A Systematic Review and Meta-Analysis of the Pharmacological Treatment of Cancer-Related Fatigue

Ollie Minton, Alison Richardson, Michael Sharpe, Matthew Hotopf, Patrick Stone

Background
Cancer-related fatigue is an important clinical problem. It is common, distressing, and often difficult to treat. There is a role for drug treatment of cancer-related fatigue, but no consensus has been reached on which drugs are useful. This systematic review and meta-analysis aims to review the available evidence and make recommendations for practice and research.

Methods
We searched the Cochrane register of controlled trials (through the second quarter 2007), Medline (January 1, 1966, through August 1, 2007), and EMBASE (January 1, 1980, through August 1, 2007) by use of a predetermined list of search terms. Cochrane Collaboration meta-analysis review methodology was used for this study. The change in fatigue score on the instrument used in each study and other outcomes of interest (adverse events and withdrawal rates) were compared between treatment and control arms by use of the standardized mean difference (SMD) with 95% confidence intervals (CIs). All statistical tests were two-sided.

Results
We identified 27 eligible trials of drug treatments for cancer-related fatigue (with a total of 6746 participants). The overall effect size for all drug classes was small. A meta-analysis of two studies (n = 264 patients) indicated that methylphenidate (a psychostimulant) was superior to placebo (standardized mean difference [SMD] in change in fatigue score = –0.30, 95% confidence interval [CI] = –0.54 to –0.05; P = .02) for treating cancer-related fatigue. A meta-analysis of 10 studies (n = 2226 patients) evaluating erythropoietin in anemic cancer patients who were undergoing chemotherapy indicated that erythropoietin was superior to placebo (SMD = –0.30, 95% CI = –0.46 to –0.29; P = .008). Among anemic patients (four studies with n = 964 patients), improvement in fatigue was associated with darbepoetin treatment compared with placebo treatment (SMD = –0.13, 95% CI = –0.27 to 0.00; P = .05). Progestational steroids and paroxetine were no better than placebo in the treatment of cancer-related fatigue.

Conclusions
There is some evidence that treatment of cancer-related fatigue with methylphenidate appears to be effective. More robust evidence indicates that treatment with hematopoietic agents appears to relieve cancer-related fatigue caused by chemotherapy-induced anemia. Further confirmatory trials are required for both observations.

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Fatigue is one of the most common symptoms experienced by cancer patients (1). The prevalence of cancer-related fatigue varies widely depending on how it is measured and which population of patients is studied. However, many studies report a prevalence of cancer-related fatigue greater than 60% during chemotherapy [for a review, see Iop et al (2)]. Increased fatigue has been found during (3,4) and after (5) treatment. Fatigue can also be a long-term problem in disease-free patients (6). In clinical practice, cancer-related fatigue is a distressing and disabling condition that is under-recognized by cancer physicians (7). These findings (especially the underrecognition and under treatment of fatigue) support the need for further investigation of this symptom.

Cancer-related fatigue is a subjective sensation that is characterized by a pervasive and persistent sense of tiredness that is not relieved by sleep or rest and that can adversely affect a person’s emotional, physical, and mental well-being (8). It has many potential causes. It is associated with anxiety and depression, but it also occurs independently of these symptoms (9,10). Prue et al. (11) have

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See “Notes” following “References.”

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Cancer-related fatigue is an important clinical problem, but which drugs are useful for treatment remains unclear.

Study design
Systematic review and meta-analysis of 27 randomized trials of drug treatments for cancer-related fatigue that met prospective criteria for review (n = 6746 participants).

Contribution
Limited evidence was found that treatment of cancer-related fatigue with methylphenidate appears to be effective. Somewhat more robust evidence was found that treatment with hemopoietic agents appears to relieve cancer-related fatigue caused by chemotherapy-induced anemia. Overall effects of the treatments on fatigue were small, however.

Implications
Because overall effect sizes are small, potential implications for treatment should be tempered. Further confirmatory trials are required for both observations.

Limitations
Some reporting bias may exist. The review did not include non-drug interactions.

From the Editors

demonstrated that the severity of cancer-related fatigue is poorly related to demographic-, disease-, or treatment-related variables. They also point out that methodological weaknesses in studies in the current literature undermine any strong conclusions being drawn about potential contributory factors to cancer-related fatigue.

The multifactorial nature of cancer-related fatigue has led to difficulties in identifying underlying mechanisms (12). A number of hypotheses have been generated to try to explain the causes of cancer-related fatigue. The two most plausible mechanisms include an abnormal or prolonged inflammatory response or disruption to the hypothalamic pituitary adrenal axis. However, clinical support for these theories is lacking. A recent systematic review (13) found some association of cancer-related fatigue with certain cytokines, although shortcomings in the measurement of cancer-related fatigue were identified. Evidence for disruption of the hypothalamic pituitary adrenal axis is more scant—one study (14) reported altered cortisol responses in fatigued cancer survivors, and another study (15) provided evidence for disruption of the hypothalamic pituitary adrenal axis in patients with metastatic disease. The available evidence does, however, indicate that there are common mechanisms across different populations. The lack of identified mechanisms has resulted in the absence of targeted treatments for cancer-related fatigue, and many interventions for managing this symptom remain empirical (16).

Wide variations in the prevalence of cancer-related fatigue have led to the development of a set of diagnostic criteria for a cancer-related fatigue syndrome (17). Although the syndrome was originally described in a population of cancer survivors, the diagnostic criteria have subsequently been used in breast cancer patients undergoing chemotherapy (18) and in a mixed-cancer palliative-care inpatient population (19). However, the need for the application of strict criteria and the use of a semi-structured psychiatric interview (used to rule out any comorbidities that could cause fatigue) has meant that these diagnostic criteria have been used only in noninterventional studies to date. Nonetheless, the limited examination that has been undertaken with these criteria across different populations has demonstrated similar rates of cancer-related fatigue. This means, in practice, that even if there are differences in the level of cancer-related fatigue, then the experience of cancer-related fatigue is similar across all groups.

Several studies have examined the role of nondrug treatments for cancer-related fatigue, such as exercise (20) or psychological treatments (21,22), and have found equivocal evidence of effectiveness. A review of nondrug therapies (23) concluded that there was some evidence of benefit from exercise. Although nonpharmacological approaches are less likely than drug treatments to cause side effects, their role in the management of cancer-related fatigue remains unclear because no meta-analysis of the current evidence has yet been published, although there now is a Cochrane review of exercise for cancer-related fatigue (24).

There is no agreement on the best pharmacological treatment for cancer-related fatigue. The US National Comprehensive Cancer Network guidelines (16,24) recommend initially treating any reversible causes of fatigue (eg, anemia, poor nutrition, or depression) and attending to general supportive measures and psychological support. The only specific drug recommendation (16), which is for the psychostimulant methylphenidate, appears to be based in part on evidence from trials conducted on patients infected with human immunodeficiency virus (25). We therefore conducted a systematic review and meta-analysis to examine the role of this and other drugs in the management of cancer-related fatigue.

Subjects and Methods
Selection of Studies
This review used the standard Cochrane methods (26) to identify randomized studies of drug treat for cancer-related fatigue. Full details of our search strategy can be found in the Cochrane library (27).

We searched the Cochrane register of controlled trials (second quarter 2007), Medline (January 1, 1966, to the week of August 1, 2007), EMBASE (January 1, 1980, to the week of August 1, 2007) with the search terms as indicated in Box I. One author (O. Minton) also hand searched the British Journal of Cancer (January 1, 1999, through March 31, 2007), Journal of Clinical Oncology (January 1, 1983, through March 31, 2007), Journal of Pain and Symptom Management (December 1, 1986, through March 31, 2007), and Palliative Medicine (January 1, 1987, through March 31, 2007).

Reference lists of all articles obtained were checked for additional studies. Experts in the field of cancer-related fatigue were contacted to identify any research that may not have been published. Published abstracts were also obtained through searches of conference proceedings, and full trial data were obtained where possible.

We used the following inclusion criteria: 1) Randomized controlled trials had to be designed to test a drug against placebo or usual care, had to have stated aims that included improvement in the level of quality of life, and had to use a multi-item measure of fatigue. 2) The trials had to use a robust measure of fatigue as an
outcome tool—that is, studies that used single-item scales and/or single visual analogue scales were excluded. Studies that compared disease-modifying treatment regimens and their effect on prognosis and quality of life were also excluded.

**Statistical Analyses**

Data extraction forms were developed a priori and included information regarding methods, participant details, dose and frequency of drug administration, attrition, and outcome measures. Data were extracted by two independent review authors (O. Minton and P. Stone), and any disagreements were resolved by consensus with the other authors (M. Hotopf, A. Richardson, and M. Sharpe). Data were analyzed with RevMan software (28). Quantitative outcomes for dichotomous and continuous data were evaluated by use of a random effects model with RevMan version 4.2.10. The random effects model was chosen a priori because it was likely that any untargeted intervention for cancer-related fatigue could have had a number of treatment effects. The random effects model provided a method of incorporating this uncertainty into a statistical analysis. Outcomes of interest were compared between treatment and control arms by use of the standardized mean difference (SMD) and odds ratios (ORs) with 95% confidence interval (CI). There was no way to determine statistical heterogeneity in many of the analyses undertaken, as determined by the $I^2$ value that is generated during meta-analysis. This value is widely used by the Cochrane Collaboration for determining statistical heterogeneity (26). Subgroup analyses were conducted to investigate the effect of study quality primarily and thus to determine the effect of removing open-label trials. However, as discussed above, there is a limited theoretical basis for subdividing studies any further by treatment or population variables. Further subgroup analysis would also have been conducted post hoc and could have resulted in multiple associations of uncertain clinical significance. It was for these reasons that no further subgroup analyses were undertaken. All statistical tests were two-sided.

**Results**

We screened a total of 5841 titles and abstracts across the four databases used. A shortlist of 116 studies was identified, of which 27 trials met our inclusion criteria and were eligible to be included in meta-analyses. Details of these 27 studies are presented in Table 1. These studies were divided by drug type for ease of analysis.

**Studies of Methylphenidate**

Two studies examined the effect of the psychostimulant drug methylphenidate (29,30). These studies used different populations and different treatment courses, although the dosing schedule was the same in both studies. Bruera et al. (29) examined a palliative care population (n = 112) receiving a 1-week treatment with methylphenidate. Lower et al. (30) examined a mixed-tumor population (n = 152) receiving chemotherapy over an 8-week treatment course.

These two studies were combined in a meta-analysis because the direction of the treatment effect was the same in both studies (Figure 1). This result indicated a statistically significant reduction in cancer-related fatigue with methylphenidate treatment compared with placebo treatment after an average of 5 weeks of treatment (overall $Z$ score = 2.40, $P = .02$; SMD = $-0.30$, 95% CI = $-0.54$ to $-0.05$). Because the two studies used the same outcome measure [ie, the Functional Assessment of Cancer Therapy—fatigue subscale (FACT F) (31)], it was possible to obtain a weighted mean difference. This difference indicated an improvement in fatigue above the previously determined minimum clinically important difference on this scale (32).

Neither study had a large effect size, and indeed one of the studies had an effect size that indicated no superiority over placebo because both arms had a positive treatment effect (29). Methylphenidate can cause adverse effects, but these side effects have been reported as minor—for example, headache or nausea. Existing data support a dose of 10–20 mg/day, depending on response.

**Studies of Hematopoietic Growth Factors**

**Erythropoietin.** We included 10 trials of erythropoietin (33–42) in the meta-analysis; these trials analyzed a total of 5712 patients. All 10 studies included anemic participants with a baseline hemoglobin level of less than 12 g/dL. Eight of the 10 trials examined participants receiving chemotherapy. In three studies (43–45), it was not possible to obtain data on fatigue score changes and these studies were therefore excluded from the analysis. There was wide variation in the populations and in the doses of erythropoietin used in the studies included in our analysis. The participants included five mixed-tumor populations (excluding hematological cancers), three breast tumor populations, two hematological tumor populations, and...
<table>
<thead>
<tr>
<th>First author of study (ref.) year</th>
<th>Study design</th>
<th>Disease, treatment (No. of participants)</th>
<th>Interventions</th>
<th>Questionnaire used</th>
<th>Jadad quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruera (29), 2006</td>
<td>Double blind</td>
<td>Any tumor type, off chemotherapy (n = 112)</td>
<td>Methylphenidate (5 mg PRN up to 20 mg/day) or placebo</td>
<td>FACT F</td>
<td>5</td>
</tr>
<tr>
<td>Fleishman (30), 2005</td>
<td>Double blind</td>
<td>Any tumor type, on chemotherapy (n = 152)</td>
<td>Methylphenidate (5 mg bd or PRN up to 20 mg/day) or placebo</td>
<td>FACT F</td>
<td>3</td>
</tr>
<tr>
<td>Bamias (43), 2003*†</td>
<td>Open label</td>
<td>Solid tumors, on platinum-based chemotherapy (n = 144)</td>
<td>EP0 (10 000 U sc, three times per week, 12/52 or UC</td>
<td>EORTC QLQ 30</td>
<td>2</td>
</tr>
<tr>
<td>Boogaerts (33), 2003§</td>
<td>Open label</td>
<td>Any tumor type, received at least three cycles of chemotherapy (n = 262)</td>
<td>EP0 (150 U/kg, three times per week, 12/52 or UC</td>
<td>FACT F</td>
<td>2</td>
</tr>
<tr>
<td>Chang (42), 2005§</td>
<td>Open label</td>
<td>Breast cancer, on chemotherapy (n = 350)</td>
<td>EP0 (40 000 U, one time per week) or UC</td>
<td>FACT F</td>
<td>2</td>
</tr>
<tr>
<td>Glossmann (34), 2003§</td>
<td>Open label</td>
<td>Lymphoma, on high-dose chemotherapy (n = 57)</td>
<td>EP0 (10 000 U, three times per week) or UC</td>
<td>EORTC QLQ 30</td>
<td>2</td>
</tr>
<tr>
<td>Iconomou (35), 2003§</td>
<td>Open label</td>
<td>Any tumor type excluding hematological tumors, on chemotherapy (n = 122)</td>
<td>EP0 (10 000 U, three times per week, 12/52 or UC</td>
<td>FACT F</td>
<td>2</td>
</tr>
<tr>
<td>Leyland–Jones (44), 2005*§</td>
<td>Open label</td>
<td>Breast cancer, any chemotherapy (n = 939)</td>
<td>EP0 (40 000 U, once a week) or placebo</td>
<td>FACT An</td>
<td>4</td>
</tr>
<tr>
<td>Littlewood (38), 2001§</td>
<td>Open label</td>
<td>Any tumor type excluding leukemia, on platinum-based chemotherapy (n = 375)</td>
<td>EP0 (150 U/kg, three times a week) or placebo</td>
<td>FACT F</td>
<td>5</td>
</tr>
<tr>
<td>O’Shaughnessy (39), 2005</td>
<td>Double blind</td>
<td>Breast cancer, on ≥4 cycles of chemotherapy (n = 94)</td>
<td>EP0 (40 000 U, weekly, 12/52) or placebo</td>
<td>FACT An</td>
<td>5</td>
</tr>
<tr>
<td>Osterborg (37), 2002§</td>
<td>Double blind</td>
<td>Hematological malignancies, off chemotherapy (n = 343)</td>
<td>EP0 (150 U/kg, three times per week, 16/52) or placebo</td>
<td>FACT F</td>
<td>4</td>
</tr>
<tr>
<td>Savonije (38), 2005§</td>
<td>Open label</td>
<td>Any tumor type, on platinum-based chemotherapy (n = 315)</td>
<td>EP0 (10 000 U, three times per week, 12/52 or UC</td>
<td>FACT F</td>
<td>2</td>
</tr>
<tr>
<td>Wilkinson (45), 2006*§</td>
<td>Open label</td>
<td>Ovarian cancer, on platinum-based chemotherapy (n = 182)</td>
<td>EP0 (10–20 000 U, three times per week, 12/52) or UC</td>
<td>FACT An</td>
<td>3</td>
</tr>
<tr>
<td>Witzig (40), 2005§</td>
<td>Double blind</td>
<td>Any tumor type, on chemotherapy (n = 344)</td>
<td>EP0 (40 000 U, weekly, 16/52) or placebo</td>
<td>FACT F</td>
<td>5</td>
</tr>
<tr>
<td>Wright (41), 2007§</td>
<td>Double blind</td>
<td>Non–small cell lung cancer any treatment (n = 79)</td>
<td>EP0 (40 000 U, weekly, 12/52) or placebo</td>
<td>FACT An</td>
<td>4</td>
</tr>
<tr>
<td>Hedenus (47), 2003§</td>
<td>Double blind</td>
<td>Lymphoproliferative tumors, on chemotherapy (n = 344)</td>
<td>Darbepoetin (2.25 µg/kg every 3 weeks) or placebo</td>
<td>FACT F</td>
<td>5</td>
</tr>
<tr>
<td>Kotasek (46), 2003§</td>
<td>Double blind</td>
<td>Any tumor type on chemotherapy (n = 249)</td>
<td>Darbepoetin (4.5–15 µg/kg, every 3 weeks) or placebo</td>
<td>FACT F</td>
<td>5</td>
</tr>
<tr>
<td>Smith (48), 2003</td>
<td>Double blind</td>
<td>Any tumor type excluding myeloid tumors, not on chemotherapy (n = 86)</td>
<td>Darbepoetin (6.75–10 µg/kg, two groups, every 3 weeks) or placebo</td>
<td>FACT F</td>
<td>3</td>
</tr>
<tr>
<td>Vansteenkiste (49), 2002§</td>
<td>Double blind</td>
<td>Lung cancer, on chemotherapy (n = 320)</td>
<td>Darbepoetin (2.24 µg/kg, weekly, 12/52)</td>
<td>FACT F</td>
<td>4</td>
</tr>
<tr>
<td>Morrow (50), 2003</td>
<td>Double blind</td>
<td>Any tumor type, on chemotherapy (n = 549)</td>
<td>Paroxetine (20 mg od, 8/52) or placebo</td>
<td>Fatigue symptom checklist</td>
<td>4</td>
</tr>
<tr>
<td>Roscoe (51), 2005</td>
<td>Double blind</td>
<td>Breast cancer, on chemotherapy (n = 94)</td>
<td>Paroxetine (20 mg od, 8/52)</td>
<td>Fatigue symptom checklist</td>
<td>5</td>
</tr>
<tr>
<td>Brueera (53), 1998</td>
<td>Cross-over placebo controlled</td>
<td>Lung and GI tumors, off chemotherapy (n = 84)</td>
<td>Megestrol acetate (480 mg od) or placebo, 7/7, and cross-over allowed</td>
<td>Piper fatigue scale</td>
<td>3</td>
</tr>
<tr>
<td>De Conno (52), 1998</td>
<td>Double blind</td>
<td>Any tumor type, off chemotherapy (n = 42)</td>
<td>Megestrol acetate (320 mg od)</td>
<td>POMS</td>
<td>4</td>
</tr>
<tr>
<td>Simons (54), 1996</td>
<td>Double blind</td>
<td>Any tumor type, off chemotherapy (n = 206)</td>
<td>Medroxyprogesterone acetate (600 mg bd, 12/52) or placebo</td>
<td>EORTC QLQ 30</td>
<td>4</td>
</tr>
<tr>
<td>Westman (55), 1999</td>
<td>Double blind</td>
<td>Any tumor type, off chemotherapy (n = 255)</td>
<td>Megestrol acetate (320 mg od, 12/52) or placebo</td>
<td>EORTC QLQ 30</td>
<td>4</td>
</tr>
<tr>
<td>Diel (57), 2004</td>
<td>Double blind</td>
<td>Breast cancer, off chemotherapy (n = 466)</td>
<td>Ibudronate (2–8 mg, every 4 weeks)</td>
<td>EORTC QLQ 30</td>
<td>2</td>
</tr>
<tr>
<td>Monk (56), 2006</td>
<td>Open label</td>
<td>Any tumor type, on docetaxel-based chemotherapy (n = 12)</td>
<td>Etanercept (a tumor necrosis factor blocker, 25 mg twice a week up to 18/52) or UC</td>
<td>Fatigue symptom inventory</td>
<td>2</td>
</tr>
</tbody>
</table>

* ref. = reference; UC = usual care with or without required transfusions; 12/52 = 12 weeks of drug treatment; 16/52 = 16 weeks of drug treatment; 8/52 = 8 weeks of drug treatment; 18/52 = 18 weeks of drug treatment; EP0 = erythropoietin; EORTC QLQ 30 = European Oncology Society 30-item quality of life questionnaire that includes a validated fatigue subscale; FACT F = functional assessment of cancer therapy, fatigue subscale; FACT An = functional assessment of cancer therapy, anemia subscale; POMS = profile of mood states fatigue subscale; GI = gastrointestinal; PRN = as required; od = once a day; bd = twice a day; sc = subcutaneously.

† The Jadad quality score is a score of up to 5 points that is based on an assessment of blinding and randomization and has a description of withdrawals (70).

‡ Missing fatigue data were so not included in meta-analysis.

§ All hematopoietic stimulant factor studies required a hemoglobin level of less than 12 g/dL as an inclusion criteria.
and one lung cancer population. The erythropoietin dose given varied from 3000 to 40000 units, and frequency of administration varied between one and three times per week (Table 1). A statistically significant effect was observed after 12 weeks of treatment (overall effect $Z$ score = 8.32, $P < .001$; SMD = –0.38, 95% CI = –0.46 to –0.29) for the reduction of cancer-related fatigue with methylphenidate vs placebo. Mean between-group differences and their 95% confidence intervals were abstracted from each study and combined to obtain a pooled SMD of all studies (diamond) of the effect of methylphenidate. The $I^2$ test statistics were used to test for the presence of heterogeneity across studies. The overall effect is given by $Z$ score. The weight given to each study was based on numbers of participants and mean difference and SD. IV = inverse variance. All statistical tests were two-sided. References: Bruera (2006) = Bruera et al. (29); Fleishman (2005) = Fleishman et al. (30).

![Figure 1](image1.png)

**Figure 1.** Methylphenidate meta-analysis. Methylphenidate was the only identified psychostimulant. Raw data are shown for the mean fatigue score change and SD for methylphenidate and placebo in each study. The plot also shows the standardized (Std.) mean differences (SMDs squares) and 95% confidence intervals (Cls, horizontal bars) for methylphenidate vs placebo. Mean between-group differences and their 95% confidence intervals were abstracted from each study and combined to obtain a pooled SMD of all studies (diamond) of the effect of methylphenidate. The $I^2$ test statistics were used to test for the presence of heterogeneity across studies. The overall effect is given by $Z$ score. The weight given to each study was based on numbers of participants and mean difference and SD. IV = inverse variance. All statistical tests were two-sided. References: Bruera (2006) = Bruera et al. (29); Fleishman (2005) = Fleishman et al. (30).

![Figure 2](image2.png)

**Figure 2.** Erythropoietin meta-analysis. Raw data are shown for the mean fatigue score change and SD for erythropoietin, placebo, and/or usual care in each study. The plot also shows the standardized (Std.) mean differences (SMDs squares) and 95% confidence intervals (Cls, horizontal bars) for erythropoietin vs placebo or usual care for each individual study. Horizontal bars with an arrow represent outlying values that are larger than the scale can accommodate. Mean between-group differences and their 95% confidence intervals were abstracted from each study and combined to obtain a pooled SMD of all studies (diamonds) of the effect of erythropoietin. The $I^2$ test statistics were used to test for the presence of heterogeneity across studies. The overall effect is given by the $Z$ score. The weight given to each study was based on numbers of participants and mean difference and SD. IV = inverse variance. All statistical tests were two-sided. References: Boogaerts (2003) = Boogaerts et al. (33); Chang (2005) = Chang et al. (42); Glossman (2003) = Glossman et al. (34); Iconomou (2003) = Iconomou et al. (35); Littlewood (2001) = Littlewood et al. (38); O’Shaughnessy (2002) = O’Shaughnessy et al. (39); Ostergard (2002) = Ostergard et al. (37); Savonije (2005) = Savonije et al. (36); Witzig (2005) = Witzig et al. (40); Wright (2007) = Wright et al. (41).
erythropoietin treatment compared with placebo treatment or usual care (Figure 2). This effect was clinically significant.

Nearly all of the studies of erythropoietin were conducted on anemic cancer patients who were receiving chemotherapy; however, several studies were conducted on anemic patients who were not receiving chemotherapy. Overall, half of the analyzed studies were open label. However, even after controlling for this potential bias (by conducting subgroup analysis), there was still an improvement in cancer-related fatigue (Figure 2). There was a wide variation in dose of erythropoietin used and treatment duration. We are unable to recommend a specific dose of erythropoietin for routine practice on the basis of our review. However, the aim of treatment should be to use the minimum required dose of erythropoietin for the shortest duration because of the theoretical increase in the risk of thromboembolic side effects with higher doses and protracted treatment courses.

**Darbepoetin.** We included four trials (46–49) of darbepoetin in this review. A total of 1065 participants were studied in these four trials; all were anemic patients with a baseline hemoglobin level of less than 12 g/dL. Three of the studies (46,47,49) included patients receiving chemotherapy. The four studies included two mixed-tumor populations (46,48), one lymphoproliferative tumor population (47), and one lung cancer population (49). We observed a borderline statistically significant effect after 12 weeks of treatment (overall Z score effect = 1.96, $P = .05$; SMD = −0.13, 95% CI = −0.27 to 0.00) for darbepoetin compared with placebo in the treatment of cancer-related fatigue (Figure 3).

**Studies of Paroxetine**

Paroxetine was the only antidepressant to have been studied in the randomized trials of cancer-related fatigue included in our meta-analysis. Two studies (50,51) were included—one examined a mixed-tumor population (50) and the other examined a breast cancer population (51). Both studies used an 8-week course of treatment in patients receiving chemotherapy. These studies had a total of 645 participants, and their outcome data were combined in a meta-analysis (Figure 4). However, no cancer-related fatigue benefit for paroxetine compared with placebo after 8 weeks of treatment was observed (overall Z effect = 1.06, $P = .29$; SMD = −0.08, 95% CI = −0.24 to 0.07).

**Studies of Progestational Steroids**

We analyzed four studies of progestational steroids for treatment of cancer-related fatigue (52–55). Three studies (52,53,55) used megestrol acetate, and one (54) used medroxyprogesterone acetate. All four studies examined a mixed-tumor palliative population who were not receiving chemotherapy. A total of 561 participants were...
Effects of Progestational Steroids on Fatigue

Mean differences (SMD, used and placebo in each study. The plot also shows standardized (Std.) effects for the mean fatigue score change and SD for the progestational steroid differences and 95% confidence interval were abstracted from each study and combined to obtain a pooled SMD of all studies (diamonds) of the effect of progestational steroids. The $I^2$ test statistics were used to test for the presence of heterogeneity across studies. The overall effect is given by Z score. The weight given to each study was based on the numbers of participants and mean difference and its SD. IV = inverse variance. All statistical tests were two-sided. References: Bruera (1998) = Bruera et al. (53); De Conno (1998) = De Conno et al. (52); Simons (1996) = Simons et al. (54); Westman (1999) = Westman et al. (55).

Study or Subgroup | Progestational steroid | Placebo | Std. Mean Difference
<table>
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<tr>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Bruera 1998</td>
<td>-0.4</td>
<td>1.5</td>
<td>27</td>
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<tr>
<td>De Conno 1998</td>
<td>-2</td>
<td>3.5</td>
<td>21</td>
</tr>
<tr>
<td>Simons 1996</td>
<td>3.6</td>
<td>19.6</td>
<td>103</td>
</tr>
<tr>
<td>Westman 1999</td>
<td>0.6</td>
<td>26.9</td>
<td>128</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>279</td>
</tr>
</tbody>
</table>

Heterogeneity: $\text{I}^2 = 0.08; \text{Chi}^2 = 6.67, df = 3 (P = 0.02); \text{I}^2 = 69%$

Test for overall effect: $Z = 1.06 (P = 0.29)$

**Figure 5.** Progestational steroid meta-analysis. Raw data are shown for the mean fatigue score change and SD for the progestational steroid used and placebo in each study. The plot also shows standardized (Std.) mean differences (SMD, squares) and 95% confidence intervals (CIs, horizontal bars) for progestational steroids vs placebo. Mean between-group differences and 95% confidence interval were abstracted from each study and combined to obtain a pooled SMD of all studies (diamonds) of the effect of progestational steroids. The $I^2$ test statistics were used to test for the presence of heterogeneity across studies. The overall effect is given by Z score. The weight given to each study was based on the numbers of participants and mean difference and its SD. IV = inverse variance. All statistical tests were two-sided. References: Bruera (1998) = Bruera et al. (53); De Conno (1998) = De Conno et al. (52); Simons (1996) = Simons et al. (54); Westman (1999) = Westman et al. (55).

No benefit for progestational steroids compared with placebo was observed after an average of 8 weeks of treatment (overall Z effect = 1.06, $P = .29$; SMD = -0.18, 95% CI = -0.52 to 0.16). There was substantial statistical heterogeneity among these trials ($I^2 = 68%$), but subgroup analysis could not identify its cause (data not shown). There were variations in dose of progestational steroids, follow-up time, and tumor type studied, all of which may have contributed to heterogeneity. Although these trials are older than most of the other trials included in this analysis, they were of good quality and placebo controlled. Thus, there is no evidence to support the use of progestational steroids for the treatment of cancer-related fatigue in current practice. There is no need for additional investigation because the analysis demonstrates a consistent negative effect across all four studies.

**Single Studies**

Two studies of other agents were identified by the review. One (56) examined the effect of etanercept (an inhibitor of tumor necrosis factor) on 12 patients with mixed-tumor types undergoing docetaxel-based chemotherapy. This was an open-label study, with six patients randomly assigned to receive an additional etanercept infusion and six patients randomly assigned to chemotherapy alone. The trial reported a statistically significant treatment effect on cancer-related fatigue.

The other study examined the effect of the bisphosphonate ibandronate on quality of life in patients with metastatic breast cancer (57) who were randomly assigned to receive various doses of ibandronate or placebo. A total of 466 participants were studied. This study reported a statistically significant treatment effect for ibandronate on cancer-related fatigue, compared with placebo.

**Safety**

There was a high rate of adverse effects in all of the trials included in our review, but this rate was not related to the type of study medication (Figure 6). The rate of withdrawal was not statistically significantly different between groups (treatment or nontreatment arms) (Figure 7). The high frequency of withdrawals most likely results from the unstable nature (ie, patients with metastatic disease and complex treatment regimens) of the population studied, and most withdrawals occurred because of disease progression and/or protocol violations.

**Discussion**

This systematic review is, to our knowledge, the first to quantify the effects of commonly used pharmacological treatments for cancer-related fatigue. The main results demonstrate reasonable evidence for the role of erythropoietin in the treatment of cancer-related fatigue and preliminary evidence for the role of methylphenidate and darbepoetin.

The conclusions must be considered in the light of several potential limitations. First, although we attempted to obtain all available data from trials examining the drug treatment of cancer-related fatigue, there is still likely to be some reporting bias. This bias is illustrated, in part, by the lack of complete study data available for certain trials. It is difficult to conduct trials in fatigued cancer patients, and so it is possible that other drugs have been (at least partially) studied but that the results have not been published. We were not able to analyze for publication bias by using funnel plot methodology because of the lack of large-scale trials (58), but the systematic methodology for study identification that we used should have minimized this bias.

Second, during the selection of studies, we identified additional candidate drugs, but none of these drugs had been examined with randomized controlled trial methodology and so were excluded from this analysis. We did not quantify the number of studies that did not meet our inclusion criteria.

Third, there are likely to be many studies that used fatigue as one of many variables assessed in generic quality of life measures in populations of cancer patients. We deliberately excluded such trials because we suspected that they would be subject to substantial reporting bias (ie, these studies would have dealt with fatigue as a secondary outcome and so would be more likely to have reported positive findings but ignored negative ones). The potentially large number of these studies would have made complete...
identification and analysis impractical. Consequently, we designed a search strategy to identify studies in which fatigue was an outcome of interest.

Fourth, the overall effect sizes that we are reporting for all classes of drugs are small. The potential implications for current practice and future research should be tempered as a result of this finding. Nevertheless, our review has been able to systematically assess the effects of a number of pharmacological interventions for cancer-related fatigue.

We found limited evidence for the use of the psychostimulant methylphenidate in the treatment of cancer-related fatigue. It is a controlled drug with a potential risk of long-term addiction and

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**Figure 6.** Adverse events meta-analysis. Odds ratio (OR, squares) and 95% confidence interval (CI, horizontal bars) for drug type vs placebo are shown. The frequency of adverse events and its 95% confidence interval were abstracted from each study and combined to obtain a pooled odds ratio for each drug class separately (diamonds). The weight given to each study was based on the numbers of events and its SD. The I² test statistics were used to test for the presence of heterogeneity across studies. The overall effect is given by Z score. M-H = Mantel-Haenszel test. All statistical tests were two-sided. References: Boogaerts (2003) = Boogaerts et al. (33); Chang (2005) = Chang et al. (42); Glossman (2003) = Glossman et al. (34); Iconomou (2003) = Iconomou et al. (35); Littlewood (2001) = Littlewood et al. (38); O'Shaughnessy (2002) = O'Shaughnessy et al. (39); Osterborg (2002) = Osterborg et al. (37); Savonije (2005) = Savonije et al. (36); Witzig (2005) = Witzig et al. (40); Wright (2007) = Wright et al. (41); Hedenus (2003) = Hedenus et al. (47); Kotasek (2003) = Kotasek et al. (48); Smith (1996) = Smith et al. (49); Simons (1996) = Simons et al. (54); Westman (1999) = Westman et al. (55); Bruera (2006) = Bruera et al. (29); Fleishman (2005) = Fleishman et al. (30); Bruera (2006) = Bruera et al. (29); Fleishman (2005) = Fleishman et al. (30).
should be given only under expert supervision (59). Further work is required to identify which groups of patients are most likely to benefit and to determine the optimal duration of treatment.

We identified two additional trials (60,61) of methylphenidate that are currently underway; results of these trials may help to answer some of the remaining questions about the relative risks and benefits associated with methylphenidate.

We found no evidence for the use of the antidepressant paroxetine in the treatment of cancer-related fatigue. This finding is important because depression and cancer-related fatigue are often regarded as being synonymous, an assumption that is reflected in prescribing practices. Thus, the evidence indicates that cancer-related fatigue and depression appear to be two distinct disease entities.
We found good evidence that erythropoietin is an effective treatment for cancer-related fatigue in anemic cancer patients receiving chemotherapy. However, we found limited evidence that darbepoetin had the same effect. The beneficial effect of darbepoetin was predicted on pharmacological grounds (62,63) because erythropoietin and darbepoetin have very similar mechanisms of action. It may be that the lack of clear improvement in fatigue could have resulted from the complex trial designs or the specific populations of patients who were studied. There is also some controversy surrounding the safety of these drugs (64,65). In practice, it is not clear which dose of erythropoietin or darbepoetin, which treatment duration, and which maintenance level of hemoglobin are optimal for maximal relief of cancer-related fatigue. In a previous meta-analysis (66), the greatest improvement in quality of life was found to be associated with increased hemoglobin levels of 8–10 g/dL. It is important to note that, at a hemoglobin level of greater than 10 g/dL, only 20% of the variance in fatigue levels is explained by hemoglobin level (64).

Two studies (41,44) have raised specific safety concerns about the use of erythropoietin. The first study (40) was terminated early because of increased mortality in the erythropoietin group, compared with the placebo group. The second study (43) also observed decreased survival in the erythropoietin group; however, this study was aiming for a maintenance hemoglobin level of 12–14 g/dL, which is higher than the current recommended treatment guidelines of 10-12 g/dL (67). Our review did not identify additional safety concerns associated with erythropoietin and/or darbepoetin treatment that have not been previously documented (64).

Future research on erythropoietin and/or darbepoetin as treatment for cancer-related fatigue should focus on studies designed to identify the optimal dose associated with better quality of life and relief of cancer-related fatigue. It is also not clear whether treatment with erythropoietin and/or darbepoetin is able to relieve fatigue in patients who are not anemic, in anemic patients who are undergoing other anticancer therapies (eg, hormone therapy or radiation therapy), or in patients with advanced cancer who are no longer receiving active therapy. Further studies in these areas are warranted.

Future research into cancer-related fatigue, however, should not focus simply on the role of drugs. As we have discussed above, many potential mechanisms and contributing factors could cause or increase the level of cancer-related fatigue. The underlying mechanism of cancer-related fatigue remains unclear. Indeed, it is unlikely that any single mechanism will ever be identified because cancer-related fatigue is almost certainly multi-factorial in origin. Although many studies have reported on the correlates of cancer-related fatigue and have speculated on the causes of this symptom, few studies have actually tested specific hypotheses about the underlying mechanism.

There are two potential areas for research in cancer-related fatigue in addition to ongoing drug studies: The first area to examine is the basic science of fatigue. Research topics include immune dysfunction, disruption of serotonin production by the central nervous system, and disturbance of the hypothalamic–pituitary axis. These nonintervention studies could use the diagnostic criteria for cancer-related fatigue syndrome as well as measures of sleep, mood, and overall quality of life. If the group being studied could be dichotomized (by use of the diagnostic criteria) into fatigued and nonfatigued subgroups, then variables could be identified that are specifically correlated with the fatigued group. If mechanisms that produce fatigue could be identified, it may also be possible to design more targeted drug therapies or other interventions.

The second area of future research could include well-designed complex intervention studies to investigate the use of tailored exercise programs and/or psychological techniques, such as cognitive behavioral therapy. However, such studies must be appropriately powered, must ensure adequate blinding of assessors, and should be explicit about the characteristic and incidental effects of any potential intervention. These intervention studies must also use well-validated outcome measures, such as the FACT F (68), so that clinically significant outcomes can be determined. Studies should also use objective measures of activity (such as wrist actigraphy—a noninvasive method of monitoring sleep and activity cycles that uses wrist movement to calculate activity) to correlate with any improvement in subjective fatigue. Recent analyses (24,69) indicate that these types of intervention have a small overall positive effect size, but there is substantial heterogeneity in the studies and overall quality is low. These studies could be conducted in parallel to drug intervention studies or as part of a factorial trial design.

In conclusion, cancer-related fatigue is an important clinical problem for patients with cancer. We have found that a variety of drug treatments are available to treat cancer-related fatigue. Methylphenidate appears to have the best evidence of efficacy, but this evidence is marginal and requires further evaluation in a larger trial. Erythropoietin and darbepoetin have evidence for their efficacy in anemic cancer patients undergoing chemotherapy but their efficacy for use outside of this group also requires additional evaluation.

References


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