

Drug therapy for the management of cancer related fatigue (Review)

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ABSTRACT

Background

Cancer related fatigue (CRF) is common, under-recognised and difficult to treat. There have been trials looking at drug interventions to improve CRF but results have been conflicting depending on the population studied and outcome measures used. No previous reviews of this topic have been exhaustive or have synthesised all available data.

Objectives

To assess the efficacy of drugs for the management of CRF.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (1st Quarter 2007), MEDLINE (1966 to March 2007) and a selection of cancer journals. We searched references of identified articles and contacted authors to obtain unreported data.

Selection criteria

Trials were included in the review if they 1) assessed drug therapy for the management of CRF compared to placebo, usual care or a non-pharmacological intervention in 2) randomised controlled trials (RCT) of 3) adult patients with a clinical diagnosis of cancer.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. Meta-analyses were performed on different drug classes using continuous variable data.

Main results

Forty-five trials met the inclusion criteria. Only 27 of these trials involving 6746 participants were judged to have used a sufficiently robust measure of fatigue and thus were deemed suitable for detailed analysis. The drugs were analysed by class (psychostimulants; haemopoetic growth factors; antidepressants and progestational steroids). Methylphenidate showed a small but significant improvement in fatigue over placebo ($Z = 2.40$; $P = 0.02$). Erythropoietin showed a small but significant improvement in fatigue (for anaemic patients receiving chemotherapy) compared to placebo ($Z = 2.67$; $P = 0.008$). Darbopoietin also demonstrated a smaller but significant improvement in fatigue over placebo ($Z = 1.96$; $P = 0.05$). Paroxetine and progestational steroids demonstrated no superiority over placebo in treating CRF. There was a very high degree of statistical and clinical heterogeneity in the trials and the reasons for this are discussed. It was not possible to determine optimum doses as a result of this review.

Authors' conclusions

Erythropoietin and darbopoietin (for anaemic patients on chemotherapy) and psychostimulant trials provide evidence for improvement in CRF at a clinically meaningful level. There are no data to support the use of paroxetine or progestational steroids for the treatment of CRF. The obvious candidate drug for use in a large scale RCT is methylphenidate to confirm the preliminary results from this review.

PLAIN LANGUAGE SUMMARY

Drug therapy for the management of cancer related fatigue

Fatigue associated with cancer is a significant problem. It can occur because of side effects of treatment or because of the disease itself. It can have a significant impact on a person's ability to function. The causes of fatigue are not fully understood and so it is very difficult to treat appropriately. This review has examined drug treatment for fatigue as it represents one of the ways this problem can be tackled. The review authors looked at trials in all types of cancer and at all stages of treatment. Forty five trials met the inclusion criteria but only 27 (6746 participants) were deemed suitable for detailed analysis as they explored fatigue in sufficient detail. They found mixed results with some drugs showing an effect on fatigue - most notably drugs that stimulate red blood cell production and also drugs that improve levels of concentration. Methylphenidate, a stimulant drug that improves concentration, is effective for the management of cancer related fatigue but the small samples used in the available studies mean more research is needed to confirm its role. Erythropoietin and darbopoetin, drugs that improve anaemia, are effective in the management of cancer related fatigue in patients who are anaemic as a result of chemotherapy. These drugs are not without side effects and they should be used under expert supervision and their effect closely monitored.

BACKGROUND

Cancer-related Fatigue (CRF) is one of the most common symptoms experienced by cancer patients (Morrow 2002). It can be problematic at the time of diagnosis, during and after treatment and in patients with advanced disease (Morrow 2002). Most studies have reported prevalence figures in excess of 60% (Stone 2002). The subjective sensations attributed to CRF are characterised by a pervasive and persistent sense of tiredness not relieved by sleep or rest. This can adversely affect a person's emotional, physical and mental well-being (Morrow 2005). CRF can also affect patients' abilities to function in terms of their usual social activities, and their ability to carry on with their normal working lives. Fatigue is not only a problem in cancer patients.

Fatigue is a recognised condition within the general population (Bultmann 2002; Lawrie 1997). It is a feature of other chronic illnesses such as multiple sclerosis (Krupp 1988) and chronic obstructive pulmonary disease (Trendall 2001). It can also be a separate diagnosis in its own right in the case of chronic fatigue syndrome (CFS) (Sharpe 1992).

While CRF in some groups may have similarities with CFS there are important differences in particular in relation to concerns about its relationship to disease progression and toxicity of treatment (Servaes 2002).

It has therefore been suggested that CRF should be considered to represent a diagnostic entity in its own right (Cella 2001; Sadler 2002). CRF is a complex condition with many physical and psychological components potentially predisposing to it. These same factors may also exacerbate and perpetuate established CRF. The complex nature of the condition makes it difficult to identify a clear underlying mechanism. Indeed, it is more than likely that no such single mechanism exists (Andrews 2004). Nevertheless, CRF is a disabling and distressing condition which is often under-recognised by cancer physicians (Stone 2000).

Previous reviews (Mock 2004; Morrow 2005; Stone 2002) and clinical guidelines (NCCN 2006) have attempted to summarise existing evidence for both pharmacological and non-pharmacological treatments for CRF. The main focus of one of these reviews (Mock 2004) was on non-pharmacological measures where there have been a number of studies investigating exercise interventions and the role of support groups. The review authors concluded that:

- exercise had a direct effect on reducing fatigue;
- there was some evidence that correction of anaemia improved quality of life and energy.

Another review group focused their review on pharmacological interventions (Morrow 2005). They considered the evidence in support of a number of treatment options:

- *Antidepressants*: on the basis of one study found by this review group (Breitbart 1995) anti-depressants were suggested as a possible treatment for fatigue associated with advanced disease or uncontrolled symptoms, or both. However, the review authors did not recommend the routine use of anti-depressants in the absence of concurrent depression. This opinion was based in part on the results of a large randomised controlled trial (RCT) conducted with paroxetine which improved mood but found no effect on fatigue in ambulatory cancer patients (Morrow 2003);
- *Erythropoietin*: this was recommended because it has been studied as a treatment for anaemia in cancer patients receiving chemotherapy and some studies reported improvements in fatigue in such patients with the correction of anaemia (Demetri 1998; Glaspy 1997).
- *Corticosteroids*: Morrow 2005 concluded that corticosteroids may produce modest improvements in quality of life including improvement in fatigue in patients with metastatic cancer but that they are limited by the side effects (Bruera 1985).

The National Comprehensive Cancer Network's (NCCN 2006) clinical guidelines also provide further options for CRF management. These suggest initially treating any underlying reversible causes of fatigue (e.g. anaemia, poor nutrition or depression) and attending to general supportive measures and psychosocial support. The most common specific recommendation for an intervention targeted at fatigue is the use of an exercise programme which is the subject of a separate Cochrane review (Cramp 2006). The main drug treatment the NCCN guidelines recommend is the use of methylphenidate in selected cases of cancer-related fatigue after other non-pharmacological approaches have been tried. However, most of the evidence for this suggestion is from a trial in HIV patients (Breitbart 2001). A recent RCT in cancer patients failed to find any significant superiority over placebo (Bruera 2006).

The previous literature reviews have made suggestions for the use of different drugs based on varying amounts and quality of evidence. No previous review has collated all of the relevant literature concerning pharmacological interventions for cancer-related fatigue in a systematic way. A Cochrane systematic review is therefore needed in order to evaluate all the available evidence for the effectiveness of pharmacological interventions for CRF. Treatment of fatigue in palliative care will be the subject of another Cochrane review prepared by Radbruch et al. (Radbruch 2007). Close collaboration between the two review groups will ensure a maximum coverage and minimum overlap of the two reviews.

OBJECTIVES

- 1) To evaluate the effectiveness and adverse events related to drugs used in the treatment of CRF at all stages of cancer treatment (including palliative care) compared with standard care or non-pharmacological interventions.
- 2) To establish optimal dose and duration of drug therapy(s).

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Only RCTs of a particular drug therapy were included. Studies that were single blind or open label were allowed.

Types of participants

The review included studies that evaluated drug therapy for CRF in adults and with a clinical diagnosis of cancer. We included studies which had recruited participants at any point of the cancer treatment spectrum, including those undergoing curative treatment, those with advanced disease receiving palliative care, and disease-free survivors

Types of intervention

Included studies compared drug therapy with placebo, standard care or an alternative non-pharmacological treatment for CRF, for example, including nutritional status or mood. Only those studies that investigated drug interventions to improve fatigue as a prior identified aim were included.

Studies comparing different types of cancer-modifying treatment (e.g. chemotherapy regimens or radiotherapy) and their effect on prognosis and quality of life were excluded.

Types of outcome measures

- 1) Differences in fatigue between intervention group and controls using patient self-reported measures or validated self-assessment tools, or both.
- 2) Adverse events

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We used the following search strategy for this review and used text and keyword and MESH terms in each database, in addition to an RCT filter.

Search strategy format for CENTRAL:

- #1 Exp NEOPLASMS
- #2 BONE MARROW TRANSPLANTATION
- #3 neoplasm* or cancer* or carcinoma* or tumour* or adenocarcinoma* or leukeni* or leukaemi* or lymphoma* or tumor* or malignan* (title, abstract & keywords)
- #4 neutropeni* or neutropaeni* (title, abstract & keywords)
- #5 Exp RADIOTHERAPY
- #6 radioth* or radiat* or irradiat* or radiochemo* or chemotherap* (title, abstract & keywords)
- #7 "bone marrow" NEAR transplant*
- #8 "bone-marow" NEAR transplant*
- #9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
- #10 FATIGUE (drug therapy)
- #11 fatigue* (title, abstract & keywords)
- #12 tired* or weary or weariness or exhaustion or exhausted or lacklustre or astheni* or asthenia*
- #13 lack* NEAR/2 energy
- #14 lack* NEAR/2 vigour
- #15 lack* NEAR/2 vigor
- #16 loss NEAR/2 energy
- #17 loss NEAR/2 vigour
- #18 loss NEAR/2 vigor
- #19 lost NEAR/2 energy
- #20 lost NEAR/2 vigour
- #21 lost NEAR/2 vigor

#22 apathy or apathetic or lassitude or letharg* or “feeling drained” or “feeling sleepy” or “feeling sluggish” or “feeling weak”

#23 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22

#24 #9 AND #23

This strategy was adapted for the following databases - for the different terms that are used in these please refer to Additional Table 01; Table 02; Table 03.

The following databases were used to obtain relevant studies for this review. There was no language restriction.

- The PaPaS group specialized register (March 2007)
- The Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 1, 2007)
- MEDLINE (1966 to week 1 March 2007)
- EMBASE (1980 to week 1 March 2007)
- CINAHL (1982 to week 1 March 2007)
- Dissertation Abstracts International (1861 to March 2007)
- Meta register of controlled trials (mRCT- to March 2007)

We searched the following journals:

British Journal of Cancer (1948 to March 2007), *Journal of Clinical Oncology* (1983 to March 2007), *Journal of Pain and Symptom Management* (1986 to March 2007) and *Palliative Medicine* (1988 to March 2007).

We checked reference lists of all articles obtained for additional studies. We also contacted experts in the field of CRF in order to identify any research that may not have been published. We checked published abstracts through searches of conference proceedings and we obtained full trial data if possible. We attempted to communicate with the study authors to secure information not presented in the papers or conference abstracts if not subsequently published as a full article.

METHODS OF THE REVIEW

Study selection

One review author (OM) screened the eligibility of retrieved articles from the title and abstract. If there was insufficient information for assessment, the full article was scrutinised by two review authors (OM and PS). Two review authors (OM and PS) independently assessed all RCTs. For a trial to be included it must have included fatigue as part of a primary outcome measure and one treatment arm must have been a drug therapy. Disagreement was resolved by consensus with other members of the review group (MS, AR, MH).

Quality assessment

Each trial was assessed for potential bias on the basis of allocation and concealment as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2006). A - adequate;

B - unclear; C - clearly inadequate; D - allocation concealment not used. We also assessed the methodological quality of each study using the three item Oxford Quality Scale (Jadad 1996).

(1) Randomisation

Was the study described as randomised? (1 = yes; 0 = no)

Was the method of randomisation well described and appropriate? (1 = yes; 0 = no); deduct one point if inappropriate

(2) Blinding

Was the study described as double-blind? (1 = yes; 0 = no)

Was the double blinding well described and appropriate? (1 = yes; 0 = no); deduct one point if inappropriate.

(3) Description of study withdrawals and dropouts

Were withdrawals and dropouts described? (1 = yes; 0 = no)

All studies also had an assessment of efforts made to match groups in terms of prognostic factors. Study quality was further assessed based on intention-to-treat analysis, standardisation and blinding of outcome assessment and percentage loss to follow up. This information was used to determine an overall risk of bias from a study - those studies felt to be at an unacceptably high risk of bias were excluded from the review. Study quality was not scored on an additive basis. Impact of study quality was determined by sensitivity analysis.

Data management

Data was organised using RevMan (version 4.2.10). Data extraction forms were developed *a priori* and included information regarding methods, participant details, dose and frequency of drug administration, attrition and outcome measures. Two review authors (OM and PS) independently extracted data and disagreements were resolved by consensus with the other members of the group (MH, AR, MS).

Heterogeneity assessment

Homogeneity of the results of the various endpoints of interest was explored using I squared (I^2) values. Heterogeneity in the results was seen as a result of many potential factors (postulated *a priori*) and efforts were made to identify sub groups for sensitivity analysis. Meta-analysis was undertaken. As a result of high statistical heterogeneity we used a random-effects model for analysis.

Potential sources of heterogeneity:

- 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.

Statistical considerations

We evaluated quantitative outcomes for dichotomous and continuous data using RevMan 4.2.10 and the random-effects models. Analysis based on intention to treat was used. Outcomes of interest were compared between treatment and control arms using odds ratios (OR) with 95% confidence intervals (CI).

The Number Needed to Treat (NNT) was not calculated because of the continuous outcome data found. A judgement on how to combine outcome measures was made depending on how information was collected. In trials where the same scale was used the weighted mean difference (WMD) was calculated to provide an effect size of clinical significance. In other trials which had different outcome measures, we calculated the standardised mean difference (SMD).

DESCRIPTION OF STUDIES

Initial searching found the following number of possible trials: (CENTRAL 817, MEDLINE 2379, EMBASE 2285). OM and PS independently screened short listed studies (116) and found 45 studies that met the criteria for inclusion. This final list was agreed by all review authors. Eighteen of these studies only used a single item for the measurement of fatigue and while they met the inclusion criteria they were not deemed robust enough for any more detailed analysis. This was decided after all the potential studies had been identified. Therefore there are 27 trials included for full analysis; 18 additional trials meeting the inclusion criteria were identified but were not analysed. Seven trial were excluded (*see* 'characteristics of excluded studies' table).

Included studies

Twenty-seven trials were analysed in more detail generating data on N = 6746 participants who had a drug intervention for CRF. This figure excludes the trials deemed unsuitable for more detailed analysis - eighteen trials with a total of N = 3827 participants.

We divided the trials by classes of drugs used for the treatment of CRF. Those groups which contained more than one study were included in subsequent meta-analyses. This yielded four separate classes of drugs and two trials in their own separate categories.

Psychostimulants

Bruera 2006 and Fleishman 2005 both used methylphenidate. Two trials with N = 264 participants in total. The Bruera 2006 trial studied participants off active treatment of any tumour type. Participants were blinded for seven days only followed by a non-randomised open label phase (results not included). The Fleishman 2005 trial studied participants on chemotherapy (any tumour type) and had eight weeks of follow up (comparison 05 01).

Haemopoetic growth factors

The majority of these trials were in the haemopoetic growth factors class. All trials examined the effect of these drugs on haemoglobin concentrations and their subsequent change in fatigue scores. All

trials recruited anaemic cancer patients (Haemoglobin <12 g/dl). This group was split into erythropoietin - thirteen trials N = 3735 participants in total (Bamias 2003; Boogaerts 2003; Chang 2005; Glossmann 2003; Iconomou 2003; Leyland-Jones 2005; Littlewood 2001; O'Shaughnessy 2005; Osterborg 2002; Savonije 2005; Wilkinson 2006; Witzig 2005; Wright 2007) and darbopoetin - four trials N = 1650 participants in total (Hedenus 2003; Kotasek 2003; Smith 2003; Vansteenkiste 2002). Darbopoetin is a synthetic derivative of erythropoietin with a similar but longer duration of action.

The trials varied in design with the majority of the erythropoietin trials being open label while the darbopoetin trials were all placebo controlled. This was not related to publication date. All trials had a minimum of 12 weeks follow up with some of up to 18 weeks. Most trials (11/13) were conducted on patients receiving chemotherapy. There was considerable variation in the dose and frequency used and this is given in more detail in the 'characteristics of included studies' table.

The groups were analysed separately and together in subsequent meta-analyses (comparison 01 01; 02 01, 06 01).

Anti-depressants

Morrow 2003 and Roscoe 2005 used paroxetine (a selective serotonin uptake inhibitor) during eight weeks of chemotherapy treatment. Two trials N = 645 participants in total. The Morrow 2003 study was a multi-centre trial examining all tumour types. The Roscoe study was a single centre trial examining breast cancer patients only (comparison 04 01).

Progestational steroids

Bruera 1998; De Conno 1998; Simons 1996 and Westman 1999 used megestrol acetate or medroxyprogesterone acetate. Four trials with N = 587 participants in total. All were placebo controlled. Bruera 1998 was a crossover study. The others were double blind parallel design. All trials studied any tumour type and all participants were off active treatment. Follow-up varied from one to twelve weeks. The trials studied all had a Oxford Quality Score of four (comparison 03 01).

Single studies

Diel 2004 used ibandronate for bone pain and reduction in bone morbidity and measured associated changes in quality of life on breast cancer participants. This was a single trial with N = 466 participants. This study used four-weekly treatments and had up to ninety-six weeks of follow up.

Monk 2006 examined etanercept (a tumour necrosis factor blocker) and its effect on CRF. This was a single trial with N = 12 participants. This trial used etanercept during docetaxel chemotherapy (for any tumour type) for 18 weeks (six cycles).

Included studies not analysed further

There were 18 included studies that were not analysed further; total N = 3827 participants (Abels 1996; Agteresch 2000;

Bruera 1990; Bruera 2003; Capuron 2002; Case 1993; Dagnelie 2003; Dammacco 2001; Della 1989; Downer 1993; Fisch 2003; Granetto 2003; Henry 1995; Inoue 2003; Moertel 1974; Popiela 1989; Semiglazov 2006; Thatcher 1999). These studies were all excluded from more detailed analysis as they either used a Visual analogue scale (VAS) to measure fatigue or the measurement tool used had only one item to measure fatigue - *See* 'characteristics of included studies' table. It was felt that a single item on fatigue was an inadequate assessment of this complex symptom and that including studies that only had a single item fatigue measure would introduce an unacceptable outcome bias into our review. In addition this group of trials used heterogeneous outcome measures such as levels of physical function or well-being. While they might be regarded as a subjective measure of fatigue and so meet our inclusion criteria we felt that they did not provide robust enough evidence for full inclusion in our analysis.

Excluded studies

There were seven excluded trials in this review. Bruera 1985 was excluded as they measured activity with no subjective measure of fatigue included in the analysis. The two trials by Glaspay *et al* (Glaspay 2003; Glaspay 2006) and Waltzman 2005 were excluded as they had active control arms. All three trials were a head to head comparison between doses of erythropoietin and darbopoietin. The other three excluded trials (Glimelius 1998; Johansson 2001; Steensma 2006) all studied varying doses of erythropoietin but did not include a usual care or placebo arm - *see* 'characteristics of excluded studies' table.

METHODOLOGICAL QUALITY

The quality of the included studies was assessed where possible in terms of the adequacy of concealment of allocation. This was done using the criteria defined in The Cochrane Handbook (Higgins 2006) where grade A is adequate concealment; grade B is uncertain allocation concealment; grade C is clearly inadequate concealment, grade D - not used). The grade given is shown in the 'characteristics of included studies' table and in the Forest plots.

The studies are grouped below by the score on the Oxford Quality Scale for quality assessment of RCTs (Jadad 1996). There are an increasing number of quality assessment tools but currently this is the one used by our review authors. It is scored zero to five with five being the highest score indicating the best quality trials.

Oxford Quality Scale Score 5 - Roscoe 2005; Vansteenkiste 2002.

Oxford Quality Scale Score 4 - Bruera 2006; Hedenus 2003; Kotasek 2003; Leyland-Jones 2005; Littlewood 2001; Morrow 2003; O'Shaughnessy 2005; Osterborg 2002; Simons 1996; Westman 1999; Wright 2007.

Oxford Quality Scale Score 3 - Bruera 1998; De Conno 1998; Diel 2004; Fleishman 2005; Savonije 2005; Smith 2003; Wilkinson 2006; Witzig 2005.

Oxford Quality Scale Score 2 - Bamias 2003; Boogaerts 2003; Chang 2005; Iconomou 2003; Glossmann 2003; Monk 2006.

The average score for the erythropoietin studies is three due to the large number of open label trials.

The darbopoietin studies have an average of four (three studies all double blinded).

The other studies have an amalgamated average of four indicating reasonable quality overall but disguising some wide variation in quality with scores ranging from two to five.

The reasons for lower scores were due to inadequate reporting of the methods used for randomisation and blinding. The Oxford Quality Scale is prescriptive in its application and does not account for the complexity of many of the trials studied. It does, however, highlight the lack of adherence to accepted reporting guidelines (Consort 2007).

RESULTS

Methylphenidate

Two studies looking at the use of methylphenidate were combined in a random effects model $N = 264$ (Bruera 2006; Fleishman 2005 - comparison 05 01). The studies are homogeneous with $I^2 = 0\%$. This is despite differences in follow up. The overall effect Z score = 2.4 ($P = 0.02$), SMD -0.30, 95% CI -0.54 to -0.05.

This is evidence of a significant effect on treating fatigue with methylphenidate over placebo for the treatment of CRF.

Haemopoetic growth factors

This is the largest group of studies and they will be sub-divided into erythropoietin and darbopoietin studies. Unfortunately due to the lack of consistency in reporting these trials much of the necessary data for meta-analysis were missing. The studies where it was not possible to obtain the relevant data were:

- Bamias 2003; Leyland-Jones 2005; Wilkinson 2006 (Total $N = 1265$).

Erythropoietin studies

Ten studies were combined in the erythropoietin analysis $N = 3735$. There were five open label studies (Boogaerts 2003; Chang 2005; Glossmann 2003; Iconomou 2003; Savonije 2005; comparison 01 01 and subcategory). There were five placebo controlled studies (Littlewood 2001; O'Shaughnessy 2005; Osterborg 2002; Witzig 2005; Wright 2007; comparison 01 01 and subcategory). Due to the difference in quality a sensitivity analysis was also performed.

Combining the ten trials in a random effects model showed a low degree of heterogeneity $I^2 = 5\%$. There was no clear difference in heterogeneity in sensitivity analysis when variation in doses was accounted for. Trials used doses from 3000 to 40,000 units a week and different dosing schedules with some trials using a three times a

week dosing and others giving a weekly dose. Tumour type studied also did not affect heterogeneity.

When the five placebo controlled trials (N = 1276) were combined in a subcategory there was homogeneity $I^2 = 0\%$. This would suggest the heterogeneity was due to study quality and lack of blinding in allocation. The overall effect Z score = 5.05 (P < 0.00001), SMD -0.31, 95% CI -0.42 to -0.19.

When the five open label studies (N = 2459) were combined in a subcategory there was a homogeneity $I^2 = 0\%$. The overall Z score = 7.15 (P < 0.0001), SMD -0.45, 95% CI -0.57 to -0.15.

For the ten trials the overall effect Z score = 8.32 (P < 0.001), SMD -0.30, 95% CI -0.46 to -0.29.

All combinations showed evidence of an effect of erythropoietin over standard care or placebo for the treatment of CRF.

Darbopoetin studies

Four trials were combined in a random effects model N = 1650; (Hedenus 2003; Kotasek 2003; Smith 2003; Vansteenkiste 2002; comparison 02 01). All were placebo controlled trials. The trials were homogenous $I^2 = 0\%$. One trial investigated patients with lymphoproliferative malignancies only (Hedenus 2003), one lung tumour patients (Vansteenkiste 2002) and one any tumour type (Kotasek 2003). The other included trial (Smith 2003) was conducted on cancer patients not on any chemotherapy. The four trials used different doses used which varied from 2.25 µg/kg to 15 µg/kg three times weekly. Only a combined mean effect has been used in the meta-analysis to avoid duplication.

The overall effect Z score = 1.45 (P = 0.05), SMD -0.13, 95% CI -0.27 to 0.00. This indicated that there is a small but statistically significant difference between darbopoetin and placebo for the treatment of CRF.

Combined Analysis

As darbopoetin is a derivative of erythropoietin and therefore a nearly identical drug with a similar mechanism of action we felt it was appropriate to combine the two groups in a combined analysis of all placebo controlled trials. The following trials were included in a random-effects model: Hedenus 2003; Kotasek 2003; Littlewood 2001; O'Shaughnessy 2005; Osterborg 2002; Vansteenkiste 2002; Witzig 2005; Wright 2007. Total N = 2801. The overall Z score = 5.08 (P < 0.001), SMD -0.23 95% CI -0.32 to -0.14. This indicated a small but consistent positive effect using either growth factor. It also suggested that the overall effect is increased with the addition of the darbopoetin trials which might be expected from the common mechanism of action. The erythropoietin studies which used the FACT F tool (functional assessment of cancer therapy - fatigue subscale) (Cella 2002) for fatigue measurement were combined in a random effects model but using weighted mean difference (WMD). The overall Z score = 6.13, SMD -4.29, 95% CI -5.04 to -2.60. This indicates that overall these trials may provide a clinically significant reduction in fatigue.

Paroxetine

Two studies N = 645 (Morrow 2003; Roscoe 2005; comparison 04 01) were combined in a random-effects meta-analysis. The studies were homogenous $I^2 = 0\%$. The test for overall effect - Z score was 1.17 (P = 0.24), SMD -0.08 95% CI -4.64 to 1.18.

This indicated no difference between paroxetine and placebo for the treatment of CRF.

Progestational steroids

Four studies N = 587 (Bruera 1998; De Conno 1998; Simons 1996; Westman 1999) were combined in a random-effects model (comparison 03 01).

The studies showed a high degree of heterogeneity ($I^2 = 98.8\%$). This may be explained by difference in dosing regime (from 160 milligrams to 320 milligrams once a day). The Simons study used medroxyprogesterone acetate while the others all used megestrol acetate. However, when this study was excluded the heterogeneity remains very high ($I^2 = 98\%$). There are other factors which may contribute. The duration of study varied widely from ten days (Bruera 1998) to 12 weeks (Simons 1996; Westman 1999).

Tumour type - apart from Bruera 1998 (only included gastrointestinal (GI) and lung tumours) any tumour was included in all the remaining studies.

Two studies allowed palliative chemotherapy or radiotherapy (Simons 1996; Westman 1999) this was in the minority of patients (10%) and matched in both treatment groups. The other two studies (Bruera 1998; De Conno 1998) did not allow any concomitant therapy.

The four studies were combined in a random-effects model as there was significant heterogeneity despite limited sensitivity analysis. The overall effect Z score is 0.78 (P = 0.44) SMD -0.49 95% CI -1.74 to 0.75. The effect of megestrol acetate alone is Z = 0.67 (P = 0.5) SMD -0.66, 95% CI -2.6 to 1.28. This indicated no difference between progestational steroids and placebo for the treatment of CRF.

Single Studies

As these are individual trials no synthesis of the data was possible.

The Ibandronate study N = 466 (Diel 2004) was a trial with long term follow up of nearly two years. It recruited participants with breast cancer only. The results showed that the ibandronate group had a statistically significant difference in fatigue scores at the 96 week outcome assessment. There was no clear dose response with different dosing schedules. All groups experienced increases in fatigue scores over the time of the study.

The other single study used etanercept in conjunction with docetaxel chemotherapy (Monk 2006). This was a trial on a very small number of participants (N = 12) but that studied all tumour types. It was a pilot study but with 'positive' results - the etanercept group showed a statistically significant reduction in fatigue compared to patients treated with docetaxel alone.

Adverse events

The majority of trials had minimal reported adverse events. The analysis for grouped adverse events (comparison 07 01) demonstrated some variation across the different drugs.

The haemopoetic growth factors had a pooled OR of 1.06, 95% CI 0.81 to 1.38 indicating a non statistically significant between group difference.

The progestational steroids had an OR of 0.8, 95% CI 0.4 to 1.51 indicating a non statistically significant between group difference. The methylphenidate studies had an OR of 2.7, 95% CI 0.91 to 7.96 indicating a non statistically significant between group difference.

The paroxetine studies had an OR of 1.71, 95% CI 0.53 to 5.48 indicating a non statistically significant between group difference.

Some of the erythropoietin trials highlighted ongoing safety concerns. Leyland-Jones 2005 was primarily a survival study. It was designed to compare mortality rates between groups not receiving chemotherapy. The erythropoietin group showed increased mortality at four months and the trial was terminated prematurely. It was felt that there may have been an increased rate of fatal thrombo-embolic events in the erythropoietin arm over placebo (1.1% versus 0.2% at four months). The rate of serious adverse events was 5% in the erythropoietin arm versus 2% with placebo. This study was designed to keep haemoglobin at 12 to 14 g/100 ml. Current prescribing guidelines state that a haemoglobin of 12 g/100 ml should not be exceeded (BNF 53).

Wright 2007 was also prematurely terminated as a result of safety concerns. The data monitoring committee suspended the trial after it was noted that the median survival in the epoetin group was worse than placebo. The cause for this discrepancy was unclear and may not have been solely due to adverse events related to the medication. Nevertheless current prescribing guidelines should be adhered to and a lower maintenance haemoglobin aimed for.

A more comprehensive and quantitative assessment of all adverse events of these agents is made in another Cochrane review (Bohlius 2007).

DISCUSSION

The aim of this Cochrane review was to look at the overall effect of drugs on CRF. The study has yielded a large number of trials of varying size and quality. It has also demonstrated the wide range of tools used for fatigue or quality of life measurement, or both. The large number of trials identified allowed for synthesis of data and the quantification of the clinical effect of the drugs used on CRF which previous narrative reviews have been unable to do.

The review was comprehensive as it was impracticable to specify in advance which drugs would be studied. The included RCTs incorporate four different drug classes where results could be combined and two separate single trials. Other drugs were identified

during the search strategy but none were examined within a RCT and so none of those trials are reported. However, some of these drugs are now being studied within a RCT. These trials are listed in the 'characteristics of ongoing studies' table. There are ongoing trials investigating the effects of modafanil (Morrow 2007); levocarnitine (Cruciani 2007); co-enzyme Q10 (Frizzell 2007); ginseng (Bauer 2007); adenosine triphosphate (Dagnelie 2007); sertraline (Stockler 2007) and donepezil (Bruera 2007). There are also three ongoing trials that will add to the data on methylphenidate (Hutson 2007; Roth 2007; Sood 2006) and one ongoing trial examining etanercept (Thomas 2007).

On viewing the current data some general comment about the trials underway are warranted before a more detailed discussion on individual analyses is given.

While the quality of some trials was mediocre on the scale used this may be due to lack of consistency in trial reporting and failure to adhere to CONSORT guidelines (Consort 2007). There is a high rate of attrition in some studies but this is due more to the population studied than reported adverse events. The rate of attrition was mainly due to disease progression and the complex nature of any concurrent treatment. This led to large withdrawals because of death or protocol violation. If this was not reported in the trial publication then the quality score given was lower. There are no between group differences in withdrawal rate for all drugs studied (see comparison 08 01). The heterogeneity of some of the trials may also have been due to a low signal:noise ratio. There were many factors such as disease progression and the unstable nature of the population which may have affected heterogeneity which it has not been possible to account for. However, for the erythropoietin trials heterogeneity was mainly due to differences in study design.

All trials demonstrated statistically non significance between group differences for important prognostic factors. This included a detailed description of stage and type of tumour and concurrent treatment (if any). If specific methods were required to match the randomised groups this was invariably achieved with stratification by tumour type and treatment. There were no exceptions to this.

There was some variation in the withdrawal rates but nearly all trials were analysed on an intention to treat basis. The exception to this was Boogaerts 2003 that used last observation carried forward (LOCF). The variations in the quality of trials and any impact in a sensitivity analysis will be commented on for each drug.

Methylphenidate

Two studies (Bruera 2006; Fleishman 2005) were combined. The SMD on analysis was positive with a small effect seen and narrow confidence interval. The two studies did differ in design and follow up but used the same outcome measure (FACT F) and so it is possible to obtain a WMD of -3.37. This translates as the value equal to the previously calculated minimal clinically significant difference on this scale (Cella 2002). This gives the result's clinical relevance - these drugs lead to an observable improvement

in fatigue. The current evidence supports the use of psychostimulants in the treatment of CRF. In addition there are two further trials being conducted with methylphenidate that may potentially increase the available evidence base (*see* 'characteristics of ongoing studies' table).

Erythropoietin

There are a number of studies included in the analysis. Ten studies were combined in total and demonstrated a positive effect. This persisted in a sensitivity analysis of placebo controlled trials although the CI was much narrower. It was not possible to generate a NNT as the data were continuous. A WMD was generated using a sub-analysis of studies using the FACT F and gave a score of 4.33. Again this value was above the minimal clinically significant difference. This would suggest that erythropoietin does provide a recognisable reduction in fatigue. This conclusion was limited to anaemic patients undergoing chemotherapy only. As there have been more recent safety concerns close monitoring of haemoglobin should also be instigated. This is especially important as previous multivariate regression (Jones 2004) has shown that haemoglobin only accounts for a small (approximately 20%) percentage of fatigue symptomatology. The authors also demonstrated that greater improvement was most likely to be seen at lower haemoglobin concentrations (8 to 10 g/100 ml). The improvement in fatigue may not necessarily be due to improvement in haemoglobin concentrations after a minimum level has been reached.

Darbopoetin

The four placebo controlled trials combined in a random-effects model showed superiority over placebo. Three of the trials (Hedenus 2003; Kotasek 2003; Smith 2003) had multiple dose treatment arms. The reporting of these trials only gave changes in fatigue score based either on dose of darbopoetin or haemoglobin change. Thus it was necessary to calculate the average response in order to undertake a meta-analysis. The authors were contacted to provide original trial data. The result seen is as expected as darbopoetin is a derivative of erythropoietin and has an almost identical mechanism of action. However, the WMD using the FACT F gave a score of -1.96 slightly below the minimal clinically significant difference. It is possible that further trials may strengthen this result but future trials need to focus on fatigue measurement with a simplified or fixed dosing regime to avoid the complex analyses from previous trials which has made data extraction so difficult.

Erythropoietin/darbopoetin

A further analysis was carried out combining all the placebo controlled trials. This demonstrated a positive result using a random-effects model. The effect size was increased when the epo/darbopoetin trials were combined over the epoetin trials alone. As we were interested in the mean effect of treatment on fatigue this data would seem to provide further evidence for their use in clinical practice. The review identified three head to head trials (Glaspy 2003; Glaspy 2006; Waltzman 2005) which suggested that neither treatment was inferior on the limited fatigue data provided.

However, it was not the aim of the review to demonstrate superiority of one treatment over another. In addition these studies were not primarily designed to look at quality of life changes for the two drugs. The combined WMD using all studies using the FACT F gave a score of 3.75 - above the minimal clinically significant difference on this scale. Data on transfusion requirements and haemoglobin changes for the two drugs can be found in another Cochrane review (Bohlius 2007).

Paroxetine

Two studies were combined (Morrow 2003; Roscoe 2005). These trials were conducted by the same group concurrently but were separate trials in their own right. The analysis fails to show any benefit of paroxetine for the treatment of CRF. There were many measures made of fatigue and mood within the trial but only the primary fatigue outcome was included in our analysis. The results of the trials demonstrate an improvement in mood with no associated improvement in fatigue. It is not clear, however, if this is a class effect related to all antidepressants. The use of antidepressants with different mechanisms of action may improve fatigue. Further trials may yet add more evidence. This is, however, an important negative result as many clinicians view the two symptoms as having a large overlap. While fatigue may be a symptom of a depressive illness this data reinforces our contention that cancer-related fatigue is an entity in its own right.

Progestational Steroids

Four studies (Bruera 1998; De Conno 1998; Simons 1996; Westman 1999) were combined. The analysis demonstrates no superiority over placebo for this class of drugs. While all these trials are older than other included trials they were of good quality and placebo controlled. There is no evidence to support their continued use for the treatment of fatigue in current practice. There is no requirement for additional trials as the analysis demonstrates a consistent negative effect.

Single Trials

There are two separate trials which were not combined.

Diel 2004 examined the use of ibandronate over a period of two years. The results indicate that there is limited evidence to support the use of ibandronate in the treatment of CRF over a long term follow-up. The effect is likely to be due to reduction in bone morbidity rather than directly improving fatigue *per se*. However, it is the only study to use a measure of fatigue over a long follow up period in patients with metastatic disease. The clinical significance of the results are unclear and further targeted trials are needed.

Monk 2006 examined the use of etanercept during chemotherapy. While the results are statistically significant the small numbers and poor design mean that further larger and better quality trials are needed to explore this effect. This trial was conducted with one type of chemotherapy only and the results cannot readily be extrapolated. There is very limited evidence to support its use currently outside of a trial setting. Future trials should be conducted

with larger numbers as the proof of concept has been achieved in this small trial.

Limitations

This review was focused on fatigue and does not make any comment on the overall quality of life (QOL) changes that may be seen with the use of these drugs. There is likely to be a relationship between improving fatigue and improving QOL. Indeed in many trials the two terms are used interchangeably. We have extracted data on fatigue changes only. During the review process if we felt that data did not provide a detailed measure of fatigue then the study was not analysed further.

We included trials that assessed outcomes using overall QOL in addition to pure fatigue scales. However, in many cases the trials were often published in ways that made extraction of the fatigue data impossible. Often only a limited comment was made on the effect on QOL with no quantitative data recorded if multiple outcome measures were included.

This was most often the case in the erythropoietin/darbopoietin trials where multiple measures of QOL were obtained but not published. This reaffirms the findings of a previous Cochrane review (Bohlius 2007) where quantifying QOL changes with these drugs was not included because of missing data. We have tried to include as much data in our analysis as possible by contacting authors to obtain data. This may have had the propensity to introduce bias into our study as this data has not been peer reviewed.

It is also possible that the difficulties in conducting these types of trials with any of these drugs may mean that trials have not been published at all. There is therefore the potential for a publication bias in this review. However, by contacting experts in this field we have attempted to reduce this bias as much as possible.

This review also demonstrated that there is still no consensus as to how QOL data should be presented. A single trial report will often not give useful data about QOL changes due to limited space for data reporting and trial complexity. It is hoped that this review will serve to highlight this weakness in trial reporting.

AUTHORS' CONCLUSIONS

Implications for practice

Two methylphenidate trials provided equivocal evidence for its use in a dose of 10 to 20 mg per day depending on response. Serious adverse effects were minimal but contra-indications to this drug should be reviewed before prescribing.

Erythropoietin and darbopoetin trials provided evidence that erythropoietin is effective in relieving CRF in anaemic patients undergoing chemotherapy. Current prescribing guidelines should be adhered to and safety concerns shared with patients to allow for informed decision making. It is not possible to recommend doses but this should be the minimum effective dose for the shortest duration.

Implications for research

This review highlighted the large number of outcome measures used to examine fatigue. It found major limitations in reporting of trials. Future trials in this area should focus on fatigue as a primary outcome using validated outcome measures.

Further large scale RCTs should be conducted using methylphenidate to further evaluate these preliminary results. Other candidate drugs needing further evaluation include darbopoetin; tumour necrosis factor blocking drugs and other classes of antidepressant drugs. Erythropoietin and darbopoetin studies could be conducted to examine their effect on anaemic cancer patients not receiving chemotherapy.

POTENTIAL CONFLICT OF INTEREST

Dr Stone previously received an unrestricted (£15k) educational grant from Orthobiotech (UK) in 2001 to undertake a small research project on erythrocyte function in patients with cancer.

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REFERENCES

References to studies included in this review

- Abels 1996** *{published data only}*
Abels RI, Larholt, Kay M, Krantz KD, Bryant EC. Recombinant human erythropoietin (rHuEPO) for the treatment of the anemia of cancer. *Oncologist* 1996;**1**(3):140–50.
- Agteresch 2000** *{published data only}*
Agteresch HJ, Dagnelie PC, van der Gaast A, Stijnen T, Wilson JHP. Randomized clinical trial of adenosine 5'-triphosphate in patients with advanced non-small-cell lung cancer. *Journal of the National Cancer Institute* 2000;**92**(4):321–8.
- Bamias 2003** *{published data only}*
Bamias AGA, Kalofonos C, Timotheadou N, Siafaka V, Vlahou I, Janinis D, et al. Prevention of anemia in patients with solid tumors receiving platinum-based chemotherapy by recombinant human erythropoietin (rHuEpo): A prospective, open label, randomized trial by the Hellenic Cooperative Oncology Group. *Oncology* 2003;**64**(2):102–10.
- Boogaerts 2003** *{published data only}*
Boogaerts M, Coiffier B, Kainz C, Epoetin beta QOLWG. Impact of epoetin beta on quality of life in patients with malignant disease. *British Journal of Cancer* 2003;**88**(7):988–95.
- Bruera 1990** *{published data only}*
Bruera EMK, Kuehn N, Hanson J, MacDonald RN. A controlled trial of megestrol acetate on appetite, caloric intake, nutritional status, and other symptoms in patients with advanced cancer. *Cancer* 1990;**66**(6):1279–82.
- Bruera 1998** *{published data only}*
Bruera E, Ernst S, Hagen N, Spachynski K, Belzile M, Hanson J. Effectiveness of megestrol acetate in patients with advanced cancer: a randomized, double-blind, crossover study. *Cancer Prevention & Control* 1998;**2**(2):74–8.
- Bruera 2003** *{published data only}*
Bruera E, Strasser F, Palmer JL, Willey J, Calder K, Amyotte G, et al. Effect of fish oil on appetite and other symptoms in patients with advanced cancer and anorexia/cachexia: a double-blind, placebo-controlled study. [see comment]. *Journal of Clinical Oncology* 2003;**21**(1):129–34.
- Bruera 2006** *{published data only}*
Bruera E, Valero V, Driver L, Shen L, Willey J, Zhang T, et al. Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. *Journal of Clinical Oncology* 2006;**24**(13):2073–8.
- Capuron 2002** *{published data only}*
Capuron L, Gumnick JF, Musselman DL, Lawson DH, Reemsnyder A, Nemeroff CB, et al. Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology* 2002;**26**(5):643–52.
- Case 1993** *{published data only}*
Case DC Jr, Bukowski RM, Carey RW, Fishkin EH, Henry DH, Jacobson RJ, et al. Recombinant human erythropoietin therapy for anemic cancer patients on combination chemotherapy. *Journal of the National Cancer Institute* 1993;**85**(10):801–6.
- Chang 2005** *{published data only}*
Chang J, Couture F, Young S, McWatters KL, Lau CY. Weekly epoetin alfa maintains hemoglobin, improves quality of life, and reduces transfusion in breast cancer patients receiving chemotherapy. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 2005;**23**(12):2597–605.
- Dagnelie 2003** *{published data only}*
Dagnelie PC, Agteresch HJ. Promising effects of adenosine triphosphate infusion on nutritional status and quality of life in advanced non-small-cell lung cancer: a randomized clinical trial. *Drug Development Research* 2003;**59**(1):146–51.
- Dammacco 2001** *{published data only}*
Dammacco F, Castoldi G, Rodjer S. Efficacy of epoetin alfa in the treatment of anaemia of multiple myeloma. *British Journal of Haematology* 2001;**113**(1):172–9.
- De Conno 1998** *{published data only}*
De Conno F, Martini C, Zecca E, Balzarini A, Venturino P, Groff L, et al. Megestrol acetate for anorexia in patients with far-advanced cancer: a double-blind controlled clinical trial. *European Journal of Cancer* 1998;**34**(11):1705–9.
- Della 1989** *{published data only}*
Della Cuna GRPA, Piazzini M. Effect of methylprednisolone sodium succinate on quality of life in preterminal cancer patients: a placebo-controlled, multicenter study. The Methylprednisolone Preterminal Cancer Study Group. *European Journal of Cancer & Clinical Oncology* 1989;**25**(12):1817–21.
- Diel 2004** *{published data only}*
Diel IJ, Body JJ, Lichinitser MR, Kreuser ED, Dornoff W, Gorbunova VA, et al. Improved quality of life after long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. *European Journal of Cancer* 2004;**40**(11):1704–12.
- Downer 1993** *{published data only}*
Downer SJS, Allbright A, Plant H. A double double blind placebo controlled trial of medroxyprogesterone acetate (MPA) in cancer cachexia. *British Journal of Cancer* 1991;**67**:1102–5.
- Fisch 2003** *{published data only}*
Fisch MJ, Loehrer PJ, Kristeller J, Passik S, Jung S-H, Shen J, et al. Fluoxetine versus placebo in advanced cancer outpatients: A double-blinded trial of the hoosier oncology group. *Journal of Clinical Oncology* 2003;**21**(10):1937–43.
- Fleishman 2005** *{published and unpublished data}*
Fleishman S, Lower E, Zeldis J, Faleck H, Manning D. A phase II, randomized, placebo-controlled trial of the safety and efficacy of dexmethylphenidate (d-MPH) as a treatment for fatigue and “chemobrain” in adult cancer patients. *Breast Cancer Research and Treatment* 2005;**94**:S214.
- Glossmann 2003** *{published data only}*
Glossmann JP, Engert A, Wassmer G, Flechtner H, Ko Y, Rudolph C, et al. Recombinant human erythropoietin, epoetin beta, in patients with relapsed lymphoma treated with aggressive sequential salvage

chemotherapy—results of a randomized trial. *Annals of Hematology* 2003;**82**(8):469–75.

Granetto 2003 {published data only}

Granetto CSR, Martoni A, Pezzela G, Testore F, Lampignano M, Tacconi F, Porozzi S. Comparing the efficacy and safety of fixed versus weight-based dosing of epoetin in anemic cancer patients receiving platinum-based chemotherapy. *Oncology Reports* 2003;**10**(5):1289–96.

Hedenus 2003 {published data only}

Hedenus M, Adriansson M, San Miguel J, Kramer MHH, Schipperus MR, Juvonen E, et al. Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: a randomized, double-blind, placebo-controlled study. *British Journal of Haematology* 2003;**122**(3):394–403.

Henry 1995 {published data only}

Henry DH, Brooks BJ Jr, Case DC Jr, Fishkin E, Jacobson R, Keller AM, Kugler J, et al. Recombinant human erythropoietin therapy for anemic cancer patients receiving cisplatin chemotherapy. *The Cancer Journal from Scientific American* 1995;**1**:252–60.

Iconomou 2003 {published data only}

Iconomou G, Koutras A, Rigopoulos A, Vagenakis AG, Kalofonos HP. Effect of recombinant human erythropoietin on quality of life in cancer patients receiving chemotherapy: results of a randomized, controlled trial. *Journal of Pain and Symptom Management* 2003;**25**(6):512–8.

Inoue 2003 {published data only}

Inoue A, Yamada Y, Matsumura Y, Shimada Y, Muro K, Gotoh M, Hamaguchi T, et al. Randomized study of dexamethasone treatment for delayed emesis, anorexia and fatigue induced by irinotecan. *Supportive Care in Cancer* 2003;**11**(8):528–32.

Kotasek 2003 {published and unpublished data}

Kotasek D, Steger G, Faught W, Underhill C, Poulson E, Colowick AB, et al. Darbepoetin alfa administered every 3 weeks alleviates anaemia in patients with solid tumours receiving chemotherapy: results of a double blind, placebo controlled randomised study. *European Journal of Cancer* 2003;**39**:2026–34.

Leyland-Jones 2005 {published data only}

Leyland-Jones B, Semiglazov V, Pawlicki M, Pienkowski T, Tjulandin S, Manikhas G, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *Journal of Clinical Oncology* 2005;**23**(25):5960–72.

Littlewood 2001 {published and unpublished data}

Littlewood TJ, Bajetta E, Nortier JW, Vercammen E, Rapoport B, Epoetin Alfa Study Group. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 2001;**19**(11):2865–74.

Moertel 1974 {published data only}

Moertel CG, Shutt A, Reitemeier R, Hahn RG. Corticosteroid therapy of preterminal gastrointestinal cancer. *Cancer* 1974;**33**(6):1607–9.

Monk 2006 {published data only}

Monk J, Phillips G, Waite R, Kuhn J, Schaaf LJ, Otterson GA, Guttridge D, et al. Assessment of tumor necrosis factor alpha blockade

as an intervention to improve tolerability of dose-intensive chemotherapy in cancer patients. *Journal of Clinical Oncology* 2006;**24**(12):1852–9.

Morrow 2003 {published data only}

Morrow GR, Hickock JT, Roscoe JA, Raubertas RF, Andrews PL, Flynn PJ, et al. Differential effects of paroxetine on fatigue and depression: a randomized, double-blind trial from the University of Rochester Cancer Center Community Clinical Oncology Program. *Journal of Clinical Oncology* 2003;**21**(24):4635–41.

O'Shaughnessy 2005 {published data only}

O'Shaughnessy JA, Vukelja SJ, Holmes FA, Savin M, Jones M, Royall D, et al. Feasibility of quantifying the effects of epoetin alfa therapy on cognitive function in women with breast cancer undergoing adjuvant or neoadjuvant chemotherapy. *Clinical Breast Cancer* 2005;**5**(6):439–46.

Osterborg 2002 {published data only}

Osterborg A, Brandberg Y, Molostova V, Iosava G, Abdulkadyrov K, Hedenus M, Messinger D. Randomized, double-Blind, placebo-controlled trial of recombinant human erythropoietin, epoetin beta, in hematologic malignancies. *Journal of Clinical Oncology* 2002;**20**(10):2486–94.

Popiela 1989 {published data only}

Popiela T, Lucchi R, Giongo F. Methylprednisolone as palliative therapy for female terminal cancer patients. The Methylprednisolone Female Preterminal Cancer Study Group. *European Journal of Cancer and Clinical Oncology* 1989;**25**(12):1823–9.

Roscoe 2005 {published data only}

Roscoe JA, Morrow GR, Hickok JT, Mustian KM, Griggs JJ, Marteson SE, Bushunow P, Qazi R, Smith B. Effect of paroxetine hydrochloride (paxil®) on fatigue and depression in breast cancer patients receiving chemotherapy. *Breast Cancer Research and Treatment* 2005;**V89**(3):243–9.

Savonije 2005 {published data only}

Savonije JH, van Groeningen CJ, van Bochove A, Honkoop AH, van Felius CL, Wormhoudt LW, Giaccone G. Effects of early intervention with epoetin alfa on transfusion requirement, hemoglobin level and survival during platinum-based chemotherapy: results of a multicenter randomised controlled trial. *European Journal of Cancer* 2005;**41**(11):1560–9.

Semiglazov 2006 {published data only}

Semiglazov VF, Stepula VV, Dudov A, Schnitker J, Mengs U. Quality of life is improved in breast cancer patients by standardised mistletoe extract PS76A2 during chemotherapy and follow-up: a randomised, placebo-controlled, double-blind, multicentre clinical trial. *Anticancer Research* 2006;**26**(2B):1519–29.

Simons 1996 {published data only}

Simons JP, Aaronson NK, Vansteenkiste JF, Ten Velde GP, Muller MJ, Drenth BM, et al. Effects of medroxyprogesterone acetate on appetite, weight, and quality of life in advanced stage non-hormone-sensitive cancer: a placebo controlled multicenter study. *Journal of Clinical Oncology* 1996;**14**:1077–84.

Smith 2003 {published and unpublished data}

Smith Jr RE, Tchekmedyan NS, Chan D, Meza LA, Northfelt DW, Patel R, et al. A dose- and schedule-finding study of darbepoetin alpha for the treatment of chronic anaemia of cancer. *British Journal of Cancer* 2003;**88**(12):1851–8.

Thatcher 1999 {published data only}

Thatcher N, De Campos ES, Bell DR, Steward WP, Vurghese G, Morant R, et al. Epoetin alpha prevents anaemia and reduced transfusion requirements in patients undergoing primarily platinum based chemotherapy for small cell lung cancer. *British Journal of Cancer* 1999;**80**(3/4):396–402.

Vansteenkiste 2002 {published and unpublished data}

Vansteenkiste J, Pirker R, Massuti B, Barata F, Font A, Fiegl M and Aranesp 980297 Study Group. Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. *Journal of the National Cancer Institute* 2002; **94**(16):1211–20.

Westman 1999 {published data only}

Westman G, Bergman B, Albertsson M, Kadar L, Gustavsson G, Thaning L, et al. Megestrol acetate in advanced, progressive, hormone-insensitive cancer. Effects on the quality of life: a placebo-controlled, randomised, multicentre trial. *European Journal of Cancer* 1999;**35**(4):586–95.

Wilkinson 2006 {published data only}

Wilkinson PM, Anapolous M, Lahousen M, Lind M, Kosmidis P. Epoetin alfa in platinum-treated ovarian cancer patients: results of a multinational, multicentre, randomised trial. *British Journal of Cancer* 2006;**94**(7):947–54.

Witzig 2005 {published data only}

Witzig TE, Silberstein PT, Loprinzi CL, Sloan JA, Novotny PJ, Mailliard JA, et al. Phase III, randomized, double-blind study of epoetin alfa compared with placebo in anemic patients receiving chemotherapy. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 2005;**23**(12):2606–17.

Wright 2007 {published and unpublished data}

Wright JR, Ung YC, Julian JA, Pritchard KI, Whelan TJ, Smith C, et al. Randomized, double-Blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. *Journal of Clinical Oncology* 2007;**25**(9):1–6.

References to studies excluded from this review**Bruera 1985**

Bruera E, Roca E, Cedaro L, Carraro S, Chacon R. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. *Cancer Treatment Reports* 1985;**69**(7-8):751–4.

Glaspay 2003

Glaspay JA, Jadeja J, Justice G, Fleishman A, Rossi G, Colowick AB. A randomized, active-control, pilot trial of front-loaded dosing regimens of darbepoetin-alfa. *Cancer* 2003;**97**(5):1312–20.

Glaspay 2006

Glaspay J, Vadhan-Raj S, Patel R, Bosserman L, Hu E, Lloyd RE. Randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia: the 20030125 study group trial. *Journal of Clinical Oncology* 2006;**24**(15):2290–7.

Glimelius 1998

Glimelius B, Linne T, Hoffman K, Larsson L, Svensson JH, Nasman P, et al. Epoetin beta in the treatment of anemia in patients with advanced gastrointestinal cancer. *Journal of Clinical Oncology* 1998; **16**(2):434–40.

Johansson 2001

Johansson JE, Wersall P, Brandberg Y, Andersson SO, Nordstram L, Group EPS. Efficacy of epoetin beta on hemoglobin, quality of life, and transfusion needs in patients with anemia due to hormone-refractory prostate cancer—a randomized study. *Scandinavian Journal of Urology and Nephrology* 2001;**35**(4):288–94.

Steensma 2006

Steensma DP, Molina R, Sloan JA, Nikcevic DA, Schaefer PL, Rowland KM, Jr, et al. Phase III study of two different dosing schedules of erythropoietin in anemic patients with cancer. *Journal of Clinical Oncology* 2006;**24**(7):1079–89.

Waltzman 2005

Waltzman R, Croot C, Justice GR, Fesen MR, Charu V, Williams D. Randomized comparison of epoetin alfa (40,000 U Weekly) and darbepoetin alfa (200 {micro}g every 2 weeks) in anemic patients with cancer receiving chemotherapy. *Oncologist* 2005;**10**(8):642–50.

References to ongoing studies**Bauer 2007**

Bauer B, Loprinzi C, Rummnas T. American Ginseng in treating patients with cancer related fatigue. www.clinicaltrials.gov Accessed 1 August 2007.

Bruera 2007

Bruera E, et al. The effect of donepezil on sedation and other symptoms. www.clinicaltrials.gov Accessed 1 August 2007.

Cruciani 2007

Cruciani R, Poretroy R. Levocarnitine in treating fatigue in cancer patients. www.clinicaltrials.gov Accessed 1 August 2007.

Dagnelie 2007

Dagnelie P. Application of adenosine-5-triphosphate infusions in palliative home care. www.clinicaltrials.gov Accessed 1 August 2007.

Frizell 2007

Frizell B. Co-enzyme Q10 in relieving treatment related fatigue in women with breast cancer. www.clinicaltrials.gov Accessed 1 August 2007.

Hutson 2007

Hutson P. Methylphenidate in treating patients with melanoma. www.clinicaltrials.gov Accessed 1 August 2007.

Morrow 2007

Morrow G. modafinil for treating fatigue in patients receiving chemotherapy for cancer. www.clinicaltrials.gov Accessed 1 August 2007.

Roth 2007

Roth A. Psychostimulants for fatigue in prostate cancer. www.clinicaltrials.gov Accessed 1 August 2007.

Sood 2006

Sood A, Dakhil S. Methylphenidate in treating fatigue caused by cancer. www.clinicaltrials.gov Accessed 1 August 2007.

Stockler 2007

Stockler M. A double blind placebo controlled trial of Zolof's effects on symptoms and survival time in advanced cancer. www.clinicaltrials.gov Accessed 1 August 2007.

Thomas 2007

Thomas CR. Etanercept versus placebo with radiation therapy to combat fatigue and anorexia. www.clinicaltrials.gov Accessed 1 August 2007.

Additional references

Andrews 2004

Andrews PLR, Morrow GR, Hickok JT, Roscoe J, Stone P. Mechanisms and models of fatigue associated with cancer and its treatment : Evidence from preclinical and clinical studies. In: Armes J, Krishnasamy M, Higginson I editor(s). *Fatigue in Cancer*. Oxford University Press, 2004.

BNF 53

British National Formulary. www.bnf.org issue section 9.1.3.

Bohlius 2007

Bohlius J, Wilson J Seidenfeld J. Erythropoietin or darbopoetin for patients with cancer. *Cochrane Database of Systematic Reviews* 2007, Issue 2.

Breitbart 1995

Breitbart W, Bruera E, Chochinov H, Lynch M. Neuropsychiatric syndromes and psychological symptoms in patients with advanced cancer. *Journal of Pain & Symptom Management* 1995;10(2):131–41.

Breitbart 2001

Breitbart W, Rosenfeld B, Kaim M, Funesti-Esch J. A randomized, double-blind, placebo-controlled trial of psychostimulants for the treatment of fatigue in ambulatory patients with human immunodeficiency virus disease. *Archives of Internal Medicine* 2001;161(3):411–20.

Bultmann 2002

Bultmann U, Kant I, Kasl SV, Beurskens AJ, van den Brandt PA. Fatigue and psychological distress in the working population: psychometrics, prevalence, and correlates. *Journal of Psychosomatic Research* 2002;52(6):445–52.

Cella 2001

Cella D, Davis K, Breitbart W, Curt G, The Fatigue C. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. *Journal of Clinical Oncology* 2001;19(14):3385–91.

Cella 2002

Cella D, Eton D Lai J, et al. combining anchor and distribution-based methods to derive minimally important clinical differences on the functional assessment of cancer therapy (FACT) fatigue and anaemia subscales. *Journal of Pain & Symptom Management* 2002;24(6):547–61.

Consort 2007

CONSORT Statement. www.consort-statement.org Accessed 1 August 2007.

Cramp 2006

Cramp F, Prue G, Gracey J. Exercise for treatment of cancer related fatigue. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD006145. DOI:10.1002/14651858.CD006145.

Demetri 1998

Demetri GD, Kris M, Wade J, et al. Quality of life in chemotherapy patients treated with erythropoietin alpha is independent of disease response or tumour type: results from a prospective community survey. *Journal of Clinical Oncology* 1998;16:3412–25.

Glaspy 1997

Glaspy JA, Bukowski R, Steinberg D, et al. Impact of therapy with erythropoietin alpha on clinical outcomes in patients with non

myeloid malignancies during chemotherapy in community oncology practice. *Journal of Clinical Oncology* 1997;15:1218–34.

Higgins 2006

Higgins JPT, Green S editors. *Cochrane Handbook for Systematic Reviews of Interventions* [updated September 2006]. www.cochrane.org/resources/handbook/hbook.htm (accessed 17 April 2007).

Jadad 1996

Jadad AR MR, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Controlled Clinical Trials* 1996;17(1):1–12.

Jones 2004

Jones M, Schenkel B, Just J, Fallowfield L. Epoetin alpha improves quality of life in patients with cancer -results from a meta-analysis. *Cancer* 2004;101(8):1720–32.

Krupp 1988

Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC. Fatigue in multiple sclerosis. *Archives of Neurology* 1988;45(4):435–7.

Lawrie 1997

Lawrie S, Manders D, Geddes J, Pelosi A. A population-based incidence study of chronic fatigue. *Psychological Medicine* 1997;27:343–53.

Mock 2004

Mock V. Evidence-based treatment for cancer-related fatigue. *Journal of the National Cancer Institute Monographs* 2004;32:112–8.

Morrow 2002

Morrow GR, Andrews PL, Hickok JT, Roscoe JA, Matteson S. Fatigue associated with cancer and its treatment. *Supportive Care in Cancer* 2002;10(5):389–98.

Morrow 2005

Morrow GR, Shelke AR, Roscoe JA, Hickok JT, Mustian K. Management of cancer-related fatigue. *Cancer Investigation* 2005;23(3):229–39.

NCCN 2006

National Comprehensive Cancer Network. Clinical practice guidelines in oncology [Supportive care guidelines]. Cancer related fatigue V3.2006 from www.nccn.org/professionals/physician_gls/PDF/fatigue.pdf 2006, issue Accessed 1 December 2006.

Radbruch 2007

Radbruch L, Elsner F, Krumm N, Peuckmann V, Trottenberg P. Drugs for the treatment of fatigue in palliative care. *Cochrane Database of Systematic Reviews* 2007, issue 4.

Sadler 2002

Sadler IJ, Jacobsen PB, Booth-Jones M, Belanger H, Weitzner MA, Fields KK. Preliminary evaluation of a clinical syndrome approach to assessing cancer-related fatigue. *Journal of Pain & Symptom Management* 2002;23(5):406–16.

Servaes 2002

Servaes P, Prins J, Verhagen S, Bleijenberg G. Fatigue after breast cancer and in chronic fatigue syndrome: Similarities and differences. *Journal of Psychosomatic Research* 2002;52(6):453–9.

Sharpe 1992

Sharpe M. Fatigue and chronic fatigue syndrome. *Current Opinion in Psychiatry* 1992;5:207–12.

Stone 2000

Stone P, Richardson A, Ream E, Smith AG, Kerr DJ, Kearney N. Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. *Cancer Fatigue Forum. Annals of Oncology* 2000;**11**(8):971–5.

Stone 2002

Stone P. The measurement causes and effective management of cancer-related-fatigue. *International Journal of Palliative Nursing* 2002;**8**(3):120–8.

Trendall 2001

Trendall J. Assessing fatigue in patients with COPD. *Professional Nurse* 2001;**16**(7):1217–20.

T A B L E S**Characteristics of included studies**

Study	Abels 1996
Methods	Double blind placebo control
Participants	N = 413 non myeloid mixed cancer population Male 197 Female 216 average age 61.9
Interventions	Erythropoetin 150 U/kg 3 x week N = 213 matching placebo N = 200 up to 8 weeks duration
Outcomes	Quality of life on VAS
Notes	Single item fatigue measurement - unsuitable for further analysis
Allocation concealment	B – Unclear

Study	Agteresch 2000
Methods	Open label
Participants	Advanced non small cell cancer patients N = 58 Male 38 Female 20 Average age 62.5
Interventions	ATP (adenosine tri-phosphate) infusion up to 75 µg/kg 2 to 4 weekly N = 28 supportive care N = 30
Outcomes	Rotterdam symptom control checklist
Notes	Single item fatigue scores -not suitable for further analysis
Allocation concealment	C – Inadequate

Study	Bamias 2003
Methods	Open label
Participants	Solid tumours receiving platinum chemotherapy N = 144 Male 74 Female 70 Average age 61
Interventions	Erythropoetin 10,000 U sc 3 x week for 12 weeks N = 72 no treatment N = 72

Characteristics of included studies (Continued)

Outcomes	EORTC QLQ 30
Notes	Fatigue subscale not mentioned - not suitable for further analysis (see footnote) Oxford Quality Score 2
Allocation concealment	C – Inadequate

Study	Boogaerts 2003
Methods	Open label
Participants	Any tumour type at least three cycles of chemotherapy N = 262
Interventions	Erythropoetin 150 u/kg 3 x week for 12 weeks N = 133 usual care and transfusion PRN N = 129 Male 98 Female 164 Average age 62
Outcomes	FACT-F score change epo = +5.5 (1.6) usual care = +0.5 (0.7)
Notes	LOCF analysis - missing data on quality of life outcomes not ITT Oxford Quality Score 2
Allocation concealment	C – Inadequate

Study	Bruera 1990
Methods	Crossover double blind placebo control
Participants	Advanced cancer not on treatment N = 40 Male 30 Female 10 average age 62
Interventions	Megestrol acetate 480 mg od or placebo for seven days and cross over
Outcomes	Single item scores in well being and energy
Notes	Single item - not suitable for further analysis
Allocation concealment	B – Unclear

Study	Bruera 1998
Methods	Cross over placebo controlled
Participants	Lung and GI tumours N = 84 Male 47 Female 37 Average age 62
Interventions	Megestrol acetate 160 mg od 10/7 or placebo and two day washout and crossover
Outcomes	Piper fatigue scale overall change megestrol = -0.4 (1.5) placebo +0.3 (2.1)
Notes	n = 19 lost due to progressive disease no adverse events due to medication Oxford Quality Score 3
Allocation concealment	A – Adequate

Study	Bruera 2003
Methods	Double blind placebo controlled
Participants	Any tumour type N = 91 Male 27 Female 63 Average age 63.8
Interventions	Fish oil capsules 1000 mg daily N = 46; placebo capsules N = 46

Characteristics of included studies (Continued)

Outcomes	VAS score changes at day 14 - tiredness
Notes	Single item score - unsuitable for further analysis
Allocation concealment	A – Adequate

Study	Bruera 2006
Methods	Parallel double blind placebo controlled
Participants	Any tumour type >4 VAS fatigue N = 112 Male 39 Female 68 Average age 56.5
Interventions	Methylphenidate 5 mg two hourly/PRN up to 20 mg/24 hrs n = 56 or matching placebo n = 56 for seven days
Outcomes	FACT-F methylphenidate +9.6 (9.8) placebo +7.5 (11.3)
Notes	Seven days double blind - no change improvement in open label phase Oxford Quality Score 5
Allocation concealment	A – Adequate

Study	Capuron 2002
Methods	Double blind placebo controlled
Participants	Resected melanoma receiving interferon alpha N = 40 for up to 12 weeks of therapy Male 20 Female 20 Average age 51
Interventions	Paroxetine 20 mg N = 20 placebo N = 20
Outcomes	Single item included in assesment of depressive symptoms
Notes	Not suitable for further analysis
Allocation concealment	B – Unclear

Study	Case 1993
Methods	Double blind placebo controlled
Participants	Any tumour type on chemotherapy N = 153 Male 62 Female 95 Average age 64
Interventions	150 u/kg erythropoetin 3 x week or matching placebo for up to 12 weeks
Outcomes	Single item VAS
Notes	Not suitable for further analysis
Allocation concealment	A – Adequate

Study	Chang 2005
Methods	Open label

Characteristics of included studies (Continued)

Participants	Breast cancer on chemotherapy N = 350 Average age 50.3
Interventions	Erythropoetin 40,000 u 1x week N = 175 standard care N = 175 for up to 12 weeks
Outcomes	FACT -F erythropoetin = +1.85 (10.52) standard care = -3.55 (11.4)
Notes	Oxford Quality Score 2
Allocation concealment	C – Inadequate

Study Dagnelie 2003

Methods	Open label
Participants	Non small cell lung ca N = 58 Male 40 Female 18 average age 57
Interventions	ATP infusions two to four weekly N = 28 Standard care N = 30 3/12 duration
Outcomes	Single item score from rotterdam symptom checklist
Notes	Not suitable for further analysis partial duplication of Agertsch 2000 data
Allocation concealment	C – Inadequate

Study Dammacco 2001

Methods	Double blind placebo controlled
Participants	Myeloma N = 145 Male 67 Female 78 average age 66.5
Interventions	Erythropoietin 150 u/kg 3 x week or matching placebo for 12 weeks
Outcomes	Single item scales
Notes	Not suitable for further analysis
Allocation concealment	A – Adequate

Study De Conno 1998

Methods	Double blind placebo controlled
Participants	Any tumour type N = 42 Male 31 Female 11 average age 61.5
Interventions	Megestrol acetate 320mg od 14/7 N = 21 placebo N = 21
Outcomes	Profile of mood states fatigue subscale MA = -2.0 (-3 to 0) placebo 0 (-0.5 to +0.1)
Notes	Oxford Quality Score 4

Characteristics of included studies (Continued)

Allocation concealment B – Unclear

Study Della 1989

Methods	Double blind placebo controlled
Participants	Any tumour type N = 403 Male 198 Female 207 average age 62.7
Interventions	Methylprednisolone 125 mg od IV daily eight weeks matching placebo
Outcomes	Single item VAS
Notes	Not suitable for further analysis
Allocation concealment	B – Unclear

Study Diel 2004

Methods	Double blind placebo controlled
Participants	Breast cancer N = 466 average age 55.4
Interventions	Ibandronate 2 mg IV four weekly N = 154 ibandronate 6 mg IV four weekly N = 154 placebo N = 158 up to 96 weeks treatment
Outcomes	EORTC QLQ 30 fatigue subscale ibandronate 2 mg = +4.58 (2.3) 6 mg = +4.84 (2.2) placebo = +10.41 (2.3)
Notes	Dose arms were open label due to infusion volumes Oxford Quality Score 2
Allocation concealment	C – Inadequate

Study Downer 1993

Methods	Double blind placebo controlled
Participants	Breast cancer N = 60 Average age 62
Interventions	Medroxyprogesterone acetate 100 mg tds six weeks N = 30 or placebo N = 30
Outcomes	Single item VAS
Notes	Not suitable for further analysis
Allocation concealment	B – Unclear

Study Fisch 2003

Methods	Double blind placebo controlled
Participants	Any tumour type N = 163 Male 80 Female 83

Characteristics of included studies (Continued)

	average age 60
Interventions	Fluoxetine 20 mg od 12 weeks N = 83 or placebo N = 80
Outcomes	Single item from FACT-G
Notes	Not suitable for further analysis
Allocation concealment	A – Adequate

Study	Fleishman 2005
Methods	Double blind placebo controlled
Participants	Any tumour type N = 152 Male 15 Female 137 average age 52.8
Interventions	Dexamethylphenidate 5 mg bd/prn N = 75 placebo N = 77 eight weeks treatment
Outcomes	FACT F methylphenidate = -11.8 (12.6) placebo = -7.1 (12.6)
Notes	ASCO full presentation - not subsequently published Author contacted - submitted for publication - to be included as meets criteria Oxford Quality Score 3
Allocation concealment	B – Unclear

Study	Glossmann 2003
Methods	Open label
Participants	Lymphoma N = 57 (on high dose chemotherapy) Male 33 Female 22 average age 37
Interventions	Erythropoetin 10,000 u 3x week N = 28 usual care N = 29 during salvage chemotherapy - up to 12 weeks
Outcomes	EORTC QLQ 30 erythropoetin = +18.9 (18.1) usual care = +39.4 (18.1)
Notes	Large loss to follow up. Oxford Quality Score 2
Allocation concealment	C – Inadequate

Study	Granetto 2003
Methods	Open label
Participants	Any tumour type undergoing chemotherapy N = 510 Male 270 Female 240 average age 61.6
Interventions	Erythropoetin 10,000 u 3 x week N = 255 erythropoetin 150 u/kg 3 x week N = 255 up to 18 weeks

Characteristics of included studies (Continued)

Outcomes	Single item fatigue scores
Notes	Not suitable for further analysis
Allocation concealment	C – Inadequate

Study Hedenus 2003

Methods	Double blind placebo controlled
Participants	Lymphoproliferative tumours N = 344 Male 166 Female 179 average age 64.6
Interventions	Darbopoetin 2.25 mcg/kg every three weeks N = 176 placebo N = 173 for 12 weeks
Outcomes	FACT F by baseline scores <24 darbopoetin +8.5 (5.0) placebo 5.4 (3.0) 25 to 36 Darbo 1.5 (1.1) placebo -0.2 (1.1) >36 darbo -1.3 (1.5) placebo -3.5 (1.5)
Notes	Overall mean changes included in meta-analysis Oxford Quality Score 5
Allocation concealment	B – Unclear

Study Henry 1995

Methods	Double blind placebo controlled
Participants	Mixed tumours N = 132 Male 62 Female 70 average age 58.5
Interventions	Erythropoetin 150 u/kg sc 3 x week N = 67 or matching placebo N = 65 for 12 weeks while on chemotherapy
Outcomes	Quality of life scales
Notes	Single item scores - not suitable for further analysis
Allocation concealment	B – Unclear

Study Iconomou 2003

Methods	Open label
Participants	Non haematological tumours N = 122 Male 51 Female 71 average age 61.8
Interventions	Erythropoetin 10,000 u 3 x week for 12 weeks N = 61 or usual care N = 61
Outcomes	FACT-F scores at 12 weeks Erythropoetin +4.6 (12.5) usual care -1.0 (12.8)
Notes	Oxford Quality Score 2
Allocation concealment	C – Inadequate

Study Inoue 2003

Methods	Double blind placebo controlled
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Characteristics of included studies (Continued)

Participants	GI tumours receiving irinotecan as 2nd or 3rd line N = 68 Male 44 Female 24 average age 59
Interventions	Dexamethasone IV 8 mg on days 2 to 4 of each cycle or matched normal saline up to 18 weeks
Outcomes	VAS of fatigue and other symptoms
Notes	Single item - not suitable for further analysis
Allocation concealment	B – Unclear

Study	Kotasek 2003
Methods	Double blind placebo controlled
Participants	Any tumour type N = 249 Male 117 Female 132 average age 57.7
Interventions	Darbopoetin 4.5 to 15 mcg/kg every three weeks for up to 12 weeks N = 198 or matching placebo N = 51
Outcomes	Darbopoetin pooled dose changes on FACT F score +4.0 (2.5) Placebo -0.5 (2.6)
Notes	Average scores on range of doses used for meta-analysis 4:1 randomisation of darbopoetin to placebo four different dosing schedules used Oxford Quality Score 5
Allocation concealment	A – Adequate

Study	Leyland-Jones 2005
Methods	Double blind placebo controlled
Participants	Breast Cancer N = 939 average age 55.5
Interventions	Erythropoetin 40,000 U once week N = 469 or matching placebo up to one year treatment N = 470
Outcomes	FACT-An data - not in paper VAS overall changes mentioned
Notes	Main analysis was on survival time Epo arm had a reduced overall survival and the trial was terminated early - possible increased thromboembolic events data on FACT-An not mentioned - author contacted (see footnote) Oxford Quality Score 5
Allocation concealment	A – Adequate

Study	Littlewood 2001
Methods	Double blind placebo controlled
Participants	Any tumour type (excluding leukaemia) receiving platinum based chemotherapy N = 375 Male 251 Female 124 average age 59.1
Interventions	Erythropoetin 150 U/kg 3 x week N = 251 or matched volume placebo N = 124 for 12 weeks
Outcomes	FACT F score change Erythropoetin +3.3 (13.2) Placebo -1.6 (12.7)
Notes	Minimal adverse events

Characteristics of included studies (Continued)

	Oxford Quality Score 5
Allocation concealment	B – Unclear
Study	Moertel 1974
Methods	Single blind placebo controlled
Participants	Any tumour type (off treatment) N = 116 Male 70 Female 46 average age 61
Interventions	Dexamethasone 0.75 mg QDS N = 33; Dexamethasone N = 1.5 mg QDS N = 36; Placebo N = 47 for eight weeks
Outcomes	VAS on strength and appetite
Notes	Single item scores unsuitable for further analysis
Allocation concealment	B – Unclear
Study	Monk 2006
Methods	Open Label
Participants	Any tumour type - receiving docetaxel chemotherapy N = 12 Male nine Female three average age 56
Interventions	Docetaxel etanercept for three cycles N = 6 or docetaxel alone up to 18 weeks duration
Outcomes	Fatigue symptom inventory docetaxel +14 (7) , docetaxel 7 etanercept + 10 (3)
Notes	Oxford Quality Score 2
Allocation concealment	C – Inadequate
Study	Morrow 2003
Methods	Double blind placebo controlled
Participants	Any tumour type on chemotherapy N = 549 Male 137 Female 412 average age 56.4
Interventions	Paroxetine 20 mg OD for eight weeks N = 277; matching placebo N = 272
Outcomes	Fatigue symptom checklist scores at beginning of cycle 4 of chemotherapy Paroxetine - 4.8 (1.28) Placebo -3.4 (1.23)
Notes	Other scales used for fatigue with single item scores only not included in meta-analysis - only main outcome scores Oxford Quality Score 4
Allocation concealment	A – Adequate
Study	O'Shaughnessy 2005
Methods	Double blind placebo controlled
Participants	Breast cancer on chemotherapy (at least four cycles) N = 94 average age 53.9
Interventions	Erythropoetin 40,000 U weekly 12 weeks N = 47; matched placebo N = 47
Outcomes	FACT An Erythropoetin scores -3.0 (11.9) Placebo -9.4 (13.8)

Characteristics of included studies (Continued)

Notes	Oxford Quality Score 5
Allocation concealment	B – Unclear

Study	Osterborg 2002
Methods	Double blind placebo controlled
Participants	Haematological malignancy N = 343 Male 170 Female 173 average age 63.5 not on treatment
Interventions	Erythropoetin 150 U/kg 3 x week for 16 weeks N = 170 ; matched placebo N = 173
Outcomes	FACT F erythropoetin +5.2 (12.2) Placebo +3.0 (12.1) at 16 weeks - intermediate scores not recorded
Notes	Oxford Quality Score 4
Allocation concealment	B – Unclear

Study	Popiela 1989
Methods	Single blind placebo controlled
Participants	Female cancer patients N = 173 average age 63
Interventions	Methylprednisolone 125 mg OD for eight weeks N = 88 or matching placebo N = 85
Outcomes	VAS on well being and energy
Notes	Single item scores - not suitable for further analysis
Allocation concealment	C – Inadequate

Study	Roscoe 2005
Methods	Double blind placebo controlled
Participants	Breast cancer N = 94 average age 52
Interventions	Paroxetine 20 mg OD for eight weeks N = 44; Placebo N = 50
Outcomes	Fatigue symptom checklist scores at start of cycle four chemotherapy - Paroxetine -5.0 (2.37) Placebo -2.5 (2.54)
Notes	Same design as Morrow 2003 - used a single tumour type and single centre but different population studied - therefore included as separate study single item fatigue measures excluded from analysis Oxford Quality Score 5
Allocation concealment	A – Adequate

Study	Savonije 2005
Methods	Open Label
Participants	Any tumour type - receiving platinum based chemotherapy N = 315 Male 179 Female 136 average age 57.5
Interventions	erythropoetin 10,000 U 3 x week for 12 weeks N = 211; Usual care N = 104
Outcomes	FACT F Erythropoetin +3.48 (12.67) Usual care -1.67 (11.61)

Characteristics of included studies (Continued)

Notes	Oxford Quality Score 2
Allocation concealment	C – Inadequate

Study	Semiglazov 2006
Methods	Double blind placebo controlled
Participants	Breast cancer N = 352 average age 46.2
Interventions	Standardised Mistletoe extract N = 176 for six cycles chemotherapy; matched Placebo N = 176 (up to 18 weeks)
Outcomes	FACT G (functional assessment of cancer therapy - general measure)
Notes	Single item on fatigue - unsuitable for further analysis
Allocation concealment	A – Adequate

Study	Simons 1996
Methods	Double blind placebo controlled
Participants	Any tumour type N = 206 Male 153 Female 53 average age 64
Interventions	Medroxyprogesterone acetate (MPA) 500 mg BD for 12 weeks N = 103; matched Placebo N = 103
Outcomes	EORTC QLQ 30 fatigue subscale: MPA +3.6 (19.6) ; Placebo +7.0 (25.1)
Notes	Oxford Quality Score 4
Allocation concealment	A – Adequate

Study	Smith 2003
Methods	Double blind placebo controlled
Participants	Any tumour type (not myeloid) not on chemotherapy N = 86 Male 34 Female 52 average age 67.5
Interventions	Darbopoetin every three weeks (6.75 mcg/kg) or every four weeks (6.75 -10 mcg/kg) N = 64 (total) or matched placebo N = 22 for 12 weeks
Outcomes	FACT F -
Notes	Oxford Quality Score 3
Allocation concealment	B – Unclear

Study	Thatcher 1999
Methods	Open Label
Participants	Small cell lung cancer (on platinum based chemotherapy) N = 130 Male 82 Female 48 average age 59.5
Interventions	Erythropoetin 150 U/kg 3 x week for four to six cycles N = 42 ; Erythropoetin 300 U/kg 3 x week for four to six cycles N = 44 ; Usual care N = 44 12 to 18 weeks total duration
Outcomes	VAS fatigue measures

Characteristics of included studies (Continued)

Notes Single item scores - not suitable for further analysis

Allocation concealment C – Inadequate

Study Vansteenkiste 2002

Methods Double blind placebo controlled

Participants Lung cancer on chemotherapy N = 320
Male 245 Female 75
average age 61.4

Interventions Darbopoetin 2.24 mcg/kg weekly for 12 weeks N = 156; Matching Placebo N = 158

Outcomes FACT F - Darbopoetin +0.8 (10.0); placebo -0.6 (10.7)

Notes Oxford Quality Score 5

Allocation concealment A – Adequate

Study Westman 1999

Methods Double blind placebo controlled

Participants Any tumour type N = 255
Male 134 Female 121
average age 70 (not on treatment)

Interventions Megestrol acetate (MA) 320 mg daily for 12 weeks N = 128; matched placebo N = 127

Outcomes EORTC QLQ 30 fatigue subscale
MA +1.3 (4.5); placebo -3.9 (2.2)

Notes Oxford Quality Score 4

Allocation concealment B – Unclear

Study Wilkinson 2006

Methods Open Label

Participants Ovarian cancer on platinum chemotherapy N = 182
average age 59.8

Interventions Erythropoetin 10 to 20,000 U 3 x week for 12 weeks or usual care

Outcomes FACT An and VAS of energy and fatigue
FACT An score changes not givenNotes 2:1 randomisation to erythropoetin
FACT An scores not given - author contacted (see footnote)
unsuitable for further analysis
Oxford Quality Score 3

Allocation concealment C – Inadequate

Study Witzig 2005

Methods Double blind placebo controlled

Participants Any tumour type on chemotherapy N = 344
Male 170 Female 174
average age 59Interventions Erythropoetin 40,000 U weekly for 16 weeks or matched placebo
QOL population Epo - N = 154 Placebo - N = 151

Outcomes	FACT F erythropoetin +3.0 (23.22) placebo +0.6 (22.08)
Notes	Oxford Quality Score 5
Allocation concealment	A – Adequate
Study	Wright 2007
Methods	Double blind placebo controlled
Participants	Non small cell lung cancer N = 70 Male 37 Female 33 (not on treatment) average age 69
Interventions	Erythropoetin 40,000 weekly for 12 weeks N = 33 ; matched placebo N = 37
Outcomes	FACT An Erythropoetin +6.5 Placebo +2.6
Notes	Proposed sample 300 - unplanned safety analysis showed worse survival in epo group and study terminated high attrition in QOL score measurement Oxford Quality Score 4
Allocation concealment	A – Adequate
<p>ASCO: American Society of Clinical Oncology Bd: bi-daily EOTRC QLQ 30: European oncology society 30 item quality of life questionnaire - includes a validated fatigue subscale FACT F: functional assessment of cancer therapy - fatigue subscale FACT An: functional assessment of cancer therapy - anaemia subscale FACT G: functional assessment of cancer therapy - general assessment IV: intravenous LOCF: last observation carried forward OD: once daily PRN: as required QDS: four times daily Sc: subcutaneously Tds: three times daily U: units VAS: visual analogue scale Bamias: author contacted successfully but no further data available Leyland-Jones: author contacted successfully but no further data available Wilkinson: author contacted successfully but no further data available</p>	

Characteristics of excluded studies

Study	Reason for exclusion
Bruera 1985	Measured activity (amongst other symptoms) but did not formally measure subjective fatigue
Glaspay 2003	Active control - erythropoetin versus multiple doses of darbopoetin No control or usual care arm
Glaspay 2006	Active control non inferiority study - erythropoetin versus darbopoetin No control or usual care arm
Glimelius 1998	Multiple doses of erythropoetin - no control or comparison arm
Johansson 2001	Multiple doses of erythropoetin - no control or comparison arm

Characteristics of excluded studies (Continued)

Steensma 2006	Different dosing schedules of erythropoetin no control or usual care arm
Waltzman 2005	Active control - erythropoetin versus darbopoetin No control or usual care arm

Characteristics of ongoing studies

Study	Bauer 2007
Trial name or title	American ginseng for treating patients with cancer related fatigue
Participants	Any tumour type one month fatigue stratified by stage of disease
Interventions	Ginseng vs placebo
Outcomes	Brief fatigue inventory
Starting date	October 2005
Contact information	Brent Bauer Mayo clinic
Notes	NCT00182780

Study	Bruera 2007
Trial name or title	The effect of donepezil on sedation and other symptoms
Participants	Any tumour type on strong opioids with sedation
Interventions	Donepezil vs placebo
Outcomes	FACT F
Starting date	November 2003
Contact information	MD Anderson cancer centre Texas USA
Notes	NCT00352664

Study	Cruciani 2007
Trial name or title	L-carnitine for treating fatigue in patients with cancer
Participants	Cancer patients on or off chemotherapy
Interventions	L carnitine versus placebo
Outcomes	Brief fatigue inventory score change at four weeks
Starting date	November 2005
Contact information	Ricardo Cruciani, MD, PhD, Study Chair, Beth Israel Medical Center - Petrie Division
Notes	NCT00091169

Study	Dagnelie 2007
Trial name or title	Application of adenosine triphosphate in palliative home care
Participants	Palliative cancer patients
Interventions	Open label - randomised to receive infusion addition to usual care
Outcomes	Changes in quality of life measures including fatigue

Characteristics of ongoing studies (Continued)

Starting date	January 2002
Contact information	Dr P Dagnelie University of Maastricht , Netherlands
Notes	CTN97280223

Study **Frizell 2007**

Trial name or title	Coenzyme Q10 in relieving treatment-related fatigue in women with breast cancer
Participants	Breast cancer patients on chemotherapy
Interventions	Co-enzyme Q10 or placebo
Outcomes	POMS F at 24 weeks
Starting date	May 2007
Contact information	Glenn J Lesser, MD, Principal Investigator, Wake Forest University
Notes	NCT00096356

Study **Hutson 2007**

Trial name or title	Methylphenidate for treating patients with melanoma
Participants	Melanoma patients
Interventions	Methylphenidate or placebo
Outcomes	Brief fatigue inventory at three weeks
Starting date	June 1999
Contact information	Paul Hutson university of Wisconsin
Notes	NCT00003266

Study **Morrow 2007**

Trial name or title	Modafinil for treating fatigue in patients receiving chemotherapy for cancer
Participants	Cancer patients on chemotherapy
Interventions	Double blind placebo controlled placebo vs modafinil
Outcomes	Change in brief fatigue inventory at cycle four of chemotherapy
Starting date	August 2002
Contact information	Prof G Morrow James P Wilmot cancer centre University of Rochester New York USA
Notes	NCT00042848

Study **Roth 2007**

Trial name or title	Psychostimulants for fatigue in prostate cancer
Participants	Prostate cancer patients
Interventions	Double blind placebo vs methylphenidate

Characteristics of ongoing studies (Continued)

Outcomes	Change in self reported fatigue
Starting date	September 2005
Contact information	Dr A Roth Memorial Sloan kettering cancer centre USA
Notes	NCT00138138

Study Sood 2006

Trial name or title	Methylphenidate in treating patients with fatigue caused by cancer
Participants	Cancer patients on chemotherapy
Interventions	Double blind placebo controlled placebo vs long acting methylphenidate
Outcomes	Change in brief fatigue inventory at week four
Starting date	September 2006
Contact information	Dr Sood Mayo clinic USA.
Notes	NCT00376675

Study Stockler 2007

Trial name or title	The effect of sertraline on symptoms and survival in patients with advanced cancer
Participants	Palliative cancer population
Interventions	Double blind placebo controlled sertaline 50 mg vs placebo
Outcomes	Change in quality of life measures (including fatigue)
Starting date	January 2002
Contact information	Dr M Stockler NHMRC clinical trials centre University of Sydney
Notes	CTN 72466475

Study Thomas 2007

Trial name or title	Enbrel versus placebo with radiation therapy to combat fatigue and cachexia
Participants	Lung/prostate patients on radiotherapy
Interventions	Etanercept versus placebo
Outcomes	Determine if the subjects who received the enbrel study drug had a better quality of life than the subjects who received placebo
Starting date	May 2001
Contact information	The University of Texas Health Science Center at San Antonio Sanchez Cancer Center
Notes	NCT 00127387

ADDITIONAL TABLES

Table 01. Search terms for MEDLINE

Search terms

- 1 Exp NEOPLASMS
- 1 Exp NEOPLASMS
- 2 Exp BONE MARROW TRANSPLANTATION/
- 3 neoplasm\$ or cancer\$ or carcinoma\$ or tumour\$ or adenocarcinoma\$ or leukeni\$ or leukaemi\$ or lymphoma\$ or tumor\$ or tumor\$ or malignan\$ (title, abstract & keywords)
- 4 neutropeni\$ or neutropaeni\$ (title, abstract & keywords)
- 5 Exp RADIOTHERAPY
- 6 radioth\$ or radiat\$ or irradiat\$ or radiochemo\$ or chemotherapy\$ (title, abstract & keywords)
- 7 (“bone marrow” adj4 transplant\$) or (“bone-marow” NEAR transplant\$))
- 8 OR/1-7
- 9 FATIGUE/ (drug therapy)
- 10 fatigue\$ (title, abstract & keywords)
- 11 tired\$ or weary or weariness or exhaustion or exhausted or lacklustre or astheni\$ or asthenia\$
- 12 ((lack\$ or loss or lost) adj2 (energy or vigour or vigor)
- 13 (apathy or apathetic or lassitude or letharg\$ or (feeling adj3 (drained or sleepy or sluggish or weak\$)))
- 14 OR/9-13

Table 02. Search terms for EMBASE

Search terms

- 1 Exp NEOPLASM
- 2 BONE MARROW TRANSPLANTATION/
- 3 neoplas\$ or cancer\$ or carcinoma\$ or tumour\$ or adenocarcinoma\$ or leukeni\$ or leukaemi\$ or lymphoma\$ or tumor\$ or tumor\$ or malignan\$ (title, abstract & keywords)
- 4 neutropeni\$ or neutropaeni\$ (title, abstract & keywords)
- 5 Exp RADIOTHERAPY
- 6 radioth\$ or radiat\$ or irradiat\$ or radiochemo\$ or chemotherapy\$ (title, abstract & keywords)
- 7 (“bone marrow” adj4 transplant\$) or (“bone-marow” NEAR transplant\$))
- 8 OR/1-7
- 9 FATIGUE/ (drug therapy)
- 10 fatigue\$ (title, abstract & keywords)
- 11 tired\$ or weary or weariness or exhaustion or exhausted or lacklustre or astheni\$ or asthenia\$

Table 02. Search terms for EMBASE (Continued)

Search terms

- 12 ((lack\$ or loss or lost) adj2 (energy or vigour or vigor)
- 13 (apathy or apathetic or lassitude or letharg\$ or (feeling adj3 (drained or sleepy or sluggish or weak\$)))
- 14 OR/9-13
- 15 8 AND 14

Table 03. Search terms for CINAHL

Search terms

- 1 Exp NEOPLASM
- 2 BONE MARROW TRANSPLANTATION/
- 3 neoplas\$ or cancer\$ or carcinoma\$ or tumour\$ or adenocarcinoma\$ or leukeni\$ or leukaemi\$ or lymphoma\$ or tumor\$ or tumor\$ or malignan\$ (title, abstract & keywords)
- 4 neutropeni\$ or neutropaeni\$ (title, abstract & keywords)
- 5 Exp RADIOTHERAPY
- 6 radioth\$ or radiat\$ or irradiat\$ or radiochemo\$ or chemotherapy\$ (title, abstract & keywords)
- 7 (“bone marrow” adj4 transplant\$) or (“bone-marow” NEAR transplant\$)
- 8 OR/1-7
- 9 CANCER FATIGUE/ (drug therapy)
- 10 fatigue\$ (title, abstract & keywords)
- 11 tired\$ or weary or weariness or exhaustion or exhausted or lacklustre or astheni\$ or asthenia\$
- 12 ((lack\$ or loss or lost) adj2 (energy or vigour or vigor)
- 13 (apathy or apathetic or lassitude or letharg\$ or (feeling adj3 (drained or sleepy or sluggish or weak\$)))
- 14 OR/9-13
- 15 8 AND 14

A N A L Y S E S

Comparison 01. Erythropoetin versus no intervention (subanalysis versus placebo)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Difference in fatigue score			Standardised Mean Difference (Random) 95% CI	Subtotals only

Comparison 02. Darbopoetin versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Fatigue score change	4	964	Standardised Mean Difference (Random) 95% CI	-0.13 [-0.27, 0.00]

Comparison 03. Progestational steroids versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Fatigue score change			Standardised Mean Difference (Random) 95% CI	Subtotals only

Comparison 04. Antidepressants versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Fatigue score change	2	643	Standardised Mean Difference (Random) 95% CI	-0.08 [-0.24, 0.07]

Comparison 05. Psychostimulants versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Fatigue score change	2	264	Standardised Mean Difference (Random) 95% CI	-0.30 [-0.54, -0.05]

Comparison 06. Haemopoetic growth factors versus no intervention

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Erythropoetin or darbopoetin versus no treatment	9	2115	Standardised Mean Difference (Random) 95% CI	-0.23 [-0.32, -0.14]
02 Studies with FACT F			Weighted Mean Difference (Random) 95% CI	Totals not selected

Comparison 07. Adverse events

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Adverse events (grouped)			Odds Ratio (Random) 95% CI	Subtotals only

Comparison 08. Withdrawals

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
02 Withdrawals			Odds Ratio (Random) 95% CI	Subtotals only

COVER SHEET

Title Drug therapy for the management of cancer related fatigue

Authors Minton O, Stone P, Richardson A, Sharpe M, Hotopf M

Drug therapy for the management of cancer related fatigue (Review)

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Contribution of author(s)	For the protocol All review authors were responsible for the background of the review, the 'Criteria for considering studies for this review', the 'Methods of the review' and for refining the final draft of the protocol. OM and PS worked in collaboration with Sylvia Bickley to develop the search strategy. For the review OM, PS were responsible for identifying studies extracting data and assessing study quality. MH, AR, MS were responsible for resolving any disagreements about study inclusion. All review authors were responsible for the final editing and production of the text.
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Review first published	2008/1
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Date of most recent SUBSTANTIVE amendment	22 October 2007
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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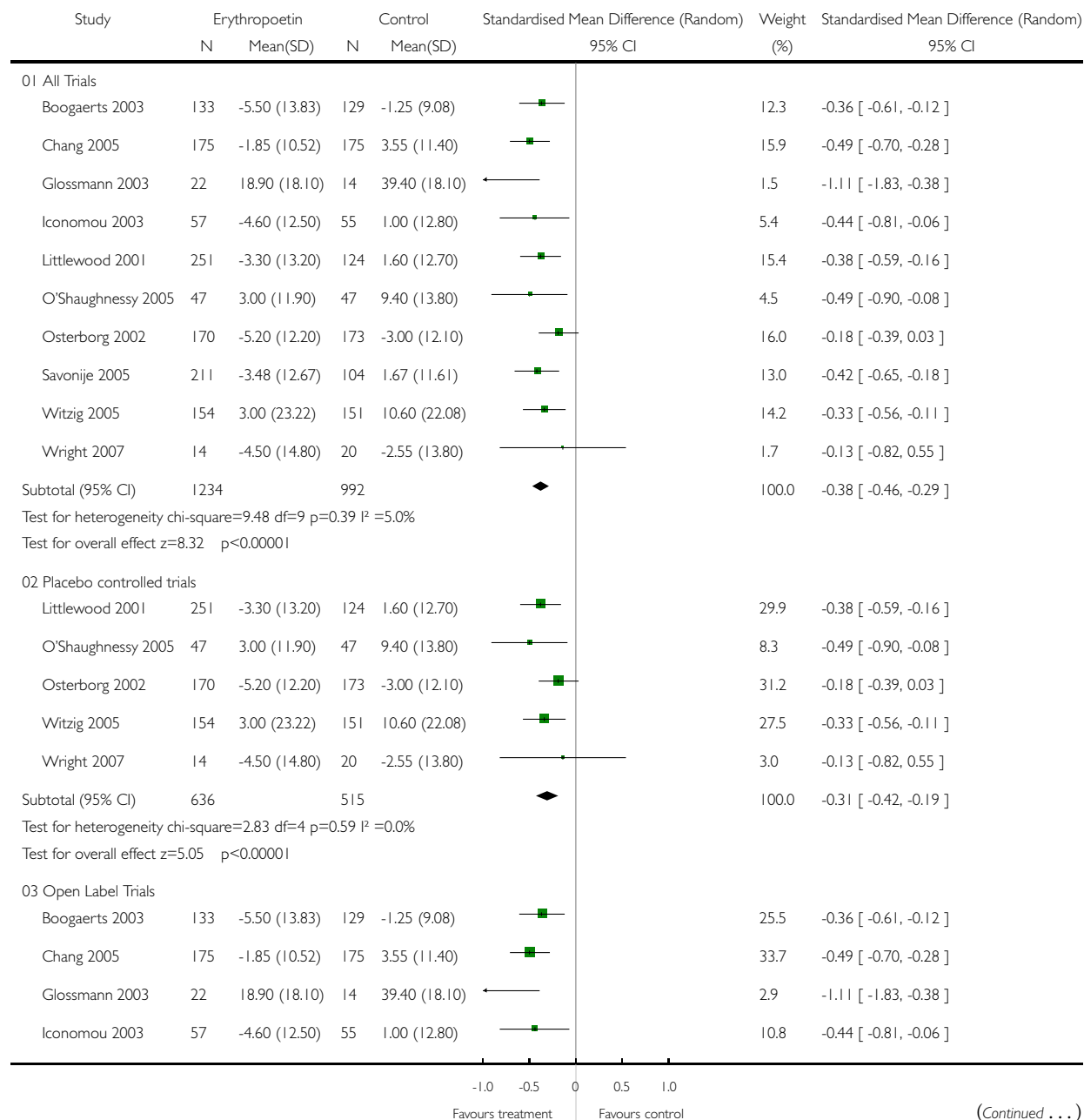
GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Erythropoetin versus no intervention (subanalysis versus placebo), Outcome 01 Difference in fatigue score

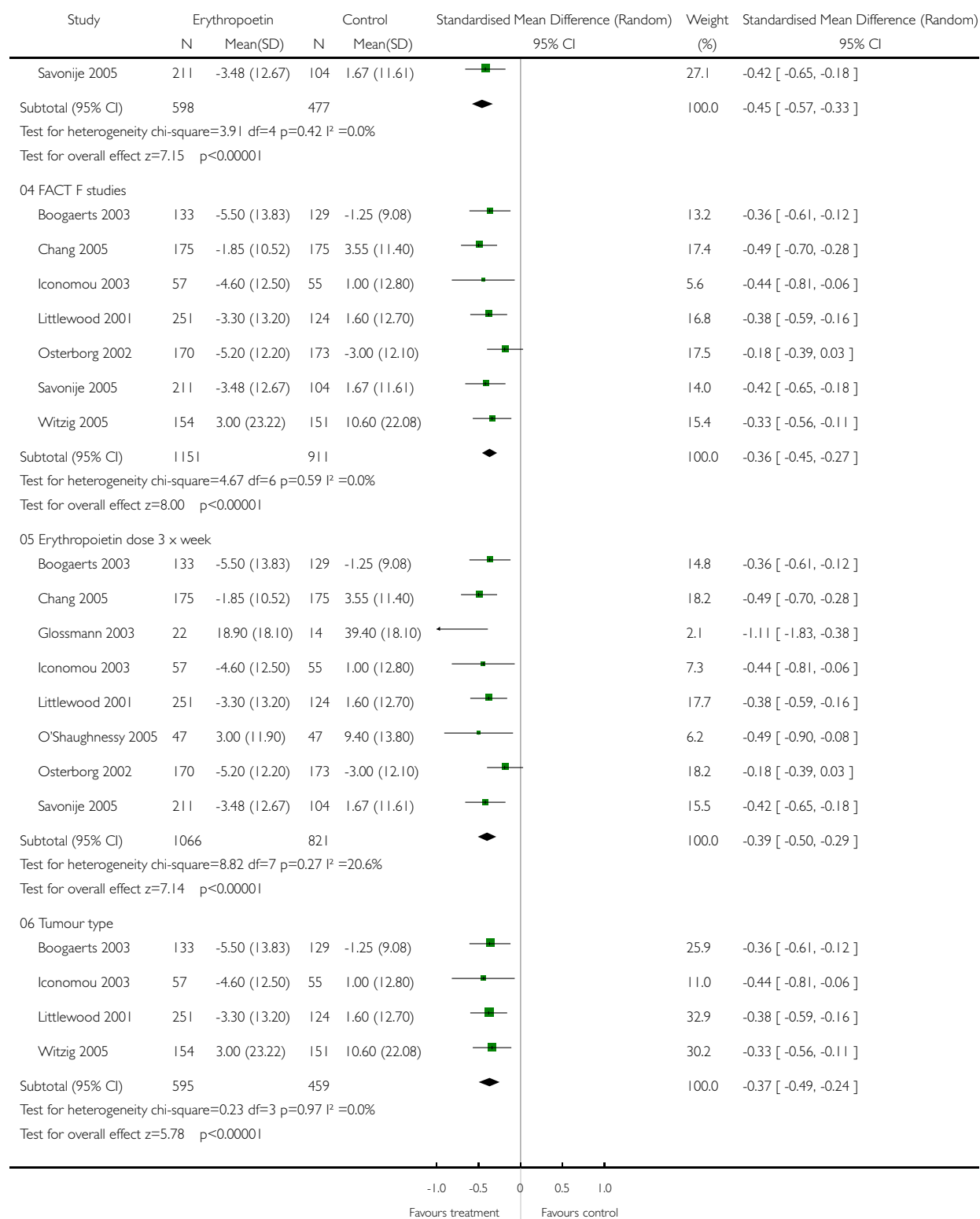
Review: Drug therapy for the management of cancer related fatigue

Comparison: 01 Erythropoetin versus no intervention (subanalysis versus placebo)

Outcome: 01 Difference in fatigue score



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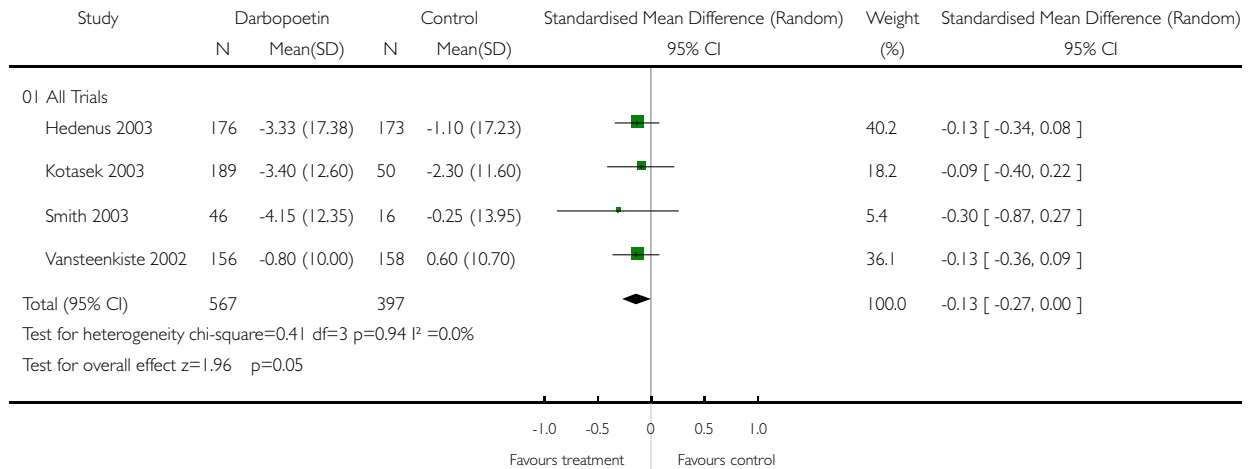


Analysis 02.01. Comparison 02 Darbopoetin versus placebo, Outcome 01 Fatigue score change

Review: Drug therapy for the management of cancer related fatigue

Comparison: 02 Darbopoetin versus placebo

Outcome: 01 Fatigue score change

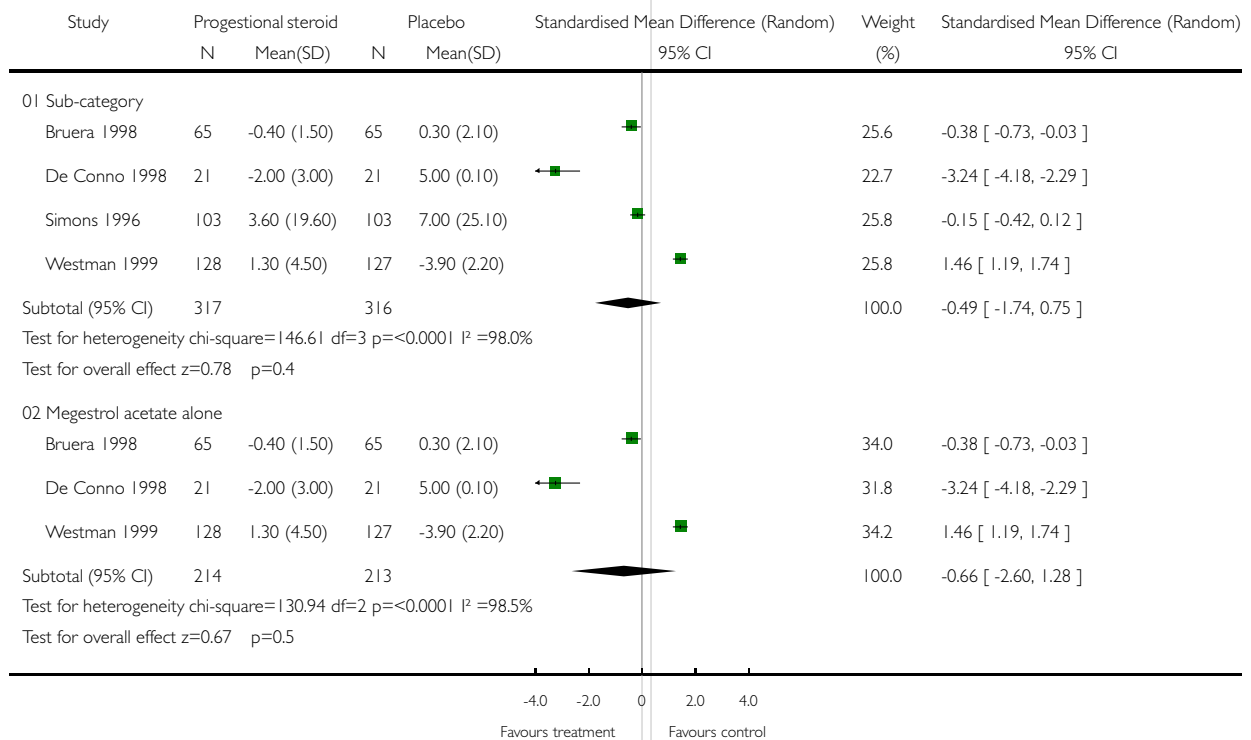


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Review: Drug therapy for the management of cancer related fatigue

Comparison: 03 Progestational steroids versus placebo

Outcome: 01 Fatigue score change

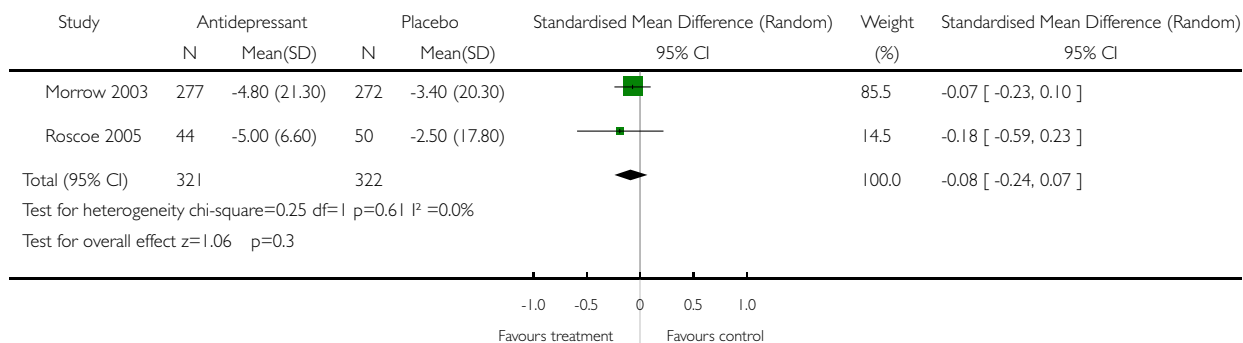


Analysis 04.01. Comparison 04 Antidepressants versus placebo, Outcome 01 Fatigue score change

Review: Drug therapy for the management of cancer related fatigue

Comparison: 04 Antidepressants versus placebo

Outcome: 01 Fatigue score change

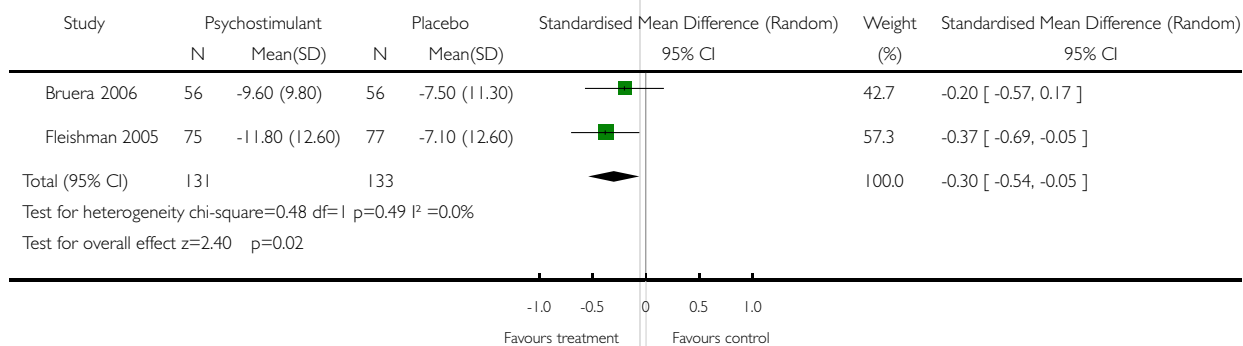


Analysis 05.01. Comparison 05 Psychostimulants versus placebo, Outcome 01 Fatigue score change

Review: Drug therapy for the management of cancer related fatigue

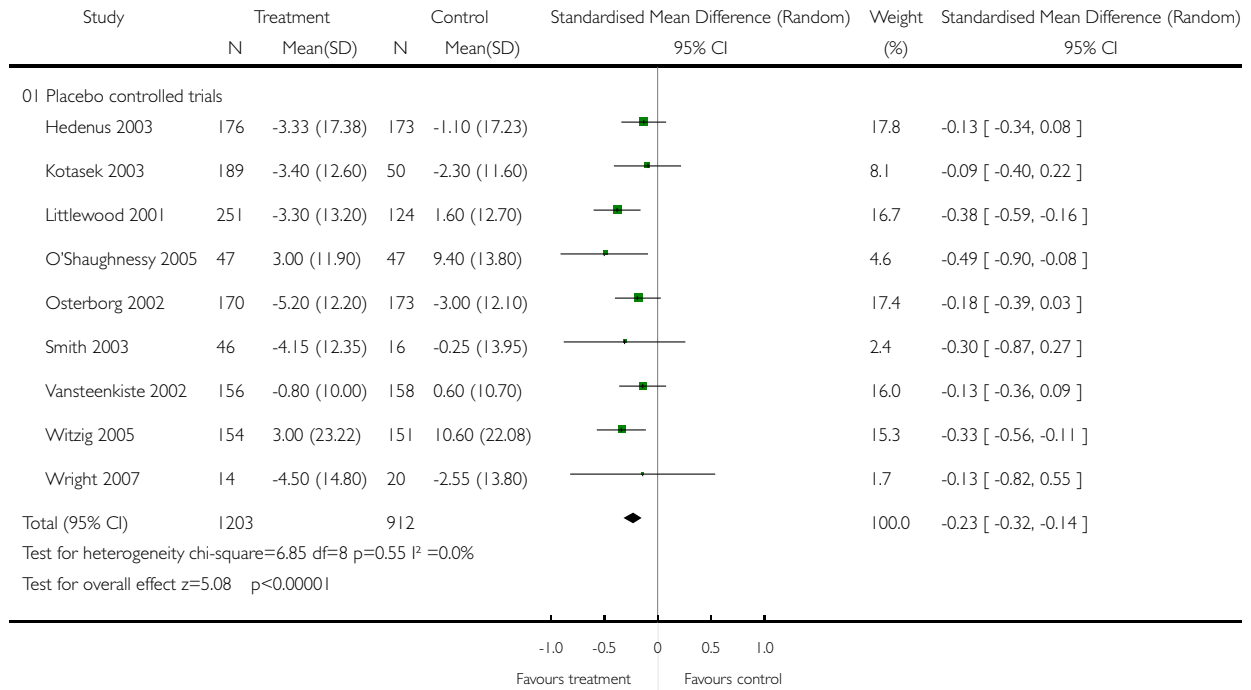
Comparison: 05 Psychostimulants versus placebo

Outcome: 01 Fatigue score change



Analysis 06.01. Comparison 06 Haemopoetic growth factors versus no intervention, Outcome 01 Erythropoetin or darbopoetin versus no treatment

Review: Drug therapy for the management of cancer related fatigue
 Comparison: 06 Haemopoetic growth factors versus no intervention
 Outcome: 01 Erythropoetin or darbopoetin versus no treatment

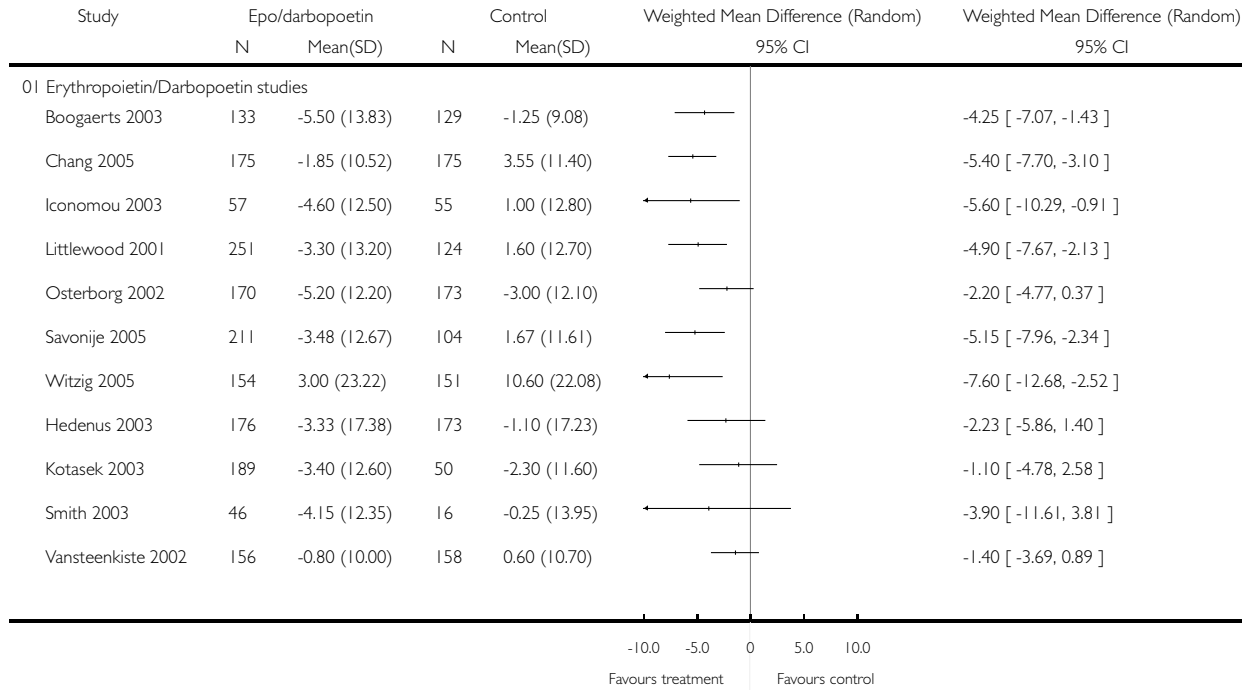


Analysis 06.02. Comparison 06 Haemopoetic growth factors versus no intervention, Outcome 02 Studies with FACT F

Review: Drug therapy for the management of cancer related fatigue

Comparison: 06 Haemopoetic growth factors versus no intervention

Outcome: 02 Studies with FACT F

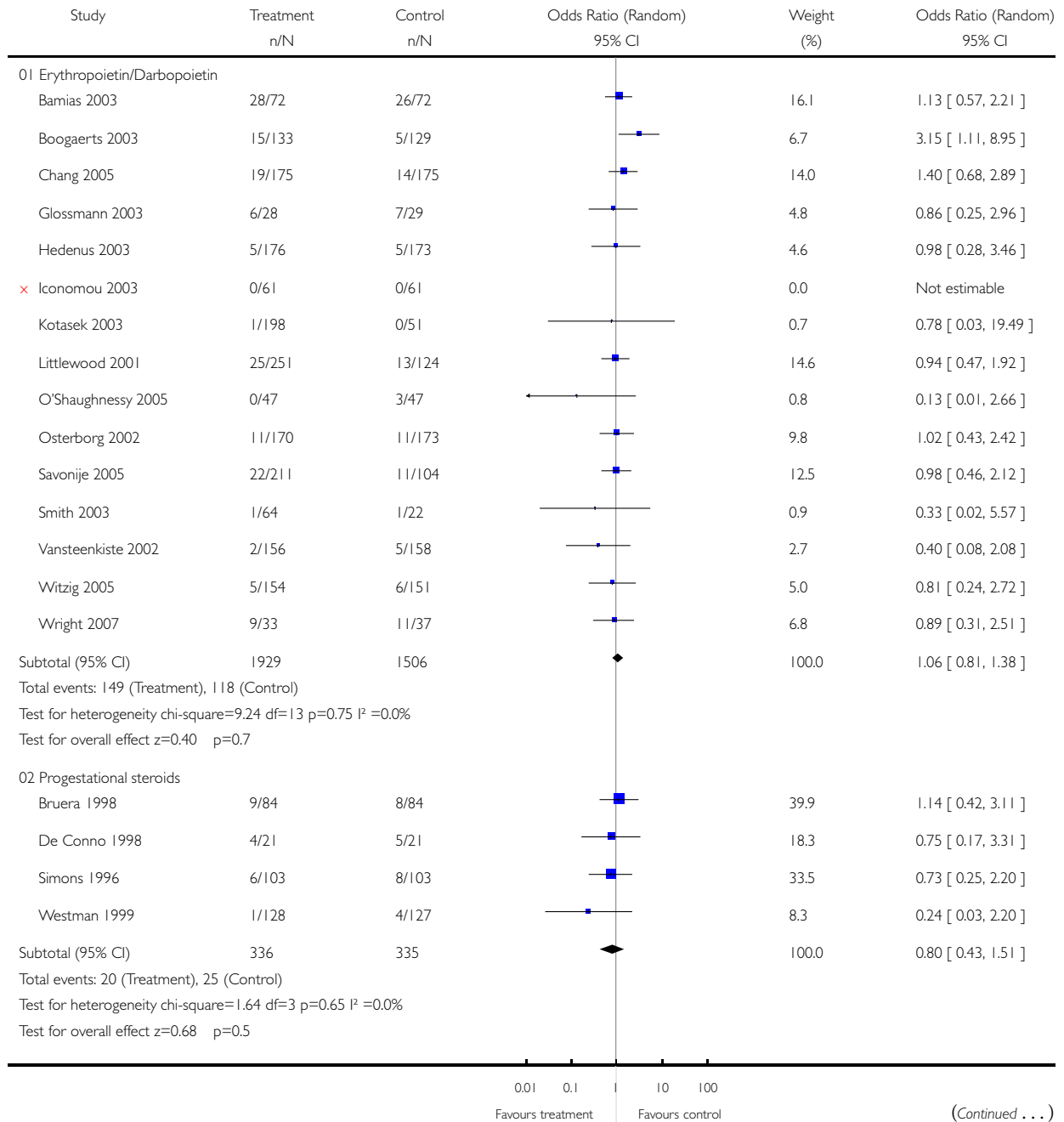


Analysis 07.01. Comparison 07 Adverse events, Outcome 01 Adverse events (grouped)

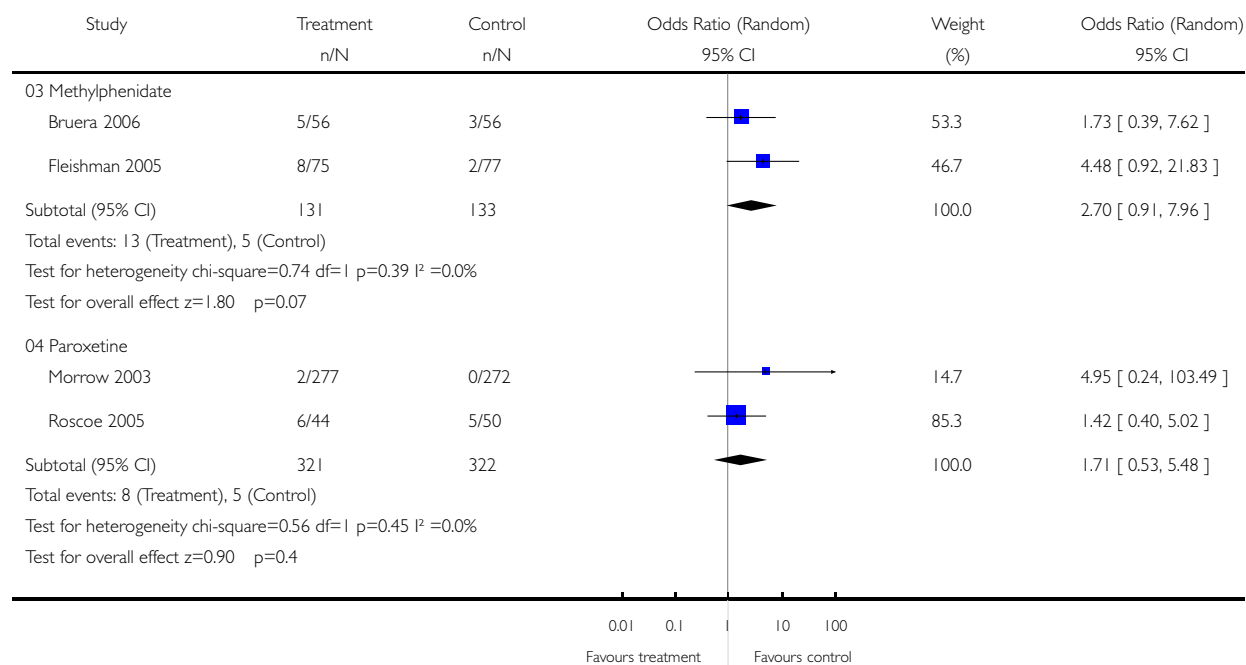
Review: Drug therapy for the management of cancer related fatigue

Comparison: 07 Adverse events

Outcome: 01 Adverse events (grouped)



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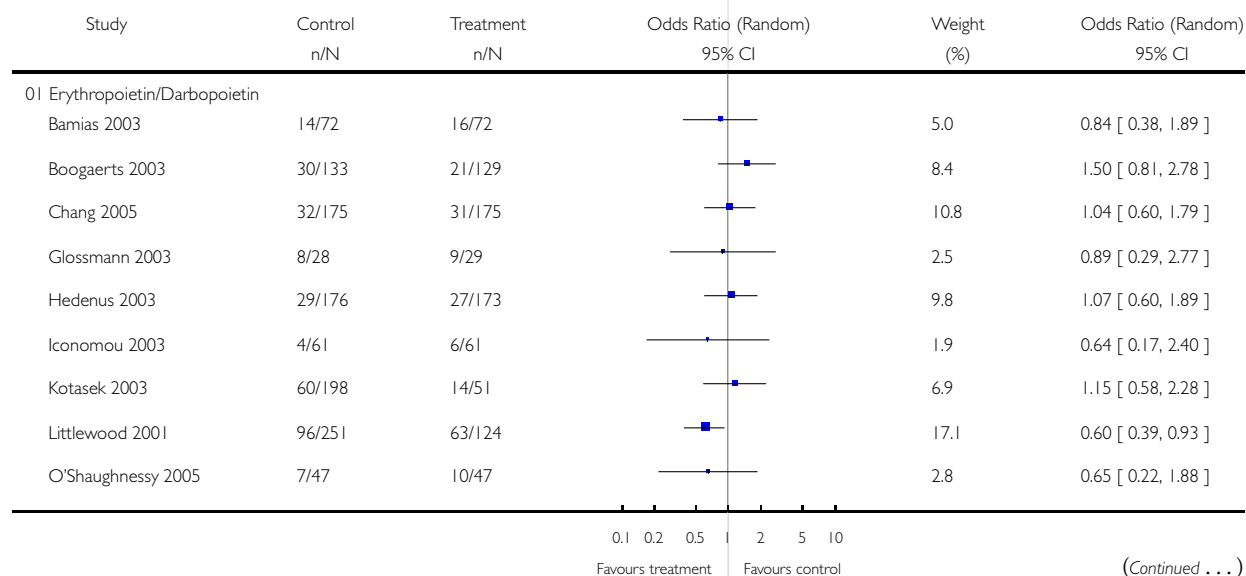


Analysis 08.02. Comparison 08 Withdrawals, Outcome 02 Withdrawals

Review: Drug therapy for the management of cancer related fatigue

Comparison: 08 Withdrawals

Outcome: 02 Withdrawals



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