the review by Minton et al (Minton 2010).
- We did not include studies comparing different types of cancer-modifying treatment and the effect on prognosis and quality of life. We also excluded those studies which did not focus on pharmacological treatment.
- We did not include studies on fatigue related to antineoplastic treatment (e.g. chemotherapy, radiotherapy, surgical intervention).

### Types of outcome measures

#### Primary outcomes

1. Patient-reported fatigue (self reported measures or validated self assessment tools, or both), substituted by caregiver or medical staff estimations only where self assessment was not possible, and measurement using reliable and valid assessment instruments (single-item scales or questionnaire instruments).
2. Improvement of fatigue. Since no gold standard for the treatment or improvement of fatigue exists, we suggested an improvement of fatigue intensity by 33% related to the range of the assessment instrument to be clinically significant. This is congruent with the improvement of pain intensity, where a 33%

reduction has been described as significant from the patient's point of view (Farrar 2003).

### Secondary outcomes

1. Asthenia (lack of strength) assessed with quality of life instruments such as SF-36.
2. Weakness assessed with scales, e.g. visual analogue scale - fatigue (VAS-F).
3. Tiredness, sedation assessed with scales such as the Chalder Fatigue Scale (CFS) or Center for Epidemiologic Studies Depression (CESD) scale.
4. Exhaustion, assessed with e.g. the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30).
5. Treatment-related burden: adverse events (including cardiac arrhythmia and thromboembolic events), morbidity or mortality measured as percentages of participants, adverse events also measured as a percentage of participants with moderate/severe intensity, probability of a causal relationship between adverse events and treatment.

### Search methods for identification of studies

For this update, we have re-engineered the search strategy (filter) of the previous review (Peuckmann-Post 2011) to facilitate the combination with another review (Minton 2010). 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 references. There were no language or date restrictions.

### Electronic searches

We searched the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 3); search strategy as detailed in Appendix 1;
- MEDLINE (OVID) from inception to 28 April 2014; search strategy as detailed in Appendix 2;
- EMBASE (OVID) from inception to 28 April 2014; search strategy as detailed in Appendix 3;
- PsycINFO (OVID) from inception to 28 April 2014; search strategy as detailed in Appendix 4.

### Searching other resources

We screened the reference lists of identified articles for additional studies.

We handsearched standard textbooks on palliative medicine (*Oxford Textbook of Palliative Medicine*, Oxford; *Textbook of Nursing, Textbook of Palliative Medicine*).

We also obtained unpublished literature through searches of conference proceedings, such as all meetings of the American Society of Clinical Oncology (ASCO) from 2000 to 2013, the 2013 meeting of the European Cancer Congress (ECCO) and the European Association of Palliative Care (EAPC) databases of all abstracts registered online from 2003 to 2014.

We contacted experts in the field of fatigue in palliative care in order to identify research awaiting publication.

## Data collection and analysis

### Selection of studies

We retrieved in full all studies in which the abstract refers to drug intervention aimed at treating fatigue in palliative care. Eligible studies had to define fatigue as a primary outcome and at least one treatment arm had to be a drug intervention.

### Data extraction and management

We organised data using the software Review Manager 5.3 (RevMan 2014). Two review authors extracted data (MM and MC) using a standard data extraction form. Two authors (MM and MC) reviewed the data from the included studies and two other authors (LR and HC) cross-checked a sub-sample. We resolved disagreement by consensus.

### Assessment of risk of bias in included studies

Two authors (MM and MC) independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion or by involving other review authors (LR, HC). We assessed the following for each study:

**Random sequence generation** (checking for possible selection bias)

We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We carefully considered studies using a non-random process.

**Allocation concealment** (checking for possible selection bias)

The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); unclear risk of bias (method not clearly

stated). We excluded studies that did not conceal allocation (e.g. open list).

**Blinding of outcome assessment** (checking for possible detection bias)

We assessed the methods used to blind study participants and outcome assessors from the knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding, e.g. identical tablets, matched in appearance and smell); unclear risk of bias (study states that it was blinded but does not provide an adequate description of how this was achieved). We excluded studies that were not double-blind.

**Incomplete outcome data** (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We assessed the methods used to deal with incomplete data as: low risk (less than 10% of participants did not complete the study and/or used 'baseline observation carried forward' analysis); unclear risk of bias (used 'last observation carried forward' analysis); high risk of bias (used 'completer' analysis).

**Size of study** (checking for possible biases confounded by small size)

We assessed studies as being at low risk of bias (200 participants or more per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (fewer than 50 participants per treatment arm).

### Measures of treatment effect

We intended to evaluate the methodological quality of each study, as well as the evidence for drug interventions to treat fatigue, using the GRADE system (Atkins 2004). We aimed to further evaluate studies by setting 'clinically relevant improvement' equal to improvement by one-third compared to baseline fatigue intensity and to calculate a number needed to treat to benefit (NNTB) accordingly (NNTB to achieve at least a 33% improvement of fatigue intensity compared to the baseline fatigue level). We aimed to calculate numbers needed to treat to harm (NNTH) for adverse events with moderate or severe intensity.

If calculation of the NNTB was not possible, 'clinically relevant improvement' would be defined as a change of 5% or more of the primary outcome instrument used in the study. This would be in accordance with the study of Cella et al, identifying changes between 3.7% and 5.8% of the aggregated summary scores as 'clinically important' (Cella 2002).

In addition, for each identified study, we aimed to extract:

- number of participants in each arm;
- type of control group;
- quality of the study (randomisation, blinding, per protocol analysis, intention-to-treat (ITT) analysis, number of withdrawals described);
- demographic characteristics, including age and sex;

- type of primary disease;
- type and stage of treatment, if applicable;
- type of drug used for the pharmacological intervention;
- duration and pharmacological regimen of drug treatment with the drug of interest;
- outcome measures employed, including means and standard deviations.

We documented outcomes of fatigue in different ways. If we identified two or more studies that investigated a specific drug with the same dose in a population with the same disease and same assessment instrument or scale, we conducted a meta-analysis. We aimed to calculate the standardised mean difference (SMD) in fatigue intensity, stating whether it had reached a potentially significant cut-off level and we aimed to compare these data to other interventions and control groups, wherever available. Wherever appropriate, we calculated standard deviations (SD) for standardisation of the mean difference (MD) as the square root of the average of the variances before and after the intervention. Similarly, if only 95% confidence intervals (CI) were described, we converted these values to SDs by dividing the difference of the CI and mean by a factor of 1.96.

A NNTB of 50% reduction has been suggested as significant for an exercise intervention in cancer-related fatigue (Cramp 2012). Since only limited information on the cut-off level for clinically significant fatigue has been identified to date, we suggested a 33% improvement as a basis for NNTB calculation, since palliative care patients are more debilitated than the population that was examined in the Cramp 2012 review. A 33% reduction of pain intensity has been described as significant from the patients' point of view in studies on breakthrough pain management (Farrar 2003).

### Unit of analysis issues

The unit of randomisation was the individual patient.

### Dealing with missing data

We contacted the original investigators to request missing data. We used intention-to-treat (ITT) analysis where possible. The ITT population consisted of participants who were randomised, took the assigned study medication and provided at least one post-baseline assessment. We assigned missing participants zero improvement (baseline observation carried forward (BOCF), where this could be done. We were aware that imputation methods might be problematic and examined trial reports for information about them.

### Assessment of heterogeneity

We explored the homogeneity of the results of the various end-points of interest using  $I^2$  statistic values. We regarded heterogeneity in the results as a result of many potential factors (postulated a

priori), and we made efforts to identify subgroups for sensitivity analysis. We undertook meta-analysis. As a result of high statistical heterogeneity, we used a random-effects model for analysis. If possible, and where applicable, we conducted subgroup analyses to explore possible sources of heterogeneity due to participants, interventions or methods.

Potential sources of heterogeneity:

- disease entities;
- performance status;
- quality of studies;
- medication dose and frequency;
- duration of treatment;
- duration of follow-up;
- rate of attrition;
- outcome measures used;
- case mix/stage of disease accessed.

### Assessment of reporting biases

To decrease the influence of potential publication bias, we conducted manual and electronic searches of multiple databases, without imposing any language restriction, to check for published or registered study protocols and to verify whether results from these studies have been published subsequently. We contacted the trial authors by email if there was insufficient information to assess reporting bias. We also contacted the authors to clarify information, if there were mismatches between study protocols and reports.

### Data synthesis

For data synthesis, we used Review Manager 5.3 (RevMan 2014), as provided by The Cochrane Collaboration. We grouped meta-analyses of the data from all included studies using the  $I^2$  statistic. If the  $I^2$  value was greater than or equal to 50% (substantial or considerable heterogeneity), we used a random-effects model. If the  $I^2$  value was less than 50%, we used a fixed-effect model. We reported the results from both models.

### Subgroup analysis and investigation of heterogeneity

We intended to conduct a subgroup analysis where data were available. We performed separate analysis for different kinds of primary diseases (such as cancer or multiple sclerosis). If it was not possible to carry out a quantitative analysis, then we considered a qualitative review and a synthesis of the study results.

In this review, we performed subgroup analyses for the following:

- different types of drug treatment;
- different types of disease;
- different types of assessment tools.

## Sensitivity analysis

We carried out sensitivity analysis for the primary outcome measurements in order to explore effect size differences and the robustness of our conclusions. We planned sensitivity analysis determined a priori based on:

- studies without study limitations with regard to a) allocation concealment; b) blinding of participants and investigators; c) recruitment bias; d) baseline imbalance between groups; e) loss to follow-up of clusters; f) adequate analysis;
- method of analysis: results of a) studies using number of patients analysed; b) studies using number of patients randomised.

## RESULTS

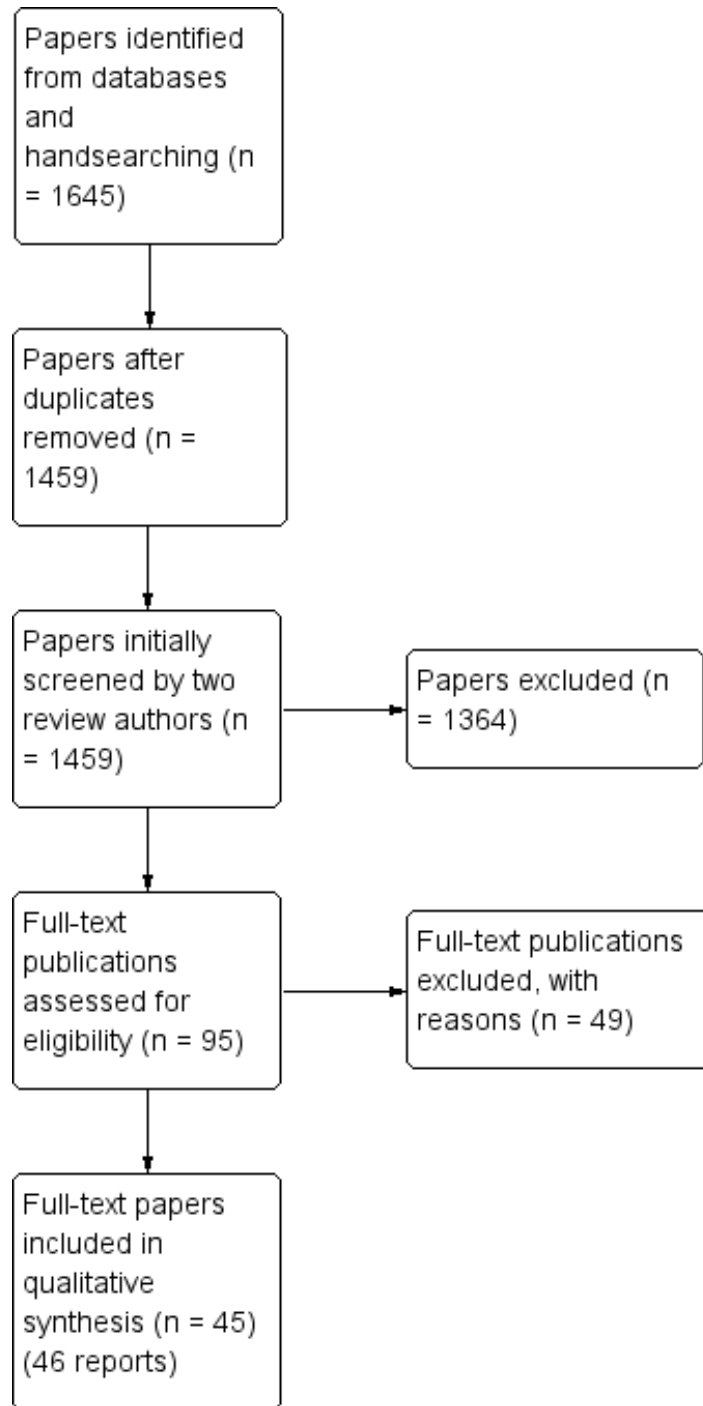
### Description of studies

This review updates and combines two existing reviews: [Minton 2010](#) and [Peuckmann-Post 2011](#). The previous review, [Minton](#)

[2010](#), found 31 studies involving 7140 participants and the review [Peuckmann-Post 2011](#) identified 22 eligible studies with a total of 1632 participants. We used a new search strategy for this update, providing 1645 results that we screened. Most of these articles did not focus on fatigue as a primary outcome but on the drug treatment of underlying disease. The updated search strategy identified 20 additional studies suitable for inclusion. Only seven of the studies included in the [Minton 2010](#) review, but all 22 of the previously included studies in [Peuckmann-Post 2011](#), matched our results. The small number of matched study results between this updated review and the [Minton 2010](#) review is due to the fact that we did not include haemopoietic growth factors in our search strategy. Safety concerns have been raised regarding the erythropoiesis-stimulating agents (erythropoietin and darbepoetin) since the last publication of the original review, therefore the use of these drugs is no longer recommended in practice ([Benet 2008](#); [Bohlius 2009](#); [EAPC 2008](#); [Glaspy 2009](#); [Glaspy 2010](#); [Tonelli 2009](#)). We found and removed 186 duplicate studies ([Figure 1](#)). We checked the retrieved articles against the inclusion criteria and included 45 studies. We identified no additional unpublished data by contacting experts in palliative care and we retrieved no additional studies from the handsearched reference lists or abstract databases on the Internet.



**Figure 1. Study flow diagram.**



Meta-analysis of data was possible for modafinil in multiple sclerosis (two studies, n = 136 participants), pemoline in multiple sclerosis (two studies, n = 103 participants) and methylphenidate in cancer patients (two studies, n = 146 participants).

See also [Characteristics of included studies](#) and [Characteristics of excluded studies](#).

## Results of the search

We screened 1645 publications, of which 45 met the inclusion criteria and we included them for further analysis. In total, we analysed data from 18 drugs and 4696 participants. 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.

## Included studies

See [Characteristics of included studies](#) table.

The 45 studies retrieved for the review yielded a broad spectrum of diseases associated with fatigue as well as different drugs ([Table 1](#)).

Fatigue was typically examined in association with diseases as follows: multiple sclerosis (13 studies), HIV/AIDS (including HIV and hypogonadism) (seven studies), cancer (including advanced cancer, cancer of different origins and brain tumours) (18 studies), post-polio (two studies), Parkinson's disease (one study), end-stage renal disease (ESRD) (one study), amyotrophic lateral sclerosis (one study), multi-type advanced disease (hospice patients) (one study) and end-stage COPD (one study).

Drug studied were as follows: amantadine (nine studies), pemoline (three studies), megestrol acetate (one study), methylphenidate (seven studies), dexamphetamine (two studies), paroxetine (two studies), acetyl-L-carnitine (four studies), testosterone (three studies), donepezil (one study), modafinil (eight studies), dexamethasone (one study), fluoxetine (two studies), alfacalcidol (one study), armodafinil (one study), mistletoe extract PS76A2 (one study), methylprednisolone (one study), medroxyprogesterone acetate (one study) and acetylsalicylic acid (two studies).

In contrast, [Morrow 2003](#) examined fatigue related to both cancer and treatment. [Wagner 2000](#) and [Rabkin 2004](#) examined fatigue in patients with depression, where it may be difficult to differentiate whether fatigue was primary or secondary to depression.

Most studies reported data from a relatively small number of participants: for the 45 studies included, only 17 reported a participant number greater than 100. Participant numbers, including controls, varied from six ([Rosenberg 1988](#)) to 544 ([Jean-Pierre 2010](#)). The total number of participants who completed the studies included in our analysis was 4696. Issues associated with inconclusive findings were as follows: differences in data reporting, heterogenous populations, inconsistent symptom assessment (the

use of instrument differed greatly) and lack of a consistent definition for a clinically significant reduction in fatigue. Therefore it was not possible to calculate the NNTB or NNTH, nor could we calculate a 5% reduction of fatigue as consistently as intended and described above.

Some trials in this review only used single-item fatigue assessment. However, it is now considered by European palliative care experts that a single-item tool could be as good as a comprehensive assessment. Single-item assessments of fatigue may have drawbacks, but more complex assessment methods may also be problematic in patients with advanced disease as they require some cognitive capacity, which is often lacking in a fatigue patient group. Excluding these studies would cause a new bias, as would excluding studies in end-of-life care and focused on patients in oncological care. Hence, we included and analysed these trials in our review.

## Excluded studies

The previous review, [Peuckmann-Post 2011](#), excluded 23 studies and the review by [Minton 2010](#) excluded 14 studies. For this update, we had to exclude 49 studies in the final selection process after reading the manuscript. Reasons for exclusion were typically a lack of inclusion criteria match (e.g. fatigue defined as a secondary outcome; case series; not a RCT), investigation of fatigue attributed to narcotic-induced sedation, data were a subset of another study which had been already included in the analysis, or data were not from patients with advanced disease. We listed these studies with the reason for exclusion in the [Characteristics of excluded studies](#) table.

## Risk of bias in included studies

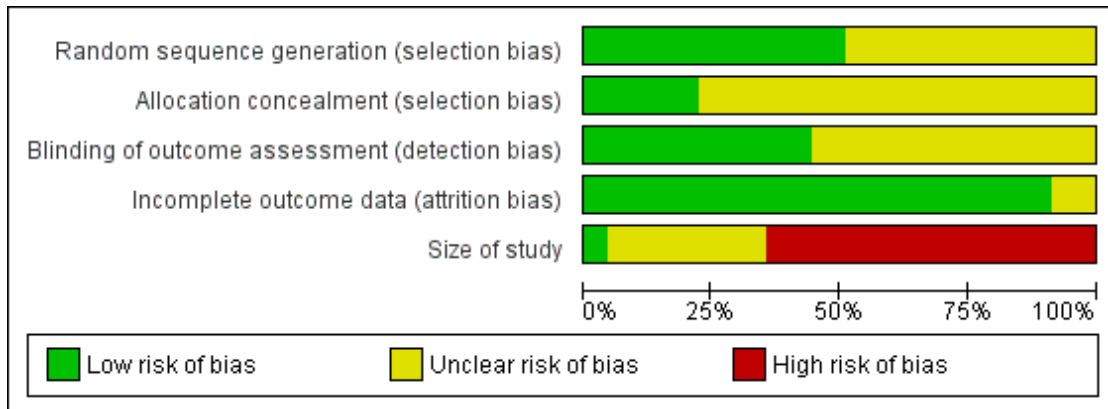
Some studies specifically described the randomisation and blinding procedure and we therefore considered them to have a minimal risk of bias concerning allocation concealment (e.g. [Cruciani 2012](#); [Roth 2010](#)). However, some studies did not specify these procedures, but used the terminology "double-blind, randomised controlled trial", allowing the assumption of a low risk of bias (e.g. [Barak 2014](#); [Lange 2009](#)).

Considering the relatively small number of participants in most of the included studies, as well as the variety of instruments used, the results have to be interpreted with caution. The small numbers of participants may be a reason for a lack of stratification (for example, for relevant health conditions such as depression or sociodemographic data such as age or sex), which may alter the outcome as demonstrated by some investigators ([Eriksen 2003](#); [Tomassini 2004](#)).

We assessed each study using the Cochrane 'Risk of bias' tool. The findings are presented in the 'Risk of bias' graph ([Figure 2](#)), which reviews the authors' judgements about each risk of bias item

shown as percentages across all included studies, and the 'Risk of bias' summary (Figure 3), which reviews the authors' judgements about each risk of bias item for each included study.

**Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**



**Figure 3. 'Risk of bias' summary: review authors' judgements about risk of bias items for each included study.**



## Allocation

All studies reported randomisation, but no more than 23 included a proper description of the methods used (Breitbart 2001; Bruera 2006; Bruera 2007; Cruciani 2009; Cruciani 2012; Fisch 2003; Jean-Pierre 2010; Kerr 2012; Knapp 2008; Moraska 2010; Morrow 2003; Rabkin 2000; Rabkin 2004; Rabkin 2009; Rabkin 2010; Rabkin 2011; Semiglazov 2006; Shaygannejad 2012; Simons 1996; Spathis 2014; Vasconcelos 2007; Westman 1999; Wingerchuk 2005). Only nine described the method used to conceal the allocation appropriately (Bruera 2006; Bruera 2007; Lacasse 2004; Moraska 2010; Rabkin 2009; Semiglazov 2006; Shaygannejad 2012; Spathis 2014; Vasconcelos 2007; Wingerchuk 2005).

## Blinding

Twenty studies were double-blind (Ashtari 2009; Auret 2009; Breitbart 2001; Butler 2007; Cruciani 2009; Cruciani 2012; Krupp 1995; Lou 2009; Morrow 2003; Rabkin 2000; Rabkin 2004; Rabkin 2009; Rabkin 2010; Rabkin 2011; Roth 2010; Semiglazov 2006; Spathis 2014; Vasconcelos 2007; Westman 1999; Wingerchuk 2005). The remainder did not provide sufficient information to assess risk of bias (unclear risk).

## Incomplete outcome data

There were only four studies lacking sufficient information to assess risk (unclear risk of bias) (Butler 2007; Krupp 1995; Weinschenker 1992; Yennurajalingam 2013). We judged the remaining 41 studies to meet the criteria for low risk of bias.

## Other potential sources of bias

Treatment group size was an issue. Small studies are thought to be at increased risk of bias, probably because the conduct of small studies is more likely to be less rigorous, allowing critical criteria to be compromised. Only two of the treatment groups in this review were large enough to give a low risk of bias (Jean-Pierre 2010; Morrow 2003). We judged 14 studies to have an unclear risk (Barak 2014; Bruera 2006; Bruera 2007; Canadian MSRG 1987; Cruciani 2012; Della Cuna 1989; Fisch 2003; Moraska 2010; Rabkin 2010; Semiglazov 2006; Simons 1996; Spathis 2014; Stankoff 2005; Westman 1999). We judged the remainder to have a high risk of bias due to size.

## Effects of interventions

Most studies reported some benefit of the active treatment. However, there was often a substantial and very similar placebo effect. Further, reviewing only fatigue-specific instruments (e.g. the

Chalder Fatigue Scale (CFS), Fatigue Severity Scale (FSS), visual analogue scale (VAS) for fatigue), these benefits could not be confirmed in many cases. See also: [Types of outcome measures](#). In general, adverse reactions were mild and had little or no impact (Table 2).

## Acetyl-L-carnitine versus placebo

Acetyl-L-carnitine was compared with placebo in a study of 29 participants with cancer-related fatigue, with no significant effect (Cruciani 2009). FACT-fatigue mean scores were 15.7 (SD 10.6) at baseline and 22.2 (10.4) at week two (P value = 0.97). A recent study of 209 participants did not show statistically significant improvement in fatigue compared to placebo (Cruciani 2012). The primary outcome, fatigue, measured using the Brief Fatigue Inventory (BFI), improved in both arms in comparison to baseline (L-carnitine: -0.96, 95% confidence interval (CI) -1.32 to -0.60; placebo: -1.11, 95% CI -1.44 to -0.78). There were no statistically significant differences between the arms (P value = 0.57), while the secondary outcomes, including fatigue measured on the Functional Assessment for Chronic Illness Therapy - Fatigue (FACIT-F) scale, did not show a significant difference between arms, with a change in mean of 31.4 (standard deviation (SD) 9.21; L-carnitine) versus 23.67 (SD 11.24; placebo) (P value= 0.61).

## Acetyl-L-carnitine versus amantadine

In another study of 36 participants, acetyl-L-carnitine was compared with amantadine in patients with multiple sclerosis (Tomassini 2004). Improvement assessed with the FSS was superior with L-carnitine compared with amantadine. In addition, L-carnitine was better tolerated than amantadine. However, differences in the absolute changes in the FSS did not reach statistical significance and the number of responders was similar for both drugs. There was no significant change for the secondary outcome of clinical scale scores (Fatigue Impact Scale, Beck Depression Inventory and Social Experience Checklist). The fatigue domain of the Kidney Disease Questionnaire (KDQ) also significantly improved after 12 weeks and 24 weeks of carnitine therapy compared with placebo in 56 patients with end-stage renal disease, but did not significantly affect the total score (Brass 2001).

## Acetylsalicylic acid versus placebo

Wingerchuk 2005 was able to show significantly better relief of fatigue with 1300 mg/day of acetylsalicylic acid compared to placebo in 26 patients with multiple sclerosis. Wingerchuk et al used the Modified Fatigue Impact Scale (MFIS) and Kurtzke Expanded Disability Status Scale (KEDSS) as instruments. In another study

of 52 patients with multiple sclerosis (Shaygannejad 2012), 500 mg/day showed a significant decrease in FSS scores. We did not perform meta-analysis due to the different doses and assessment instruments.

### **Alfacalcidol versus placebo**

A recent study using alfacalcidol 1 µg/day compared with placebo was conducted to treat fatigue in 158 multiple sclerosis patients. The Fatigue Impact Scale (FIS) total score decreased significantly. 'RAYS' quality of life assessments also improved significantly in the psychological and social subscale (Barak 2014).

### **Amantadine versus placebo**

Amantadine was used in seven studies of 370 participants with multiple sclerosis with heterogenous outcomes, showing a tendency towards improved outcomes with amantadine with different fatigue instruments and scales (Ashtari 2009; Canadian MSRG 1987; Krupp 1995; Murray 1985; Rosenberg 1988; Shaygannejad 2012; Tomassini 2004). Amantadine was significantly better than placebo on the MS-Fatigue scale. One study of 25 participants used amantadine post-polio using the Fatigue Severity Scale (FSS) without proving efficacy (Stein 1995).

### **Amantadine versus other drugs**

Krupp 1995 tested amantadine against pemoline (93 participants). No difference between amantadine and pemoline was seen on the FSS. On the other hand, Tomassini 2004 performed a comparison of amantadine against acetyl-L-carnitine (ALCAR). ALCAR showed superior effect to amantadine. Shaygannejad 2012 tested amantadine against acetylsalicylic acid. Both groups showed a significant decrease in the FSS.

### **Armodafinil versus placebo**

Armodafinil was tested in 70 patients with HIV to evaluate its efficacy and safety for fatigue and depressive symptoms. In intention-to-treat analyses, the fatigue response rate to armodafinil was 75% and to placebo 26% (Rabkin 2011). Armodafinil appeared to be effective in alleviating fatigue and was well tolerated. For the secondary endpoint depression, measured with the Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI), a significant effect was not shown. However, further multicentre studies with larger samples are needed.

### **Dexamethasone versus placebo**

Dexamethasone 4 mg was compared with placebo in a recent study to treat fatigue in 84 participants with advanced cancer. The study showed that dexamethasone was significantly superior to

placebo (Yennurajalingam 2013). However, there was no significant difference in the improvement of individual symptoms on the Edmonton Symptom Assessment Scale (ESAS), psychological distress, anxiety scores on the Hospital Anxiety and Depression Scale (HADS) or HADS depression scores in the dexamethasone group compared with placebo. Further dexamethasone studies are needed.

### **Dextroamphetamine versus placebo**

Dextroamphetamine was compared with placebo to treat fatigue in a study of 39 cancer patients (Auret 2009) and in 22 patients with HIV (Wagner 2000). Neither study showed significant effects. The secondary outcome quality of life, which was measured using the McGill Quality of Life Questionnaire (MQOL), also showed no significant effect (Auret 2009).

### **Donepezil versus placebo**

In a large study with 142 participants with cancer, donepezil significantly relieved fatigue intensity in both the intervention and control arms, with no significant difference as measured by the FACIT-F scale. Edmonton Symptom Assessment Scale (ESAS) and sleep pattern assessment were also used as supplemental scales. Neither showed significant effects. Thus, donepezil did not appear to be superior to placebo (Bruera 2007).

### **Fluoxetine versus placebo**

Another study of 129 patients with multiple sclerosis showed that 20 mg of fluoxetine over 12 weeks appeared to be superior to placebo as measured by the change in Functional Assessment of Cancer Therapy - General (FACT-G) scores. The fluoxetine group also showed significant improvement on the depression scale (P value = 0 .0005) compared with placebo, which was measured using the Brief Zung Self-Rating Depression Scale (BZSDS) (Fisch 2003).

### **Fluoxetine versus testosterone**

Fluoxetine was inferior to testosterone in 90 patients with HIV and fatigue, while the difference in the effect on depression, as measured with the HDRS, was non-significant (P value = 0.38) (Rabkin 2004).

### **Medroxyprogesterone versus placebo**

Medroxyprogesterone was tested in only one study of 134 participants using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) (Simons 1996). The use of 500 mg twice a day over 12 weeks showed no significant effect.

### Megestrol acetate versus placebo

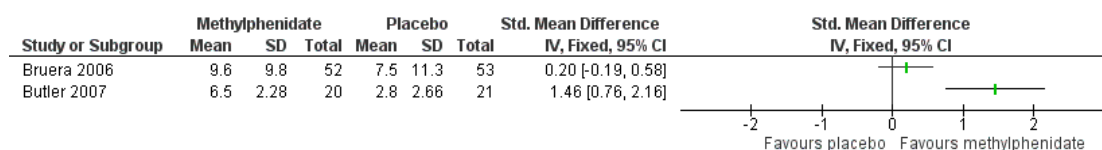
Megestrol acetate was tested in 255 patients with cancer. The administration of 320 mg/day for 12 weeks was performed to investigate the effect of megestrol acetate on quality of life, appetite, weight and survival. However, megestrol acetate does not appear to improve global quality of life as measured by the EORTC QLQ-C30 (Westman 1999).

### Methylphenidate versus placebo

Five studies tested methylphenidate in 318 cancer patients (Bruera 2006; Butler 2007; Escalante 2014; Moraska 2010; Roth 2010). Meta-analysis was possible only for two studies (Bruera 2006;

Butler 2007), which used FACIT-F as the assessment tool in fatigue, comparing methylphenidate with placebo. The studies showed a slightly superior effect of methylphenidate compared to placebo (standardised mean difference (SMD) 0.49, 95% confidence interval (CI) 0.15 to 0.83; Analysis 1.1; Figure 4). Moraska 2010 used the Brief Fatigue Inventory (BFI) instrument, and could not show significant effects of methylphenidate (18 mg to 54 mg) compared with placebo. Escalante 2014 used a stable dose (18 mg) for two weeks. They reported that methylphenidate improved cancer-related fatigue according to the BFI scores. The smallest dose was used by Roth 2010 (5 mg to 30 mg). In this study, clinically significant improvement was seen on the BFI.

**Figure 4. Forest plot of comparison: I Methylphenidate vs Placebo in cancer, outcome: I.1 FACIT-F score change.**



The other study of 30 participants using methylphenidate concerned the treatment of fatigue in multi-type advanced disease (hospice) patients (Kerr 2012). The study showed that methylphenidate was superior to placebo, although the improvement of the fatigue score was dose-dependent, as measured by Piper Fatigue Scale, Visual Analogue Scale for Fatigue and ESAS. However, secondary outcomes of depressive symptoms, measured with the revised Beck Depression Inventory-II (BDI-II), the ESAS depression score and the Center for Epidemiologic Studies Depression Scale (CESD), showed no statistically significant differences.

Methylphenidate was also investigated in 209 HIV patients and compared with pemoline and placebo (Breitbart 2001). This study demonstrated a significantly higher number of responders using methylphenidate compared with placebo.

### Methylprednisolone versus placebo

Methylprednisolone (125 mg/day for eight weeks) was used with significant effect in only one study of 403 participants with cancer-related fatigue (Della Cuna 1989).

### Mistletoe extract PS76A2 versus placebo

Mistletoe extract was tested in 337 patients with breast cancer (Semiglazov 2006). It showed a significant positive effect using the

FACT-G.

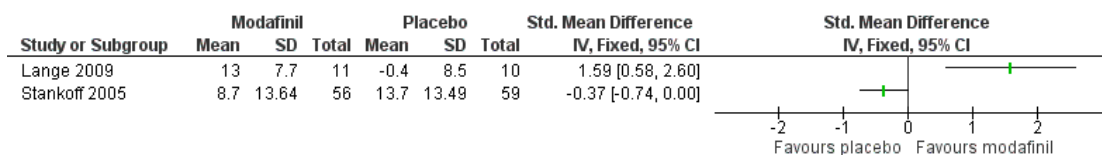
### Modafinil versus placebo

Modafinil has been explored for the treatment of fatigue in two studies of 704 patients with cancer (Jean-Pierre 2010; Spathis 2014). The Jean-Pierre 2010 study showed a significant interaction between treatment condition (modafinil 200 mg/day) and baseline fatigue, where patients with severe baseline fatigue benefited from modafinil and patients with mild or moderate fatigue did not. A recent study demonstrated that both modafinil (100 to 200 mg/day) and placebo led to a clinically significant improvement in FACIT-F scores (Spathis 2014). However, there was no significant difference between placebo and modafinil.

Though modafinil has been tested in several studies in multiple sclerosis, we found only two controlled trials (Lange 2009; Stankoff 2005). The Stankoff 2005 study included a larger number of participants (n = 115), but failed to demonstrate the superiority of modafinil versus placebo. Lange 2009 included only 21 participants and stated that they used a subpopulation of a larger trial. Thus, although there was a clear beneficial effect of modafinil, this result must be interpreted with caution due to the small participant numbers. Meta-analysis of these two studies also failed to demonstrate a significant effect, with a SMD of -0.14

(95% CI -0.48 to 0.21; Analysis 2.1; Figure 5).

**Figure 5. Forest plot of comparison: 4 Modafinil in multiple sclerosis, outcome: 4.1 Modafinil.**



Modafinil was also tested for the treatment of fatigue in 33 participants with post-polio syndrome (Vasconcelos 2007). However, in this study modafinil failed to demonstrate superiority over placebo. There was also a trial using modafinil for fatigue in 105 HIV/AIDS patients (Rabkin 2010). In the intention-to-treat analyses, the fatigue response rate to modafinil was 73% and to placebo 28%; the attrition rate was 9%. Secondary endpoints (depression), including the Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI), did not show a significant effect.

#### Paroxetine versus placebo

Paroxetine was tested in a study of 479 patients with cancer (Morrow 2003), and a study of 15 patients with end-stage chronic obstructive pulmonary disease (COPD; Lacasse 2004). Neither study showed significant effects. However, the Center for Epidemiological Studies Depression (CESD) score, controlling baseline depression scores, confirmed that the dose of paroxetine provided was more effective than placebo in reducing depression (P value = 0 .001).

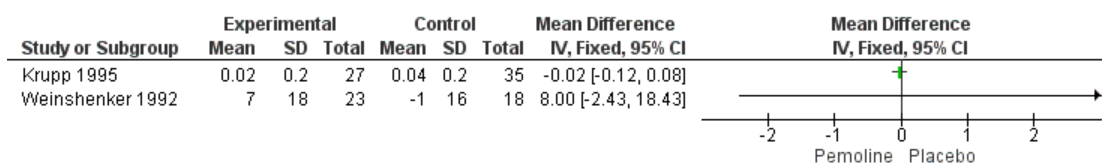
#### Pemoline versus placebo

Pemoline was used for the treatment of fatigue in 41 participants with multiple sclerosis. However, in this study pemoline failed to demonstrate superiority over placebo (Weinshenker 1992).

#### Pemoline versus other drugs

Pemoline was tested in 93 patients with multiple sclerosis and severe fatigue (Krupp 1995). The drug did not appear to be superior to placebo. One study with HIV patients compared pemoline to methylphenidate and to a placebo (Breitbart 2001). The Breitbart 2001 study demonstrated a significantly higher number of responders with pemoline and methylphenidate compared with placebo. Meta-analysis was possible for two studies in multiple sclerosis patients as they all included a control group with placebo and reported continuous outcome indicators (Krupp 1995; Weinshenker 1992). There was no superior effect of pemoline (SMD -0.02; 95% CI -0.12 to 0.08; Figure 6).

**Figure 6. Forest plot of comparison: 3 Pemoline in multiple sclerosis, outcome: 3.1 Fatigue score change.**



However, the US Food and Drug Administration (FDA) has decided to withdraw pemoline products (marketed as Cylert) due to the risk of liver toxicity, which outweighs the benefits of the drug. All manufacturers have agreed to stop the sale and marketing of pemoline (FDA 2005).

#### Testosterone versus placebo

Testosterone cypionate was investigated in 208 patients with HIV in three studies by the same workgroup (Knapp 2008; Rabkin 2000; Rabkin 2004). The older study included HIV patients with symptoms of hypogonadism and found that testosterone relieved



these symptoms in patients with fatigue at baseline (Rabkin 2000). However, fatigue intensity on the CFS merely showed a positive trend, but no significant difference from placebo. The newer study did not show any significant benefit of testosterone compared to fluoxetine or placebo (Rabkin 2004). Only Knapp 2008 showed superiority of testosterone over placebo.

## DISCUSSION

This review updates the original review 'Pharmacological treatments for fatigue associated with palliative care' (Peuckmann-Post 2011) and also incorporates 'Drug therapy for the management of cancer-related fatigue' (Minton 2010). Peuckmann-Post 2011 and Minton 2010 included 22 and 31 studies, respectively. This updated review includes seven studies from Minton 2010 and 22 studies from Peuckmann-Post 2011.

### Summary of main results

This systematic review update 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. Methylphenidate and pemoline seem to be effective in patients with HIV, but this is based only on one study per intervention, with only a moderate number of participants in each study. Meta-analysis shows an estimated superior effect for methylphenidate in cancer-related fatigue, but not for pemoline and modafinil in multiple sclerosis. Therapeutic effects could not be described for dexamphetamine, paroxetine or testosterone.

Acetylsalicylic acid demonstrated surprising efficacy in patients with multiple sclerosis (Shaygannejad 2012; Wingerchuk 2005). However, this result was not supported by other studies. For clinical recommendation, further research confirming this positive effect is needed.

Some studies used other drugs, for example mistletoe extract, megestrol acetate and medroxyprogesterone acetate (Semiglazov 2006; Simons 1996; Westman 1999), but these studies lacked strong evidence and the clinical use of these drugs is rather rare. Further studies need to demonstrate their clinical efficacy.

The available evidence from randomised controlled trials (RCTs) is scarce, even though there is a surplus of case reports and uncontrolled trials. It has to be kept in mind that many of the included studies involved only a small number of participants (Lacasse 2004; Rosenberg 1988), 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 (Breitbart 2001; Wagner 2000), making it difficult to distinguish from primary fatigue. Fatigue often occurs in clusters, and fatigue and emotional distress are often concurrent factors.

The National Comprehensive Cancer Network (NCCN) guidelines discuss studies, some of which show fatigue as an independent factor of depression, while others report moderate correlation. The 2014 NCCN guidelines recommended that the psychostimulant methylphenidate may be considered with caution for the pharmacological treatment of fatigue in selected patients. However, corticosteroids are recommended for short-term but not long-term therapy, due to their toxicity (NCCN 2014).

Treatment of secondary fatigue should be initiated with the treatment of the underlying cause. Some causes of secondary fatigue, such as anaemia, depression, infection, dehydration, malnutrition, hypercalcaemia, hypomagnesaemia, other metabolic disorders or the side effects of treatment with opioids and other sedative drugs, should also be treated, though little evidence from randomised trials is available on the efficacy of these treatments (EAPC 2008). This review only included studies specifically focusing on palliative care in patients with advanced disease with the aim of relieving fatigue. Studies investigating curative treatment (e.g. treatment of early breast cancer) and fatigue directly related to treatment were not included in this review.

In addition, the results of the literature search indicate that recent research interest focuses on modafinil (eight studies) and its use in fatigue management for palliative care patients. This may be an interesting future perspective.

### Potential biases in the review process

None of the authors of this review were involved in any of the excluded or included studies. In addition, none of the authors has any conflict of interest. Our search strategy was as comprehensive as possible. All studies were independently assessed for inclusion by two review authors so we are confident that we have included all relevant studies and attempted to reduce bias in the review process.

Due to difficulties in conducting these types of trials for any of these drugs, trials may not have been published at all. Therefore, there is the potential for publication bias in this review. However, by contacting experts in this field we have attempted to reduce this bias as much as possible.

### Agreements and disagreements with other studies or reviews

There have been two previous Cochrane Reviews (Minton 2010; Peuckmann-Post 2011), which are merged in this systematic review using a new search strategy to increase its coverage. Minton 2010 concluded in their last published version that there is increasing evidence that psychostimulant trials improve cancer-related fatigue at a clinically meaningful level. This review described the need for a large-scale RCT of methylphenidate to confirm the preliminary results from their review. They recommended

haemopoietic growth factors for the treatment of cancer-related fatigue. However, with new safety data indicating increased adverse outcomes, these drugs can no longer be recommended in the treatment of cancer-related fatigue (Bennet 2008; Bohlius 2009; EAPC 2008; Glaspy 2009; Tonelli 2009). Peuckmann-Post 2011 concluded that, based on limited evidence, they could not recommend a specific drug for the treatment of fatigue in palliative care patients. The review pointed out that until 2009, corticosteroids had not been the focus of research on fatigue treatment, although these drugs were frequently used in clinical practice. This review also stated that fatigue research seems to focus on modafinil, which may be beneficial, although there is no evidence.

## AUTHORS' CONCLUSIONS

### Implications for practice

This review update found no evidence to support the use of a specific drug to treat fatigue in palliative care patients. Amantadine seems to be promising in patients with multiple sclerosis and fatigue, while methylphenidate is advantageous in patients with cancer-related fatigue. However, since the number of studies examining the effect of these drugs on fatigue, as well as the participant numbers, were relatively low, the evidence remains weak. Whether amantadine also relieves fatigue in cancer patients and whether methylphenidate relieves fatigue in multiple sclerosis patients has not been shown but should be investigated. Further studies are needed in patients with advanced disease and fatigue to show whether dexamethasone, methylprednisolone, donepezil, carnitine or modafinil may be beneficial, since the available evidence currently does not support these interventions.

Overall, most adverse effects of the investigated drugs seemed to be fairly moderate. Patients with HIV/AIDS and fatigue should be offered treatment with methylphenidate or pemoline. Similarly, other drugs may be tested, if the above-mentioned drugs are not available.

Clinical practice includes corticosteroids as a short-term therapeutic option for relief of fatigue in palliative care (Radbruch 2008; Yennurajalingam 2013). However, only one randomised controlled trial (RCT) from our literature search matched the inclusion criteria (Yennurajalingam 2013). There are still not enough studies to show the therapeutic benefits of corticosteroids for this indication.

### Implications for research

#### Patient group

Trials with a higher participant numbers may be able to detect small differences between groups. Palliative care studies in patients

with advanced diseases, with the aim of relieving primary or secondary fatigue, should remain a focus of research. Further trials investigating subpopulations with different diseases in the end stage may be helpful. Stratification according to sociodemographic variables should be performed since, for example, younger age and male sex have been shown to predict worse fatigue (Auret 2009; Butler 2007).

#### Interventions

Amantadine, methylphenidate, carnitine, acetylsalicylic acid, dexamethasone, alfacalcidol, armodafinil and modafinil have been used in a few studies in this review with positive results. These drugs should be investigated in more detail to confirm their efficacy and should be examined for potentially similar efficacy in populations with different diseases and related fatigue. For instance, amantadine has been studied exclusively in multiple sclerosis patients and in post-polio studies. Therefore, it may be relevant to examine the effect of amantadine in other populations, such as cancer patients. Also, investigation of corticosteroids in RCTs would be highly relevant.

#### Comparisons

Future trials should compare one anti-fatigue drug to another anti-fatigue drug, combined with placebo-controlled comparisons.

#### Outcomes

There is no consensus on threshold values for relief of fatigue or on criteria for the responder. Patient-reported fatigue and variance in the outcome instruments could be used to measure the improvement of fatigue. Outcomes should also clearly define both the response and adverse effects from the treatment. It would be helpful to agree on the use of particular measurement instruments in order to perform better comparisons and analysis (Minton 2009).

#### Trial design

Further research is needed to identify effective and safe treatment for fatigue in palliative care. Multi-centre RCTs are recommended to assess the value of pharmacological treatments for fatigue. Additional data are required to confirm the results of this review and to provide a more significant estimate of efficacy.

Overall, this review demonstrates a lack of evidence rather than a lack of efficacy of the interventions. With regard to future research, studies with larger participant numbers are needed. However, the difficulties of low recruitment and high attrition rates have been described repeatedly in research in palliative care, as patients with advanced and life-threatening diseases are involved. It would also be helpful to limit the diversity of scales and scores used. Since no standardised recommendations for assessment of fatigue yet exist, it is difficult to determine whether the outcome measures were appropriate. Minton and Stone have suggested using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) fatigue subscale or the

Functional Assessment of Cancer Therapy fatigue scale (Minton 2009).

Interestingly, there were no more than two studies with a focus on corticosteroids and fatigue as the primary outcome (Della Cuna 1989; Yennurajalingam 2013), although corticosteroids have been recommended (EAPC 2008) and are frequently used for this indication by clinicians since clinical experience shows a beneficial effect on many of the symptoms experienced by palliative care patients. The impact of corticosteroids should be investigated in future studies.

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