Pharmacological treatments for fatigue associated with palliative care (Review)

Mücke M, Mochamat, Cuhls H, Peuckmann-Post V, Minton O, Stone P, Radbruch L

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2015, Issue 5

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[Intervention Review]

Pharmacological treatments for fatigue associated with palliative care

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 5, 2015.
Review content assessed as up-to-date: 28 April 2014.

Citation: Mücke M, Mochamat, Cuhls H, Peuckmann-Post V, Minton O, Stone P, Radbruch L. Pharmacological treatments for fatigue associated with palliative care. *Cochrane Database of Systematic Reviews* 2015, Issue 5. Art. No.: CD006788. DOI: 10.1002/14651858.CD006788.pub3.

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 (lack of iron), 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 pharmacological 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, alfacalcidol 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 endpoints 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:

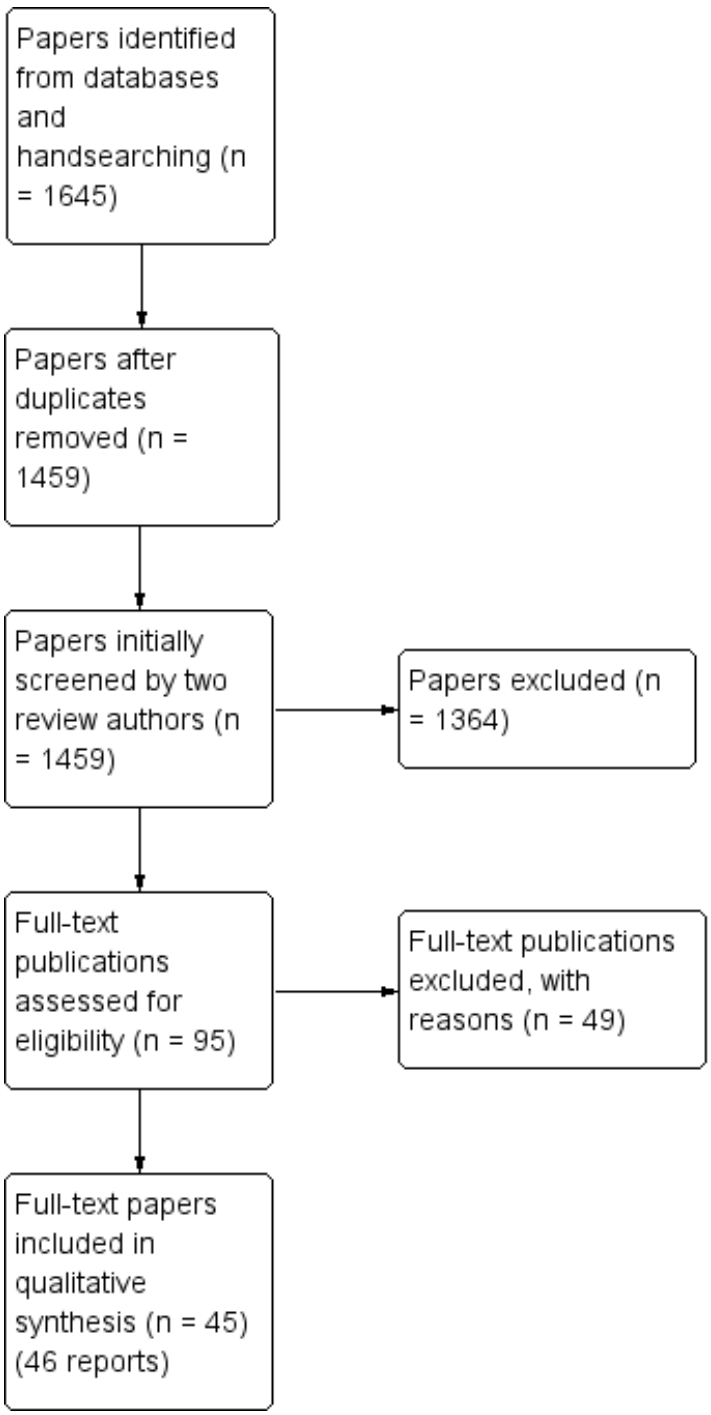
- studies without study limitations with regard to a) allocation concealment; b) blinding of participants and investigators; c) recruitment bias; d) baseline imbalance between groups; e) loss to follow-up of clusters; f) adequate analysis;
- method of analysis: results of a) studies using number of patients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

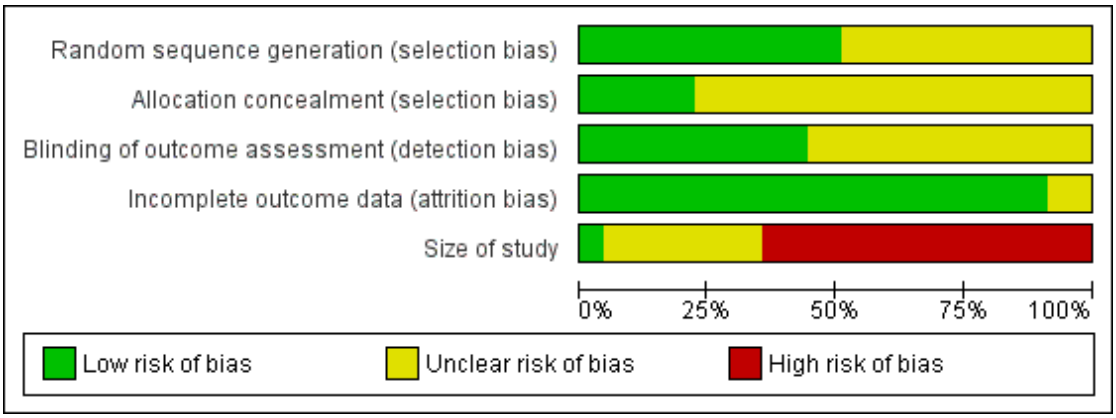
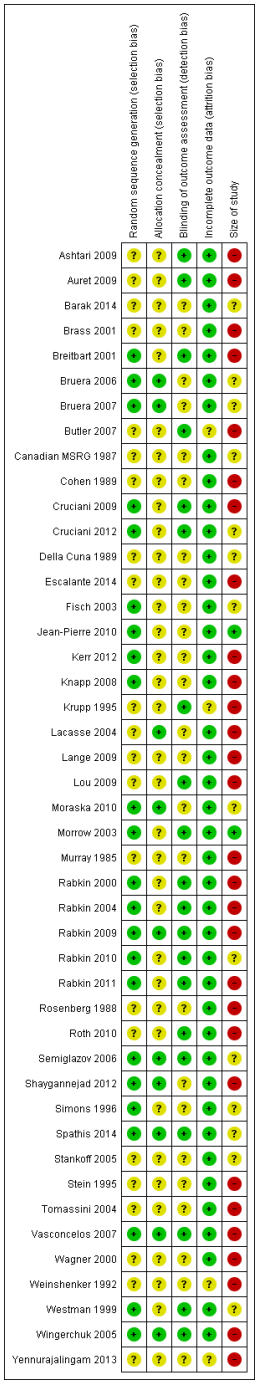


Figure 3. 'Risk of bias' summary: review authors' judgements about risk of bias items for each included study.



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; Weinshenker 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.

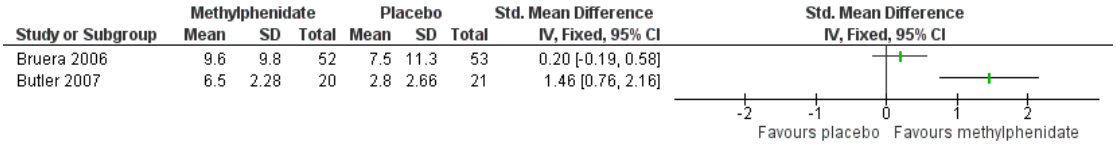
Megestrol acetate versus placebo

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: 1 Methylphenidate vs Placebo in cancer, outcome: 1.1 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.

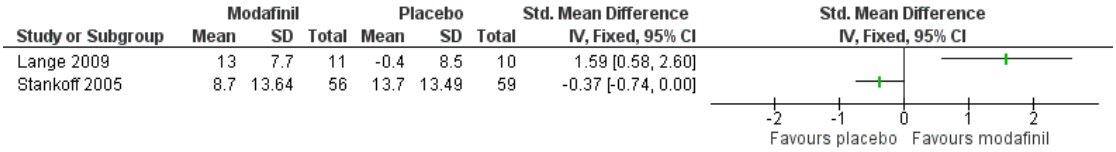
Modafinil versus placebo

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).

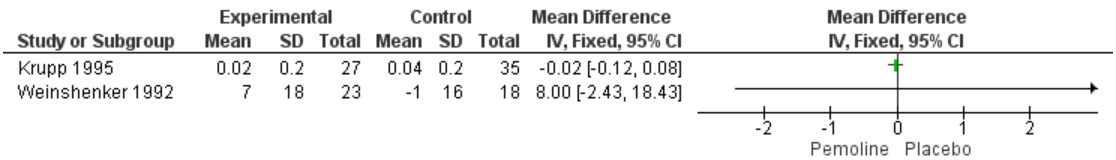
Pemoline versus placebo

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 heterogenous 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.

ACKNOWLEDGEMENTS

We would like to thank Frank Elsner, Norbert Krumm and Peter Trottenburg for their preparatory work. We would like to acknowledge the authors of the previous review: Ollie Minton, Alison Richardson, Michael Sharpe, Matthew Hotopf and Patrick Stone. We thank Anna Mücke, Putri Nastiti, Birgit Jaspers, Johannes Kögler, Grace and Anna Hobson for their helpful support during all stages of the report and their never-ending patience with all delays that occurred, and Roman Rolke who gave valuable feedback for the drafting of the review.

CRG Funding Acknowledgement: The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane PaPaS Group. Disclaimer: The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ashtari 2009

Methods	Placebo-controlled RCT
Participants	N = 42 patients with multiple sclerosis who were divided randomly into 2 groups
Interventions	Amantadine 200 mg/day Duration: 2 months
Outcomes	FSS scores at baseline and 2 months later were compared in the 2 groups
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Identical preprinted medication code labels
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals < 10%
Size of study	High risk	< 50 participants per treatment arm

Auret 2009

Methods	Placebo-controlled, DB, RCT
Participants	N = 70 pts with advanced cancer and cancer considered, 50 included
Interventions	Dexamphetamine 10 mg/twice a day or placebo Duration: 8 days ITT basis
Outcomes	BFI, McGill Quality of Life Questionnaire, ECOG; side effects monitored. Pts were included if they reported fatigue as at least 4 of 10 on a 0 to 10 NRS. Reduction by 2 points on a 10-point scale (BFI) was considered a minimum important clinical difference
Notes	-

Auret 2009 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The active drug and the placebo were pre-packed in identical generic capsules
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	High risk	< 50 participants per treatment arm

Barak 2014

Methods	Double-blind, randomised, placebo-controlled trial
Participants	N = 158 pts with multiple sclerosis (mean age 41.1 + 9.2 years)
Interventions	Patients were randomly assigned to receive alfacalcidol (1 µg) or placebo once daily for 6 months
Outcomes	FIS and QOL
Notes	-

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Baseline observation carried forward

Barak 2014 (*Continued*)

Size of study	Unclear risk	Participants 50 to 199 per treatment arm

Brass 2001

Methods	Placebo-controlled, DB, RCT
Participants	N = 60 pts with end-stage renal disease (ESRD)
Interventions	Patients were randomised and divided into 2 groups 1:1; placebo and treatment Study A: treatment with L-carnitine 20 mg/kg IV for 24 weeks Study B: treatment with L-carnitine dose-ranging 10 to 20 to 40 mg/kg for 24 weeks
Outcomes	KDQ
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis; withdrawals < 10%
Size of study	High risk	< 50 participants per treatment arm

Breitbart 2001

Methods	Placebo-controlled, DB, RCT
Participants	HIV pts with fatigue receiving ambulatory care
Interventions	Titration up to max. 60 mg methylphenidate or 150 mg pemoline, or 8 capsules placebo daily Duration 6 weeks
Outcomes	PFS, VAS-F; side effects monitored

Breitbart 2001 (*Continued*)

Notes	The authors concluded that pts responded favourably to both treatments. However, while the PFS total score showed a significant difference, the VAS total fatigue scale (in which the energy score was significant only) did not. Therefore, the authors' conclusion seems to be too positive A confounding factor may have been improvement in fatigue due to an antidepressant effect, according to the authors	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Used block randomisation
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All medications were prepared in identical capsules
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	High risk	< 50 participants per treatment arm

Bruera 2006

Methods	Placebo-controlled, patient-controlled, DB, RCT	
Participants	N = 112 cancer pts with a fatigue score of at least 4 on a scale of 0 to 10 were included	
Interventions	Pts were randomised to methylphenidate 5 mg PO or placebo every 2 hours prn (max 4 times/day) for 1 week, followed by a 4-week open-label trial of methylphenidate	
Outcomes	FACIT-F, ESAS, daily diary. The authors proposed to detect a decrease in fatigue in the methylphenidate group over and above the placebo group, of half the SD, or a score of approximately 7 on the FACIT-F scale. They therefore adjusted the sample size to declare this difference statistically significant, assuming a one-sided significance level of 0.05 and 80% power	
Notes	The authors stated that a longer study duration of more than 1 week was justified	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Bruera 2006 (*Continued*)

Random sequence generation (selection bias)	Low risk	Restricted random assignment with random balance points from 1 to 5 blocks
Allocation concealment (selection bias)	Low risk	A list of random assignments was prepared and the next eligible patient was entered on the next available assignment line
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis; withdrawals < 10%
Size of study	Unclear risk	Participants 50 to 199 per treatment arm

Bruera 2007

Methods	PC, DB, RCT
Participants	Pts with fatigue score of at least 4 on a scale of 0 to 10 were included; 112 of 142 pts with cancer fatigue were assigned to treatment (71 each)
Interventions	Patients were randomised to donepezil 5 mg PO or placebo every morning for 1 week. Second week: open-label
Outcomes	FACIT-F, ESAS
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Restricted random assignment with random balance points from 1 to 5 blocks
Allocation concealment (selection bias)	Low risk	A list of random assignments was prepared and the next eligible patient was entered on the next available assignment line
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis

Bruera 2007 (*Continued*)

Size of study	Unclear risk	Participants 50 to 199 per treatment arm

Butler 2007

Methods	PC, DB, RCT, phase III trial
Participants	N = 68 pts with primary or metastatic brain tumour scheduled to receive radiotherapy; 34 pts included in each group
Interventions	D-threo-methylphenidate HCl 5 mg/twice a day, titrated to max. 15 mg/twice a day, duration 12 weeks
Outcomes	Cognitive function, FACIT-F, Center for Epidemiologic Studies scale, MMSE, KPS Assessed at baseline, end of RT and 4, 8 and 12 weeks after brain RT
Notes	This study examines prophylactic treatment (before and after RT). The population was quite heterogenous, since approximately half of the pts had metastatic disease and 75% received radiotherapy without chemotherapy. The age range was 28 to 83 years (median 52 for verum and 60 years for placebo group) There was a 71% drop-out from baseline (n = 33 methylphenidate group, n = 29 placebo group) until weeks 5 to 12 (n = 9 each group). Further, the post-treatment effect of radiotherapy during a 12-week course may vary concerning fatigue and pain, for example, which in part may be caused or relieved by the treatment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants received a bottle of pills containing either the study drug or a matched placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Used 'baseline observation carried forward' analysis
Size of study	High risk	< 50 participants per treatment arm

Canadian MSRG 1987

Methods	PC, DB, RCT, cross-over; multicentre trial (11 MS centres)
Participants	N = 115 of 159 were randomised to treatment Eligible participants had at least a 6-month history of "definite multiple sclerosis" and a 3-month history of chronic, persistent, moderate to severe daily fatigue
Interventions	Amantadine 100 mg/twice a day or placebo 10 weeks duration 2 x 3-week treatment periods Each treatment period was preceded by a single-blind, 2-week placebo period
Outcomes	KEDSS; BDI; VAS-F
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	Unclear risk	Participants 50 to 199 per treatment arm

Cohen 1989

Methods	DB, RCT, cross-over, single centre
Participants	N = 29 eligible participants had "satisfied criteria for a definite/probable diagnosis of multiple sclerosis" at least 6 months before diagnosed; all had daily symptomatic fatigue for at least 3 months
Interventions	Random assignment to 100 mg amantadine Hcl twice a day or placebo for 4 weeks, followed by a 2-week wash-out, then cross-over to an alternate treatment (verum/placebo) for another 4-week-period
Outcomes	Kurtzke rating; mBDI, "Stroop Interference Test" (attentional measure of freedom from distracting information). "Overall fatigue" was averaged across mean diary ratings for 7 indices of fatigue on a 5-point scare; 1 = poor; 5 = excellent)

Cohen 1989 (*Continued*)

Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	High risk	< 50 participants per treatment arm

Cruciani 2009

Methods	PC, DB, RCT
Participants	N = 149 eligible pts with carnitine deficiency, cancer and fatigue (n = 27 were excluded due to screen failure)
Interventions	L-carnitine (initial dose 0.5 g/day for 2 days, followed by 1 g/day for 2 days, then 2 g/day for 10 days or placebo), followed by an open-label phase, during which all pts received L-carnitine for 2 weeks
Outcomes	FACT-An, LASA, MMSE, KPS
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer program
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The liquid carnitine and placebo were prepared by a research pharmacist and were identical in appearance and taste

Cruciani 2009 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	High risk	< 50 participants per treatment arm

Cruciani 2012

Methods	PC, DB, RCT phase III trial
Participants	376 pts with cancer
Interventions	Pts were randomly assigned to either 2 g/day of L-carnitine oral supplementation or matching placebo for 4 weeks
Outcomes	BFI, FACIT-F
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised randomisation system
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Drug and placebo matched in appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	Unclear risk	Participants 50 to 199 per treatment arm

Della Cuna 1989

Methods	PC, DB, RCT
Participants	403 pts with cancer Average age 62.7
Interventions	Methylprednisolone 125 mg/day IV 8 weeks Matching placebo
Outcomes	NOSIE, LASA, the Physicians' Global

Della Cuna 1989 (*Continued*)

Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	Unclear risk	Participants 50 to 199 per treatment arm

Escalante 2014

Methods	Placebo-controlled, DB, RCT - cross-over
Participants	N = 42 pts were enrolled and were diagnosed with lymphoma, myeloma or breast, gastrointestinal or lung cancers, and either undergoing chemotherapy or hormonal treatment or completed treatment in the previous 12 months
Interventions	The study duration was 4 weeks. Patients were randomised into 1 of 2 arms: Methylphenidate (18 mg/day) for 2 weeks followed by placebo for 2 weeks (arm A) or placebo for 2 weeks followed by methylphenidate (18 mg/day) for 2 weeks (arm B)
Outcomes	BFI at the end of each 2-week period
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described

Escalante 2014 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	High risk	< 50 participants per treatment arm

Fisch 2003

Methods	PC, DB, RCT
Participants	163 pts with cancer
Interventions	Fluoxetine 20 mg/day 12 weeks
Outcomes	FACT-G, BZSDS
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Preprinted randomisation table
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	Unclear risk	Participants 50 to 199 per treatment arm

Jean-Pierre 2010

Methods	Placebo-controlled, DB, RCT, phase III
Participants	877 cancer patients enrolled in the study N = 431 (modafinil) and n = 436 (placebo) Majority of sample were Caucasian and reported diverse marital status and educational level. 67% of the participants were females at baseline
Interventions	100 mg of modafinil or placebo on day 10 of the chemotherapy cycle, then increase to the full dose of 200 mg of modafinil or placebo after 3 days and continue on this regimen until day 7 of study cycle 4

Jean-Pierre 2010 (*Continued*)

Outcomes	BFI, ESS, POMS-DD Fatigue and depression were assessed during cycles 2 to 4 using psychometrically valid measures Group differences (treatment versus control) in the worst level of fatigue during the previous week at cycle 4 were examined using an analysis of covariance (ANCOVA) adjusting for baseline fatigue (cycle 2)
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number generator program
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	Low risk	> 200 participants per treatment arm

Kerr 2012

Methods	Placebo-controlled, DB, RCT
Participants	N = 30 pts with advanced disease in hospice hospital 2 weeks duration
Interventions	Pts were randomly assigned to receive either 5 mg of methylphenidate or placebo at 8 am and 1 pm. Doses of methylphenidate were titrated every 3 days according to response and adverse effects. Home care patients were monitored daily by telephone and visited by a research nurse on study days 0 (baseline), 3, 7 and 14
Outcomes	PFS, VAS-F, ESAS, BDI-II, ESAS depression score, CESD
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Kerr 2012 (*Continued*)

Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	High risk	< 50 participants per treatment arm

Knapp 2008

Methods	PC, DB, RCT
Participants	61 patients with HIV
Interventions	300 mg IM of testosterone enanthate or placebo for 16 weeks
Outcomes	Body composition, muscle strength, physical function and MOS-30
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	High risk	< 50 participants per treatment arm

Krupp 1995

Methods	PC, DB, RCT
Participants	N = 119 pts with multiple sclerosis and severe fatigue were eligible (FSS score at least 4 of 7; 9 items, each with potential score of 1 to 7; scoring is done by calculating the average response)
Interventions	Pts were randomised to treatment with pemoline (18.75 mg/day for 1 week, 37.5 mg/day for week 2, and 56.25 mg weeks 3 to 6) or placebo or amantadine (amantadine 100 mg twice a day) for 6 weeks
Outcomes	FSS, MS SFS, subjective response (verbal rating)
Notes	Authors conclude that "amantadine was significantly better than placebo in treating fatigue in MS patients", however, this applies only to ratings on the MS Specific Fatigue Scale, not on the FSS. Interestingly, the authors chose a FSS cut-off score as an inclusion criterion, which highlights this scale as a key instrument. Thus, a clear effect of amantadine on fatigue seems questionable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Drugs including the matching placebo were delivered by the pharmaceutical industry
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Used 'baseline observation carried forward' analysis
Size of study	High risk	< 50 participants per treatment arm

Lacasse 2004

Methods	PC, DB, RCT
Participants	N = 23 of 342 pts with end-stage COPD were found eligible (n = 82 refusals) 12-week duration
Interventions	Paroxetine was started at a dose of 5 mg/day, with weekly 5 mg increments up to a maximum of 20 mg/day "or the highest dose not associated with any side effect"
Outcomes	SF-36, "chronic respiratory questionnaire (CRQ)": 1 of 4 domains was fatigue (each domain includes 4 to 7 items and each item is scored on a 7-point-scale.); geriatric

Lacasse 2004 (*Continued*)

	depression scale
Notes	342 pts were assessed for eligibility; 319 pts were excluded to ineligibility (237 pts) and refusal (82 pts) Primary outcome was quality of life Very low number of participants. Power analysis was conducted: 80% was reached at sample size of 9 to detect large treatment effects (type I error 0.05). This number has not been reached

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Low risk	Random numbers table was used to allocate participants to treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	High risk	< 50 participants per treatment arm

Lange 2009

Methods	PC, DB, RCT
Participants	N = 21 pts with multiple sclerosis and fatigue 8-week duration
Interventions	Placebo or modafinil was started at a dose of 100 mg/day for the first week and 200 mg/day for the subsequent 7 weeks
Outcomes	FSS, FSS sum score was used (potential scores 4 to63), alertness test, NHPT, TMS
Notes	The authors state that "the TMS subgroup consisted of 21 consecutive multiple sclerosis pts from a larger, randomised, double-blind trial"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Lange 2009 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	High risk	< 50 participants per treatment arm

Lou 2009

Methods	PC, DB, RCT pilot study
Participants	19 pts with Parkinson's disease Duration 8 weeks
Interventions	Participants took their regular medications and were randomly assigned to the treatment group (9 participants, modafinil 100 mg capsule twice a day PO) or placebo group (10 participants) twice a day for 8 weeks
Outcomes	MFI, ESS, CESD
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo group and treatment had the same appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis; withdrawals < 10%
Size of study	High risk	< 50 participants per treatment arm

Moraska 2010

Methods	PC, DB, RCT phase III study
Participants	148 pts with cancer were enrolled for this study
Interventions	Pts were randomly assigned to receive 1 tablet of methylphenidate or placebo on days 1 through 7, 2 tablets on days 8 through 14, and 3 tablets on days 15 through 28. Each methylphenidate tablet was 18 mg, resulting in the goal dose of 54 mg/day for the final 2 weeks of the study. Tablets were to be taken in the morning
Outcomes	BFI, SED, SF-36 Vitality Subscale, LASA, PSQI, SGIC
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Centrally allocated randomisation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	Unclear risk	Participants 50 to 199 per treatment arm

Morrow 2003

Methods	PC, DB, RCT
Participants	N = 549 of 704 cancer patients with fatigue (recruited on days 1 to 3 undergoing chemotherapy)
Interventions	Paroxetine 20 mg/day oral or placebo for 8 weeks
Outcomes	FSC, MAF (total score was substituted by score of question no. 1; potential score 1 to 10), MPMM, CESD. Assessments were performed at cycles 3 and 4 of chemotherapy
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Morrow 2003 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer-generated random numbers table
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Medication and placebo were identical
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	Low risk	> 200 participants per treatment arm

Murray 1985

Methods	PC, DB, CT, cross-over
Participants	N = 40 pts with multiple sclerosis and persistent fatigue of at least 3 months' duration
Interventions	Amantadine 100 mg or placebo twice a day 6 weeks "with one week wash-out period between active drug and placebo"
Outcomes	KDSS; improvement of fatigue measured by percentage of participants who felt improvement
Notes	The authors reported that "In only a few instances the same patients were used in more than one study". Date of study investigation was 1985 and methods may have been different

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	High risk	< 50 participants per treatment arm

Rabkin 2000

Methods	PC, DB, RCT
Participants	N = 74 HIV-positive men with hypogonadal symptoms (diminished libido, depressed mood, low energy, depleted muscle mass) and symptomatic HIV illness
Interventions	Testosterone cypionate IM injections (initial dose 200 mg, increased to 400 mg) bi-weekly for 6 weeks, followed by 12-week open-label maintenance
Outcomes	CGI scale ratings for libido, mood, energy and erectile function; CFS (7-item scale measured by response options from 1 = never to 5 = always)
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list of numbers
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Matching coded vials containing medication or placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis; withdrawals < 10%
Size of study	High risk	< 50 participants per treatment arm

Rabkin 2004

Methods	PC, DB, RCT
Participants	HIV-positive men N = 123 men were found eligible
Interventions	Testosterone cypionate IM injections (initial dose 200 mg, increased to 400 mg bi-weekly, or fluoxetine up to 60 mg/day (starting dose not mentioned; final mean dose 34 mg, range 20 mg to 40 mg)
Outcomes	CGI scale rating "was expanded to include ratings of energy, as well as mood and a global rating (CGI), significant improvement was defined as score of 1 or 2 on CGI"; HDRS; CFS scores (7-item scale measured by response options from 1 = never to 5 = always)
Notes	Overall, the authors did not recommend testosterone as first-line treatment for depressive disorders in HIV-positive men, but suggested further investigation in pts experiencing fatigue as well as depression

Rabkin 2004 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated list of numbers
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Matching coded vials containing medication or placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis; withdrawals < 10%
Size of study	High risk	< 50 participants per treatment arm

Rabkin 2009

Methods	PC, DB, RCT
Participants	32 patients with amyotrophic lateral sclerosis (ALS)
Interventions	Modafinil 300 mg/day Duration 4 weeks
Outcomes	CGI improvement scale, FSS, ESS, BDI, RFS and VAS
Notes	-

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Low risk	Centrally allocated randomisation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Medication and placebo were identical
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis

Rabkin 2009 (*Continued*)

Size of study	High risk	< 50 participants per treatment arm

Rabkin 2010

Methods	PC, DB, RCT
Participants	115 pts with HIV/AIDS
Interventions	Modafinil with maximum dose 200 mg/day for 8 weeks
Outcomes	CGI improvement, FSS, HDRS, BDI. Safety assessment used assays of CD4 cell count and HIV RNA viral load
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated list of numbers
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Medication and placebo were identical in appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	Unclear risk	Participants 50 to 199 per treatment arm

Rabkin 2011

Methods	PC, DB, RCT
Participants	70 pts with HIV
Interventions	Maximum trial dose of armodafinil was 250 mg/day for 4 weeks
Outcomes	CGI, FSS, HDRS and BDI. Safety was assessed with assays of CD4 cell count and HIV RNA viral load and the SAFTEE side effects rating scale
Notes	-

Risk of bias

Rabkin 2011 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list of numbers
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Medication and placebo were identical in appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis; withdrawals < 10%
Size of study	High risk	< 50 participants per treatment arm

Rosenberg 1988

Methods	PC, DB, RCT
Participants	N = 10 pts with multiple sclerosis
Interventions	Amantadine 200 mg/day or placebo for 1 week, followed by a 1-week wash-out, followed by a cross-over to another drug for 1 week
Outcomes	KEDSS (potential range 0 to 10; 0 = normal neurological examination, 10 = death), patient preference
Notes	Baseline values of KEDSS were not provided; very small participant number. No information concerning a power analysis given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis

Rosenberg 1988 (*Continued*)

Size of study	High risk	< 50 participants per treatment arm

Roth 2010

Methods	PC, DB, RCT
Participants	N = 32 pts ambulatory with prostate cancer
Interventions	The patients were randomly allocated to receive either methylphenidate or placebo for a period of 6 weeks. Methylphenidate was administered in capsules containing 5 mg each, with a starting dose of 1 capsule in the morning The dose was increased by 1 capsule (5 mg) on day 3, added as a midday dose, if fatigue was not substantially reduced, there was no toxicity from the study treatment and if the patient was willing to increase the dose. Dosage was titrated upwards (or down) every 2 to 3 days to a maximum of 6 capsules daily, divided into morning and midday doses (equivalent to a total maximum daily dose of 30 mg of methylphenidate)
Outcomes	BFI
Notes	The authors suggest the need to monitor pulse and blood pressure during the treatment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Medication and placebo were identically appearing capsules
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	High risk	< 50 participants per treatment arm

Semiglazov 2006

Methods	PC, DB, RCT
Participants	Pts with breast cancer N = 352 Average age 46.2

Semiglazov 2006 (*Continued*)

Interventions	Standardised mistletoe (PS76A) extract for 6 cycles of chemotherapy; matched placebo up to 18 weeks
Outcomes	FACT-G
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Centrally allocated randomisation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Medication and placebo were identical in terms of appearance, colour and packaging
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	Unclear risk	Participants 50 to 199 per treatment arm

Shaygannejad 2012

Methods	PC, DB, RCT, cross-over
Participants	N = 52 pts with multiple sclerosis Age range 21 to 53 years old
Interventions	The first group received amantadine (100 mg twice a day) for a total of 4 weeks. The second group received 500 mg/day acetylsalicylic acid (ASA) for 4 weeks. After a 2-week wash-out period, they crossed over to the alternative treatment for 4 weeks
Outcomes	FSS
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list

Shaygannejad 2012 (*Continued*)

Allocation concealment (selection bias)	Low risk	Group assignments were concealed in an opaque, sealed envelope
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis; withdrawals < 10%
Size of study	High risk	< 50 participants per treatment arm

Simons 1996

Methods	PC, DB, RCT
Participants	N = 206 Male 153, female 53 Average age 64
Interventions	Medroxyprogesterone acetate (MPA) 500 mg twice a day for 12 weeks
Outcomes	EORTC-QLQ-C30 fatigue subscale
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation in permutation blocks of 4
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	Unclear risk	Participants 50 to 199 per treatment arm

Spathis 2014

Methods	PC, DB, RCT
Participants	N = 208 pts with non-small cell lung cancer (NSCLC)
Interventions	Modafinil (100 mg on days 1 to 14; 200 mg on days 15 to 28) or matched placebo
Outcomes	FACIT-F, ESS, HADS, QOL-LAS
Notes	Future trials need to have sufficient power to evaluate the effect in those patients with severe fatigue and could incorporate a placebo wash-in period to minimise the influence of the placebo effect

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Central telephone system
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The over-encapsulated active drugs and placebo capsules were matched
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	Unclear risk	Participants 50 to 199 per treatment arm

Stankoff 2005

Methods	PC, DB, RCT
Participants	N = 115 pts with multiple sclerosis and "stable disability", minimal baseline score on MFIS of 45 N = 56 modafinil, N = 59 placebo
Interventions	Modafinil initial dose 200 mg for 1 week, increased by 100 mg weekly up to 400 mg/day max., then continued for 2 weeks or placebo 5-week duration
Outcomes	MFIS; score range 0 to 84; lower score indicating less fatigue, VAS-F, ESS
Notes	-

Risk of bias

Stankoff 2005 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Blocks of 4 randomisation
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	Unclear risk	Participants 50 to 199 per treatment arm

Stein 1995

Methods	PC, DB, RCT
Participants	N = 25 pts with post-polio syndrome and fatigue were eligible
Interventions	Amantadine 100 mg twice a day or placebo for 6 weeks
Outcomes	FSS; improvement of fatigue as noted by participants given in percentage
Notes	Very small participant numbers. Power analysis was calculated to detect 50% reduction in fatigue with 80% power and probability of type I error 0.05

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	High risk	< 50 participants per treatment arm

Tomassini 2004

Methods	DB, RCT, cross-over pilot trial
Participants	N = 36 pts with multiple sclerosis and fatigue
Interventions	Amantadine 100 mg twice a day or acetyl-L-carnitine (ALCAR) 1 g twice a day for 3 months, followed by a 3-month wash-out period, then followed by a cross-over to alternative treatment for 3 months
Outcomes	FSS, FIS, BDI, SEC; reduction of FSS scores observed in participants given in percentage
Notes	Inclusion of relapsing-remitting and secondary progressive multiple sclerosis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	High risk	< 50 participants per treatment arm

Vasconcelos 2007

Methods	DB, RCT, cross-over trial
Participants	N = 36 pts with post-polio syndrome N = 18 (modafinil) and n = 18 (placebo)
Interventions	Treatment with modafinil or equivalent placebo lasted for 6-week periods, being separated by a 14-day wash-out interval. First 3 weeks of treatment, patients received half of the targeted dose (i.e. 200 mg/day supplied as 2 x 100 mg capsules, 1 at breakfast and lunch). At the end of the 3rd week patients doubled their intake (i.e. 400 mg/day, 200 mg at breakfast and lunch)
Outcomes	FSS, VAS-F, FIS, SF-36 QOL
Notes	-

Risk of bias

Vasconcelos 2007 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Concealed allocations from investigators by securing treatment codes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Active drug and placebo had the same appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	High risk	< 50 participants per treatment arm

Wagner 2000

Methods	PC, DB, RCT
Participants	N = 23 pts with HIV, depression and debilitating fatigue
Interventions	Dextroamphetamine initial dose 2.5 mg twice a day, titrated up to maximum of 40 mg/day. Mean dose was 26 +/- 12 mg daily, range 10 to 40 mg/day or placebo for 2 weeks, followed by 24 weeks of open-label trial
Outcomes	SCID; HDRS, BFI, BHS, VAS for mood, CFS (possible range 0 to 28), VAS for energy level
Notes	Groups were heterogenous concerning major depression, which was diagnosed in 12 of the 23 participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis; withdrawals < 10%

Wagner 2000 (*Continued*)

Size of study	High risk	< 50 participants per treatment arm

Weinshenker 1992

Methods	DB, RCT, cross-over; 2-centre trial
Participants	N = 46 pts with multiple sclerosis and fatigue (patients with multiple sclerosis exacerbation during study period were excluded)
Interventions	Pemoline titration in 1 week (18.75 mg to 75 mg/day), continued for 3 weeks or placebo, followed by a cross-over to the other treatment
Outcomes	VAS-F, KEDSS, mBDI; tolerance of adverse effects and checklist to identify their nature
Notes	Interestingly, the authors noted increasing benefit from pemoline over the 2-week study period and supposed that there may have been a larger treatment effect if the study period was longer. Of 13 patients who chose to continue taking the drug, 7 were still taking it after 1 year and reported benefit

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Used 'last observation carried forward' analysis
Size of study	High risk	< 50 participants per treatment arm

Westman 1999

Methods	DB, RCT, cross-over trial
Participants	N = 255 pts with cancer Male 134, female 121 Average age 70 (not on treatment)
Interventions	Megestrol acetate (MA) 320 mg/day

Westman 1999 (*Continued*)

Outcomes	EORTC-QLQ-C30	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation in permutation blocks of four
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Active drugs and placebo had the same shape, size, appearance, colour and taste
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis; withdrawals < 10%
Size of study	Unclear risk	Participants 50 to 199 per treatment arm

Wingerchuk 2005

Methods	PC, DB, RCT, cross-over	
Participants	N = 30 pts with multiple sclerosis and fatigue	
Interventions	Acetylsalicylic acid (ASA) 1300 mg/day or placebo for 6 weeks, followed by 2-week wash-out period, followed by cross-over to alternative treatment	
Outcomes	MFIS (possible score 0 to 84), KEDSS, CESD, Global Fatigue Change self assessment, VAS	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Generated random number list
Allocation concealment (selection bias)	Low risk	Allocation concealment from investigators by securing the results in the pharmacy

Wingerchuk 2005 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Active drug and placebo had the same appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used 'baseline observation carried forward' analysis
Size of study	High risk	< 50 participants per treatment arm

Yennurajalingam 2013

Methods	PC, DB, RCT
Participants	N = 84 pts with advanced cancer (dexamethasone = 43, placebo = 41)
Interventions	Patients were randomly assigned to either dexamethasone 4 mg or placebo orally twice per day for 14 days
Outcomes	ESAS, FACIT-F, HADS, FAACT
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Used 'baseline observation carried forward' analysis
Size of study	High risk	< 50 participants per treatment arm

BDI = Beck Depression Inventory; BFI = Brief Fatigue Inventory; BHS = Beck Hopelessness Scale; BZSDS = Brief Zung Self-Rating Depression Scale; CESD = Center for Epidemiologic Studies Depression; CFS = Chalder Fatigue Scale; CRQ = Chronic Respiratory Questionnaire; DB = double-blind; ECOG = performance status according to the Eastern Cooperative Oncology Group Scale; EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; ESAS = Edmonton Symptom Assessment System; ESS = Epworth Sleepiness Scale; FAACT = Functional Assessment of Cancer Therapy-Anorexia-Cachexia; FACIT-F = Functional Assessment for Chronic Illness Therapy - Fatigue; FACT-An = Functional Assessment of Cancer Therapy - Anaemia; FIS = Fatigue Impact Scale; FSC = Fatigue Symptom Checklist; FSS = Fatigue Severity Scale; HADS =

Hospital Anxiety and Depression Scale; HDRS = Hamilton Depression Rating Scale; IM = intramuscular; ITT = intention-to-treat; IV = intravenous; KDQ = Kidney Disease Questionnaire; KEDSS = Kurtzke Expanded Disability Status Scale; KPS = Karnofsky Performance Status; LASA = Linear Analogue Scale Assessments; MAF = Multidimensional Assessment of Fatigue; mBDI = Modified Beck Depression Inventory; MFI = Multidimensional Fatigue Inventory; MMSE = Mini Mental State Examination; MOS-30 = Medical Outcomes Study-Short Form 30; MPMM = Monopolar Profile of Mood States; MS = multiple sclerosis; MS SFS = Multiple Sclerosis Specific Fatigue Scale; NHPT = Nine Hole Peg Test; NOSIE = Nurses' Observational Scale for Inpatient Evaluation; NRS = numeric rating scale; PC = placebo-controlled; PFS = Piper Fatigue Scale; PO = per oral; POMS-DD = Depression-Dejection subscale of the Profile of Mood States; prn = as needed; PSQI = Pittsburgh Sleep Quality Index; pts = participants; QOL = RAYS quality of life; QOL-LAS = quality of life linear analogue scale; RCT = randomised controlled trial; RFS = Role Function Scale; RT = radiation therapy; SAFTEE = Systematic Assessment for Treatment Emergent Events; sc = subcutaneous; SCID = depression according to Structured Clinical Interview for DSM-IV; SD = standard deviation; SE = standard error; SEC = Social Experience Checklist; SED = Symptom Experience Diary; SF-36 = Short Form-36; SGIC = Subject Global Impression of Change; TMS = transcranial magnetic Social Experience Checklist; VAS = visual analogue scale; VAS-F = visual analogue scale - fatigue

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agteresch 2000	Open-label study
Bruera 1987	Focus of this study was sedation related to narcotics, not fatigue
Bruera 1998	Focus of study was cancer cachexia
Bruera 2003	Focus of this study was sedation related to narcotics, not fatigue
Capuron 2002	Main focus of this study was not fatigue
Carter 2005	Open-label study, case series
Cerchietti 2004	Not blinded, not a RCT
Cruciani 2004	Open-label study
Cruciani 2006	Phase I/II study
Cueva 2012	Phase II study
Cullum 2004	Open-label study, case series
De Conno 1998	Main focus of this study was depression and appetite
Diel 2004	Part of the study was open-label
Downer 1993	Main focus of this study was cachexia
Dunlop 2007	Focus of this study was depression

(*Continued*)

Gehring 2012	Open-label study
Graziano 2002	The drug was intended to treat fatigue, which was induced by a treatment not a disease
Hannestad 2011	The participants were not at an advanced stage of illness or in a palliative situation
Hovey 2014	The drug was intended to treat fatigue, which was induced by a treatment not a disease
Inoue 2003	The drug was intended to treat fatigue, which was induced by a treatment not a disease
Lauretti 2013	Focus of this study was pain
Laval 2008	This article was published only as a protocol; no original results
Lower 2009	The drug was intended to treat fatigue, which was induced by a treatment not a disease
Mar Fan 2008	The drug was intended to treat fatigue, which was induced by a treatment not a disease
McElhiney 2010	Primary focus of this study was not fatigue
McElhiney 2013	Main focus of this study was cognitive function
Mercadante 2001	Consecutive study, not randomised
Metz 2004	No randomisation
Moertel 1974	Single-blind study
Mohr 2003	Fatigue was not the primary outcome
Monk 2006	Open-label study
Moss 2006	Open-label study, case series
Popiela 1989	Single-blind study
Rabkin 2000a	Investigators used pre-selection ("mood responders were maintained" after an open-label trial)
Rabkin 2011a	This study was a subset of another study
Rammohan 2002	Phase II study
Romani 2004	Authors state that "Due to the design of the study, [the similarly decreased fatigue scores in both groups] cannot be disjoined from a placebo effect."
Roscoe 2005	Patients cannot be considered to be in a palliative care situation

(*Continued*)

Sailer 2000	24 patients were assigned to 4 groups and patients were very heterogenous concerning disease duration
Shaw 2006	Phase II study
Shaw 2013	Phase II study
Spathis 2009	Open-label trial; aim of study was to determine feasibility of conducting a RCT for fatigue in lung cancer
Stockler 2007	Fatigue was studied as secondary outcome
Torta 2007	Main focus was depression. Fatigue was secondary outcome
Wade 2002	Investigators focus on disability, not fatigue
Wagner 1997	Open-label study, case series
Weitzner 2002	Fatigue was not the primary outcome
Wilwerding 1995	Focus was not fatigue, but narcotic-induced sedation
Zifko 2002	Open-label study

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Methylphenidate versus placebo in cancer

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FACIT-F score change	2		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 2. Modafinil versus placebo in multiple sclerosis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fatigue score change	2		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 3. Pemoline versus placebo in multiple sclerosis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fatigue score change	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

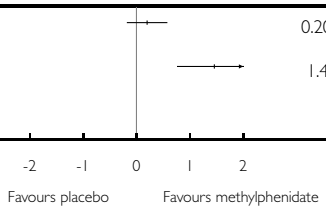
Analysis 1.1. Comparison 1 Methylphenidate versus placebo in cancer, Outcome 1 FACIT-F score change.

Review: Pharmacological treatments for fatigue associated with palliative care

Comparison: 1 Methylphenidate versus placebo in cancer

Outcome: 1 FACIT-F score change

Study or subgroup	Methylphenidate N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Std. Mean Difference IV,Fixed,95% CI
Bruera 2006	52	9.6 (9.8)	53	7.5 (11.3)		0.20 [-0.19, 0.58]
Butler 2007	20	6.5 (2.28)	21	2.8 (2.66)		1.46 [0.76, 2.16]



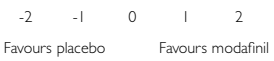
Analysis 2.1. Comparison 2 Modafinil versus placebo in multiple sclerosis, Outcome 1 Fatigue score change.

Review: Pharmacological treatments for fatigue associated with palliative care

Comparison: 2 Modafinil versus placebo in multiple sclerosis

Outcome: 1 Fatigue score change

Study or subgroup	Modafinil N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Std. Mean Difference IV,Fixed,95% CI
Lange 2009	11	13 (7.7)	10	-0.4 (8.5)		1.59 [0.58, 2.60]
Stankoff 2005	56	8.7 (13.64)	59	13.7 (13.49)		-0.37 [-0.74, 0.00]



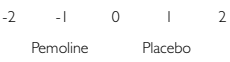
Analysis 3.1. Comparison 3 Pemoline versus placebo in multiple sclerosis, Outcome 1 Fatigue score change.

Review: Pharmacological treatments for fatigue associated with palliative care

Comparison: 3 Pemoline versus placebo in multiple sclerosis

Outcome: 1 Fatigue score change

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Krupp 1995	27	0.02 (0.2)	35	0.04 (0.2)		-0.02 [-0.12, 0.08]
Weinshenker 1992	23	7 (18)	18	-1 (16)		8.00 [-2.43, 18.43]



ADDITIONAL TABLES

Table 1. Drug treatment of fatigue: Populations, substances and outcome measures

Patient population	Substance	Outcome measures	Study
Fatigue in advanced cancer	Amphetamine	BFI, McGill Quality of Life Questionnaire, ECOG	Auret 2009
	L-carnitine	FACT-An, LASA, MMSE, KPS	Cruciani 2009
	L-carnitine	BFI, FACIT-F, depression and pain instrument	Cruciani 2012
	Paroxetine	FSC, MFI, Monopolar Profile of Mood States	Morrow 2003
	Methylphenidate	FACIT-F, ESAS, daily diary	Bruera 2006
	Methylphenidate	Cognitive function, FACIT-F, CESD, MMSE, KPS	Butler 2007
	Methylphenidate	BFI, SED, SF-36 vitality subscale, LASA, PSQI, SGIC	Moraska 2010
	Methylphenidate	BFI	Roth 2010
	Methylphenidate	BFI	Escalante 2014
	Donepezil	FACIT-F, ESAS	Bruera 2007
	Methylprednisolone	NOSIE, LASA, Physician's Global	Della Cuna 1989
	Modafinil	BFI, ESS, POMS-DD	Jean-Pierre 2010
	Modafinil	FACIT, ESS, HADS, QOL-LAS	Spathis 2014
	Fluoxetine	FACT-G	Fisch 2003
	Standardised Mistletoe extract	FACT-G	Semiglazov 2006
	Medroxyprogesterone acetate (MPA)	FACT-G	Simons 1996
	Megestrol acetate	EORTC-QLQ-C30 instrument	Westman 1999

Table 1. Drug treatment of fatigue: Populations, substances and outcome measures (*Continued*)

Fatigue in amyotrophic lateral sclerosis (ALS)	Modafinil	CGI-E, FSS, ESS, BDI, RFS, VAS	Rabkin 2009
Fatigue in HIV/AIDS	Methylphenidate	PFS	Breitbart 2001
	Pemoline	PFS	Breitbart 2001
	Armodafinil	CGI-I, FSS, HDRS, BDI	Rabkin 2011
	Modafinil	CGI-I, FSS, HDRS, BDI	
	Amphetamine	SCID; HDRS, BFI, BHS, VAS for mood, CFS, VAS for energy level	Wagner 2000
	Testosterone	CGIS "was expanded to include ratings of energy, as well as mood and a global rating. Significant improvement was defined as score of 1 or 2 on CGIS"; HDRS, CFS	Rabkin 2004
	Testosterone	CGIS ratings for libido, mood, energy and erectile function; CFS	Rabkin 2000
	Testosterone	Body composition, muscle strength and physical function, MOS-30	Knapp 2008
	Fluoxetine	Body composition, muscle strength and physical function, MOS-30	Rabkin 2004
Fatigue in multiple sclerosis	Pemoline	VAS-F, KEDSS, mBDI; tolerance of adverse effects and checklist to identify their nature	Weinshenker 1992
	Pemoline	FSS, MS Specific Fatigue Scale, subjective response (verbal rating)	Krupp 1995
	L-carnitine	FSS, Fatigue Impact Scale, Beck Depression Inventory, Social Experience Checklist	Tomassini 2004
	Amantadine	FSS, Fatigue Impact Scale, Beck Depression Inventory, Social Experience Checklist	Tomassini 2004

Table 1. Drug treatment of fatigue: Populations, substances and outcome measures (*Continued*)

	Amantadine	KEDSS; mBDI, "Stroop Interference Test" (attentional measure of freedom from distracting information)	Cohen 1989
	Amantadine	KEDSS; mBDI, "Stroop Interference Test" (attentional measure of freedom from distracting information)	Krupp 1995
	Amantadine	KEDSS	Murray 1985
	Amantadine	KEDSS, patient preference	Rosenberg 1988
	Amantadine	KEDSS; BDI; VAS-F	Canadian MSRG 1987
	Amantadine	FSS	Ashtari 2009
	Amantadine	FSS	Shaygannejad 2012
	Acetylsalicylic acid	MFIS, KEDSS, CESD, SGIC, FSS	Wingerchuk 2005
	Acetylsalicylic acid	FSS	Shaygannejad 2012
	Modafinil	FSS, alertness test, NHPT, TMS	Lange 2009
	Modafinil	MFIS, VAS-F, ESS	Stankoff 2005
	Modafinil	FSS, VAS-F, FIS, SF-36 QOL	Vasconcelos 2007
	Dexamethasone	FIS, QOL	Yennurajalingam 2013
	Alfacalcidol (Vit. D)	FIS, QOL	Barak 2014
End-stage renal disease (ESRD)	L-carnitine	KDQ	Brass 2001
Parkinson's disease	Modafinil	MFI, ESS, CESD	Lou 2009
Multi-type advanced disease (hospice patients)	Methylphenidate	PFS, VAS-F, ESAS	Kerr 2012
End-stage COPD	Paroxetine	SF-36, chronic respiratory questionnaire: 1 of 4 domains was fatigue, geriatric depression	Lacasse 2004

Table 1. Drug treatment of fatigue: Populations, substances and outcome measures (*Continued*)

		scale	
Postpolio syndrome	Amantadine	FSS	Stein 1995

BDI = Beck Depression Inventory; BFI = Brief Fatigue Inventory; BHS = Beck Hopelessness Scale; CESD = Center for Epidemiologic Studies Depression; CFS = Chalder Fatigue Scale; DB = double-blind; ECOG = performance status according to the Eastern Cooperative Oncology Group Scale; EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; ESAS = Edmonton Symptom Assessment System; ESS = Epworth Sleepiness Scale; FACIT-F = Functional Assessment for Chronic Illness Therapy - Fatigue; FACT-An = Functional Assessment of Cancer Therapy - Anaemia; FIS = Fatigue Impact Scale; FSC = Fatigue Symptom Checklist; FSS = Fatigue Severity Scale; HADS = Hospital Anxiety and Depression Scale; HDRS = Hamilton Depression Rating Scale; IM = intramuscular; ITT = intention-to-treat; IV = intravenous; KDQ = Kidney Disease Questionnaire; KEDSS = Kurtzke Expanded Disability Status Scale; KPS = Karnofsky Performance Status; LASA = Linear Analogue Scale Assessments; MAF = Multidimensional Assessment of Fatigue; mBDI = Modified Beck Depression Inventory; MFI = Multidimensional Fatigue Inventory; MMSE = Mini Mental State Examination; MOS-30 = Medical Outcomes Study-Short Form 30; MPMM = Monopolar Profile of Mood States; MS = multiple sclerosis; MS SFS = Multiple Sclerosis Specific Fatigue Scale; NHPT = Nine Hole Peg Test; NOSIE = Nurses' Observational Scale for Inpatient Evaluation; NRS = numeric rating scale; PC = placebo-controlled; PFS = Piper Fatigue Scale; PO = per oral; POMS-DD = Depression-Dejection subscale of the Profile of Mood States; prn = as needed; PSQI = Pittsburgh Sleep Quality Index; pts = participants; QOL = RAYS quality of life; QOL-LAS = quality of life linear analogue scale; RCT = randomised controlled trial; RFS = Role Function Scale; RT = radiation therapy; sc = subcutaneous; SCID = depression according to Structured Clinical Interview for DSM-IV; SD = standard deviation; SE = standard error; SEC = Social Experience Checklist; SED = Symptom Experience Diary; SF-36 = Short Form-36; SGIC = Subject Global Impression of Change; TMS = transcranial magnetic Social Experience Checklist; VAS = visual analogue scale; VAS-F = visual analogue scale - fatigue

Table 2. Overview of adverse reactions associated with fatigue treatment

Drug and indication	Impact of adverse reaction	Symptoms	Study
Acetyl-L-carnitine and amantadine in multiple sclerosis	1 (carnitine) and 5 (amantadine) of 36 patients withdrew	Carnitine: insomnia, nervousness Amantadine: nausea, dizziness	Tomassini 2004
Amantadine in multiple sclerosis	7 of 32 reported adverse reactions (versus 6 of 32 on placebo)	Hallucinations, nausea, gastric irritation, early morning wakening, hyperactivity, flu-like illness	Murray 1985
Amantadine in multiple sclerosis	-	Constipation, nausea, anxiety, influenza-like illness	Cohen 1989
Amantadine, pemoline in multiple sclerosis	No severe adverse reaction (did not lead to withdrawal)	Pemoline: palpitations, nausea, mood change, sleep disturbance, Amantadine: sleep disturbance, palpitations	Krupp 1995
Dextroamphetamine in HIV-positive men with fatigue	None of 23 patients discontinued during the 2 weeks of DB, PC RCT	Overstimulation, heart palpitation, sleep deprivation, loss of appetite and/or weight,	Wagner 2000

Table 2. Overview of adverse reactions associated with fatigue treatment (*Continued*)

		headache. The authors reported that adverse reactions generally were "transient, reversible, and well managed with dose reduction; no serious medical side effects were reported"	
Dexamphetamine in advanced cancer	Drop-out rate in verum group compared to placebo group was statistically not significant	Significant increase in pulse rate. Transient increase of dry mouth, insomnia, tremor, anorexia on days 6 and 8 (of 8)	Auret 2009
Pemoline in multiple sclerosis	3 of 46 dropped out because of adverse reaction; 25% of patients did not tolerate pemoline well according to the authors	Most common side effects were anorexia, irritability, "jitteriness" and insomnia	Weinshenker 1992
Acetylsalicylic acid in multiple sclerosis	No serious adverse reaction	Nausea, transient epigastric pain (nausea, headache and diarrhoea occurred with placebo)	Wingerchuk 2005
Methylphenidate and pemoline in HIV	Severe side effects relatively uncommon; 5 withdrew (2 on methylphenidate, 2 on pemoline, 1 on placebo)	Hyperactivity, jitteriness, dry mouth, rapid heart beat, difficulty sleeping, constipation, neuropathic pain (1 patient)	Breitbart 2001
Methylphenidate in advanced cancer	No severe adverse effects	Most pts reported insomnia, anorexia, restlessness, behavioural change and vertigo. Numbers in placebo groups were similar	Bruera 2006
Donepezil in advanced cancer	No severe adverse effects	Most pts reported anorexia, nausea, restlessness, dizziness, behaviour change, vertigo	Bruera 2007
Amantadine in multiple sclerosis	No statistically significant difference in prevalence of adverse events reporting	Most pts reported headache, insomnia, nausea, anxiety, dizziness, ataxia	Canadian MSRG 1987
Paroxetine in end-stage COPD	Only 1 of 12 pts dropped out because of adverse effects related to the drug	Somnolence was reported by 5 pts, constipation, nausea, headache tremor were rated by 2 pts each	Lacasse 2004
Testosterone for HIV-positive pts	3 of 46 pts discontinued because of adverse reactions	Acne, irritability, insomnia, headache, nasal congestion	Rabkin 2000

Table 2. Overview of adverse reactions associated with fatigue treatment (*Continued*)

Testosterone and fluoxetine in HIV	-	Fluoxetine: diarrhoea, nausea, nonspecific discomfort Testosterone: sleepiness; all treatments: dry mouth, sleepiness, loose bowels	Rabkin 2004
Modafinil for HIV patients	-	Treatment-emergent side effects were relatively uncommon CD4 cell count did not show either statistically or clinically significant changes	Rabkin 2010
Armodafinil in HIV	Armodafinil was well tolerated, with few and transient adverse events	The most common was headache	Rabkin 2011
Amantadine in post-polio syndrome	-	Insomnia was the commonest reported adverse reaction; dry mouth was noted by 1 patient	Stein 1995
L-carnitine in end-stage renal disease (ESRD)	No serious adverse event was believed by the investigators to be certainly or probably drug-related	Flu syndrome, injection-site reaction, pain, pharyngitis, headache and hypertension showed no difference in frequency between L-carnitine and placebo	Brass 2001
Methylphenidate in cancer	No serious adverse effect	Some pts experienced nausea, vomiting, facial rash	Escalante 2014
Fluoxetine in cancer	A total of 16 adverse events were judged to be possibly due to the treatment and 6 to taking the placebo	Allergic reaction, cardiac arrhythmia, dyspnoea, headaches, dizziness, mood change, myalgia, fever, diarrhoea, abdominal pain	Jean-Pierre 2010
Methylphenidate in cancer	There was a significant difference in self reported toxicities (SED)	Increased levels of nervousness and appetite loss in the methylphenidate group	Moraska 2010
Methylphenidate in cancer	No severe adverse reaction	4 (31%) men who started receiving methylphenidate had to be discontinued from the study due to increased blood pressure	Roth 2010
Medroxyprogesterone acetate (MPA) in cancer	-	Nausea and vomiting	Simons 1996

Table 2. Overview of adverse reactions associated with fatigue treatment (*Continued*)

Acetylsalicylic acid and amantadine in multiple sclerosis	Acetylsalicylic acid and amantadine are both well tolerated	The most common side effects of acetylsalicylic acid were nausea (n = 53) and transient epigastric pain (n = 51). The most common side effect of amantadine was also nausea (n = 51)	Shaygannejad 2012
Modafinil in cancer	Modafinil seemed to be well tolerated	Most symptoms are nausea, vomiting, anxiety and headache	Spathis 2014
Dexamethasone in multiple sclerosis	2 adverse events were probably related to study treatment	Pain grade 3 and vomiting grade 2	Yennurajalingam 2013

COPD = chronic obstructive pulmonary disease; DB = double-blind; PC = placebo-controlled; pts = participants RCT = randomised controlled trial

APPENDICES

Appendix 1. CENTRAL search strategy

Subject search was run on 28 April 2014

#	1.	NEOPLASMS
#	2.	(neoplasm* or cancer* or carcinoma* or tumour* or tumor* or adenocarcinoma* or leukeni* or lymphoma* or malignan*) :ti,ab,kw
#	3.	MULTIPLE SCLEROSIS
#	4.	"multiple sclerosis":ti,ab,kw
#	5.	AMYOTROPHIC LATERAL SCLEROSIS
#	6.	"amyotrophic lateral sclerosis":ti,ab,kw
#	7.	ACQUIRED IMMUNODEFICIENCY SYNDROME
#	8.	AIDS-RELATED COMPLEX
#	9.	HIV
#	10.	HIV WASTING SYNDROME

(*Continued*)

#	11.	"acquired immunodeficiency syndrome":ti,ab,kw
#	12.	"AIDS related complex":ti,ab,kw
#	13.	"HIV":ti,ab,kw
#	14.	"human immunodeficiency virus":ti,ab,kw
#	15.	LUNG DISEASES
#	16.	PULMONARY DISEASE CHRONIC OBSTRUCTIVE
#	17.	HEART DISEASES
#	18.	"lung disease*" or "heart disease*" or "pulmonary disease*"
#	19.	HEART FAILURE
#	20.	"cardiac failure" or "heart failure"
#	21.	"incurable disease*" or "incurable illness*"
#	22.	((terminal or advanced or progressive or "end stage" or end-stage) and (illness* or disease*))
#	23.	BONE MARROW TRANSPLANTATION
#	24.	(neutropeni* or neutropaeni*):ti,ab,kw
#	25.	RADIOTHERAPY
#	26.	(radioth* or radiat* or irradiat* or radiochemo* or chemotherapy*):ti,ab,kw
#	27.	"bone marrow" NEAR transplant*
#	28.	"bone-marrow" NEAR transplant*
#	29.	(fatigue near/4 treatment) or (treated near/4 treated) or (fatigue near/4 therapy) or (fatigue near/4 intervention)
#	30.	(asthenia near/4 treatment) or (treated near/4 treated) or (fatigue near/4 therapy) or (fatigue near/4 intervention)
#	31.	((tired* near/4 treatment) or (tired* near/4 treated) or (tired* near/4 therapy) or (treatment near/4 exhausted) or (exhausted near/4 therapy) or (exhaustion near/4 therapy))
#	32.	apathy or apathetic or lassitude or lethargy* or "feeling drained" or "feeling sleepy" or "feeling sluggish" or "feeling weak*"
#	33.	(FATIGUE or cancer-related fatigue or cancer related fatigue):ti,ab,kw
#	34.	tired* or weary or weariness or exhaustion or exhausted or lackluster or astheni* or asthenia*

(*Continued*)

#	35.	lack* NEAR/2 energy
#	36.	lack* NEAR/2 vigour
#	37.	lack* NEAR/2 vigor
#	38.	loss NEAR/2 energy
#	39.	loss NEAR/2 vigour
#	40.	loss NEAR/2 vigor
#	41.	lost NEAR/2 energy
#	42.	lost NEAR/2 vigour
#	43.	lost NEAR/2 vigor
#	44.	palliati* or hospice or "end of life"
#	45.	#1-#28/OR
#	46.	#29-#44
#	47.	#45 AND #46
#	48.	dexamphetamine or dextroamphetamine
#	49.	ANTIDEPRESSIVE AGENTS
#	50.	ADRENERGIC UPTAKE INHIBITORS
#	51.	glucocorticoid or steroid or steroids or dexamethason or dexamethasone or methylprednisolone or corticosteroid or corticosteroids
#	52	Carnitine or L-carntine
#	53.	modafinil
#	54.	amantadine or donepezil or pemoline
#	55.	Methylphenidate or d-threo-methylphenidate
#	56.	paroxetine
#	57.	Aspirin or acetylsalicylic acid
#	58.	citalopram

(*Continued*)

#	59.	bupropion
#	60.	testosteronecypionate
#	61.	#48 - #60/OR
#	62.	#47 AND #61

Appendix 2. MEDLINE search strategy

Subject search combined with the recommended study design filter was run on 28 April 2014 (using OVID)

#	1.	exp Neoplasms/
#	2.	(cancer* or malignan*).mp.
#	3.	multiple sclerosis.af.
#	4.	amyotrophic lateral sclerosis.af.
#	5.	(sclerosis adj4 (amyotroph* or multiple)).mp.
#	6.	exp acquired immune deficiency syndrome/
#	7.	aids related complex.mp.
#	8.	exp Human immunodeficiency virus/
#	9.	(HIV or AIDS).mp.
#	10.	bone marrow transplantation.mp.
#	11.	radiotherapy.mp.
#	12.	(carcinoma* or tumour* or adenocarcinoma* or leukeni* or leukaemi* or lymphoma* or tumor*).mp
#	13.	(neutropeni$ or neutropaeni$).mp.
#	14.	(radioth* or radiat* or irradiat* or radiochemo* or chemotherap*).mp
#	15.	Lung Disorders.mp.
#	16.	heart disorders.mp.
#	17.	congestive heart failure.mp.

(*Continued*)

#	18.	cor pulmonale.mp.
#	19.	cancer fatigue.mp.
#	20.	(cancer-related fatigue or cancer related fatigue).mp.
#	21.	exp FATIGUE/
#	22.	(tired$ or weary or weariness or exhaustion or exhausted or lacklustred or ((astheni$ or asthenia$) and syndrome)).mp
#	23.	((lack$ or loss or lost) adj2 (energy or vigour or vigor)).mp
#	24.	(apathy or apathetic or lassitude or letharg$ or (feeling adj3 (drained or sleepy or sluggish or weak$))).mp
#	25.	((advanced or terminal* or progressi* or end-stage or endstage or "endstage") adj6 (disease or illness)).mp
#	26.	palliati*.mp.
#	27.	(dexamphetamine or dextroamphetamine).mp.
#	28.	(methylphenidate or threo$methylphenidate or d-threo-methylphenidate).mp
#	29.	donepezil.mp.
#	30.	amantadine.mp.
#	31.	(Carnitine or L-carntine).mp.
#	32.	pemoline.mp.
#	33.	modafinil.mp.
#	34.	paroxetine.mp.
#	35.	(testosteronecypionate or androgen).mp.
#	36.	(acetylsalicylic acid or aspirin).mp.
#	37.	fluoxetin.mp
#	38.	citalopram.mp
#	39.	(glucocorticoid or steroid or steroids or dexamethason or dexamethasone or methylprednisolone or corticosteroid or corticosteroids).mp
#	40.	bupropion.mp.

(*Continued*)

#	41.	(anti depressant agents or anti depressive agents or Selective serotonin reuptake inhibitors).mp
#	42.	random*.ti,ab.
#	43.	factorial*.ti,ab.
#	44.	(crossover* or cross over* or cross-over*).ti,ab.
#	45.	placebo*.ti,ab.
#	46.	(doubl* adj blind*).ti,ab.
#	47.	(singl* adj blind*).ti,ab.
#	48.	randomized controlled trial.mp.
#	49.	assign*.ti,ab.
#	50.	allocat*.ti,ab.
#	51.	evaluation study*.ti,ab.
#	52.	prospective study*.ti,ab.
#	53.	comparative study*.ti,ab.
#	54.	(animal* or nonhuman* or animal experiment*).ti,ab.
#	55.	#1-#18/OR
#	56.	#19-26/OR
#	57.	#27-41/OR
#	58.	#42-53/OR
#	59.	#55 AND #56 AND #57 AND #58
#	60.	#59 NOT #54

Appendix 3. EMBASE search strategy

Subject search combined with the recommended study design filter was run on 28 April 2014

#	1.	neoplasm/exp
#	2.	(cancer* or malignan*)
#	3.	'multiple sclerosis'/exp
#	4.	'amyothropic lateral sclerosis'/exp
#	5.	sclerosis (amyotroph*4 or multiple)
#	6.	(('acquired immune deficiency syndrome'/exp) OR ('aids related complex'/exp))
#	7.	'Human immunodeficiency virus'/exp
#	8.	(HIV or AIDS)
#	9.	'lung disease'/exp
#	10.	'heart disease'/exp
#	11.	'cor pulmonale'/exp
#	12.	'congestive heart failure'/exp
#	13.	(neoplasm* or cancer* or carcinoma* or tumour* or adenocarcinoma* or leukemi* or leukaemi* or lymphoma* or tumor* or tumor* or malignan*):ti,ab
#	14.	(neoplasm* or cancer* or carcinoma* or tumour* or adenocarcinoma* or leukemi* or leukaemi* or lymphoma* or tumor* or tumor* or malignan*)/mj
#	15.	(neutropeni* or neutropaeni*):ti,ab
#	16.	(neutropeni* or neutropaeni*)/mj
#	17.	RADIOTHERAPY/exp
#	18.	(radioth* or radiat* or irradiat* or radiochemo* or chemotherapy*):ti,ab
#	19.	(radioth* or radiat* or irradiat* or radiochemo* or chemotherapy*)/mj
#	20.	(('bone marrow' transplant*4) or ('bone-marrow' NEAR transplant*))
#	21.	advanced or terminal*6 or progressi*6 or end-stage or endstage or 'end stage' (disease or illness)
#	22.	FATIGUE/exp

(*Continued*)

#	23.	(Fatigue or 'cancer-related fatigue' or 'cancer related fatigue'):ab,py
#	24.	'FATIGUE':de
#	25.	tired* or weary or weariness or exhaustion or exhausted or lackluster or (asteni* or asthenia*) and syndrome
#	26.	loss OR lost OR lack*2 AND (energy OR vigour OR vigor)
#	27.	apathy or apathetic or lassitude or lethargy* or (feeling (drained or sleepy or sluggish or weak*3))
#	28.	palliati* or hospice or 'end of life'
#	29.	#1 - #12/OR
#	30.	#13 - #21 /OR
#	31.	#22- #28 /OR
#	32.	#29 and #30 and #31
#	33.	(dexamphetamine or dextroamphetamine):ti,ab
#	34.	(methylphenidate or threomethylphenidate or d-threo-methylphenidate):ti,ab
#	35.	Donepezil:ti,ab
#	36.	amantadine:ti,ab
#	37.	Carnitine or l-carnitine:ti,ab
#	38.	Pemoline:ti,ab
#	39.	Modafinil:ti,ab
#	40.	Paroxetine:ti,ab
#	41.	(testosteronecypionate or androgen):ti,ab
#	42.	(acetylsalicylic acid or aspirin):ti,ab
#	43.	fluoxetin:ti,ab
#	44.	Citalopram:ti,ab
#	45.	(glucocorticoid or steroid or steroids or dexamethason or dexamethasone or methylprednisolone or corticosteroid or corticosteroids):ti,ab
#	46.	Bupropion:ti,ab

(*Continued*)

#	47.	('anti depressant agents' or 'anti depressive agents' or 'Selective serotonin reuptake inhibitors'):ti,ab
#	48.	#33 - #47 / OR
#	49.	#32 and #48
#	50.	controll*:ti,ab
#	51.	factorial:ti,ab
#	52.	(crossover or 'cross over' or 'cross-over'):ti,ab
#	53.	placebo:ti,ab
#	54.	'double blind':ti,ab
#	55.	'single blind':ti,ab
#	56.	assign*:ti,ab
#	57.	allocate*:ti,ab
#	58.	'crossover procedure'
#	59.	'DOUBLE-BLIND PROCEDURE'
#	60.	'RANDOMIZED CONTROLLED TRIAL'
#	61.	'SINGLE BLIND PROCEDURE'
#	62.	'evaluation study'
#	63.	'prospective study'
#	64.	'comparative study'
#	65.	'animal experiment' OR 'nonhuman experiment'
#	66.	#50-#64/OR
#	67.	#49 AND #66 AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND [embase]/lim
#	68.	#67 NOT #65

Appendix 4. PsycINFO search strategy

Subject search combined with the recommended study design filter was run on 28 April 2014 (using OVID).

#	1.	exp Neoplasms/
#	2.	(cancer* or malignan*).mp.
#	3.	multiple sclerosis.af.
#	4.	amyotrophic lateral sclerosis.af.
#	5.	(sclerosis adj4 (amyotroph* or multiple)).mp.
#	6.	exp acquired immune deficiency syndrome/
#	7.	aids related complex.mp.
#	8.	exp Human immunodeficiency virus/
#	9.	(HIV or AIDS).mp.
#	10.	bone marrow transplantation.mp.
#	11.	radiotherapy.mp.
#	12.	(cancinoma* or tumour* or adenocarcinoma* or leukeni* or leukaemi* or lymphoma* or tumor*).mp
#	13.	(neutropeni$ or neutropaeni$).mp.
#	14.	(radioth* or radiat* or irradiat* or radiochemo* or chemotherap*).mp
#	15.	Lung Disorders.mp.
#	16.	heart disorders.mp.
#	17.	congestive heart failure.mp.
#	18.	cor pulmonale.mp.
#	19.	cancer fatigue.mp.
#	20.	(cancer-related fatigue or cancer related fatigue).mp.
#	21.	exp FATIGUE/
#	22.	(tired$ or weary or weariness or exhaustion or exhausted or lacklustred or ((astheni$ or asthenia$) and syndrome)).mp
#	23.	((lack$ or loss or lost) adj2 (energy or vigour or vigor)).mp

(*Continued*)

#	24.	(apathy or apathetic or lassitude or letharg$ or (feeling adj3 (drained or sleepy or sluggish or weak$))).mp
#	25.	((advanced or terminal* or progressi* or end-stage or endstage or "endstage") adj6 (disease or illness)).mp
#	26.	palliati*.mp.
#	27.	(dexamphetamine or dextroamphetamine).mp.
#	28.	(methylphenidate or threo$methylphenidate or d-threo-methylphenidate).mp
#	29.	donepezil.mp.
#	30.	amantadine.mp.
#	31.	(Carnitine or L-carntine).mp.
#	32.	pemoline.mp.
#	33.	modafinil.mp.
#	34.	paroxetine.mp.
#	35.	(testosteronecypionate or androgen).mp.
#	36.	(acetylsalicylic acid or aspirin).mp.
#	37.	fluoxetin.mp
#	38.	citalopram.mp
#	39.	(glucocorticoid or steroid or steroids or dexamethason or dexamethasone or methylprednisolone or corticosteroid or corticosteroids).mp
#	40.	bupropion.mp.
#	41.	(anti depressant agents or anti depressive agents or Selective serotonin reuptake inhibitors).mp
#	42.	random*.ti,ab.
#	43.	factorial*.ti,ab.
#	44.	(crossover* or cross over* or cross-over*).ti,ab.
#	45.	placebo*.ti,ab.
#	46.	(doubl* adj blind*).ti,ab.

(*Continued*)

#	47.	(singl* adj blind*).ti,ab.
#	48.	randomized controlled trial.mp.
#	49.	assign*.ti,ab.
#	50.	allocat*.ti,ab.
#	51.	evaluation study*.ti,ab.
#	52.	prospective study*.ti,ab.
#	53.	comparative study*.ti,ab.
#	54.	(animal* or nonhuman* or animal experiment*).ti,ab.
#	55.	#1-#18/OR
#	56.	#19-26/OR
#	57.	#27-41/OR
#	58.	#42-53/OR
#	59.	#55 AND #56 AND #57 AND #58
#	60.	#59 NOT #54

WHAT'S NEW

Last assessed as up-to-date: 28 April 2014.

Date	Event	Description
27 May 2015	Amended	Contact details amended.

HISTORY

Protocol first published: Issue 4, 2007

Review first published: Issue 11, 2010

Date	Event	Description
19 January 2015	New citation required and conclusions have changed	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). The updated search strategy identified 20 additional studies suitable for inclusion
6 June 2014	New search has been performed	We used an updated search strategy and included 'Risk of bias' tables in this update
5 November 2010	Amended	Minor amendment to title - text was italicised on publication and update of contact details
7 November 2008	Amended	Further RevMan 5 conversion changes.
13 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

MM, MC, LR: guarantors of the review, conceived the review, designed the search strategy, responsible for write up of the protocol and review.

MM and MC: responsible for the update of the review.

MM, MC: extracted data from papers and entered data into RevMan.

MM, MC, HC, LR: organised retrieval of papers, undertook searches and screened retrieved papers against inclusion criteria.

OM, PS: were involved in the original development of the search strategy (first published in Issue 3, 2007) and the appraisal of papers relating to pharmacological management of cancer-related fatigue, and approved the final manuscript.

LR, VP: were involved in the original development of the search strategy (first published in Issue 4, 2007) and the appraisal of papers relating to pharmacological treatments for fatigue associated with palliative care, and approved the final manuscript.

DECLARATIONS OF INTEREST

Martin Mücke has no relevant conflicts of interest to declare.

Mochamat has no relevant conflicts of interest to declare.

Henning Cuhls has no relevant conflicts of interest to declare.

Vera Peuckmann-Post has no relevant conflicts of interest to declare.

Ollie Minton has no relevant conflicts of interest to declare.

Patrick Stone has no relevant conflicts of interest to declare.

Lukas Radbruch has no relevant conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- Department of Palliative Medicine, University Hospital of Bonn, Bonn, Germany.
- Department of General Medicine and Family Medicine, University Hospital of Bonn, Bonn, Germany.

External sources

- Department of Anesthesiology and Intensive Care, University of Diponegoro/Kariadi Hospital Semarang, Indonesia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We modified the search strategy to match the inclusion criteria better and to prevent technical error. NNTB and NNTH calculations were not possible, as the information required to calculate these indicators was not included in the papers.

This updated review also incorporates another Cochrane review, 'Drug therapy for the management of cancer-related fatigue' (Minton 2010).

INDEX TERMS

Medical Subject Headings (MeSH)

*Palliative Care; Amantadine [therapeutic use]; Benzhydryl Compounds [therapeutic use]; Carnitine [therapeutic use]; Central Nervous System Stimulants [therapeutic use]; Chronic Disease; Fatigue [*drug therapy; etiology]; Kidney Failure, Chronic [complications]; Methylphenidate [therapeutic use]; Multiple Sclerosis [complications]; Neoplasms [complications]; Pemoline [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans