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Pharmacologic Treatment of Cancer-Related Fatigue

Jennifer K. Carroll, Sadhna Kohli, Karen M. Mustian, Joseph A. Roscoe, Gary R. Morrow

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Key Words. Cancer • Fatigue • Hematopoietic • Corticosteroids • Psychostimulants

Abstract
Fatigue is the most commonly reported symptom in patients with cancer, with a prevalence of over 60% reported in the majority of studies. This paper systematically reviews pharmacologic agents in the treatment of cancer-related fatigue (CRF). We conducted a literature review of clinical trials that assessed pharmacologic agents for the treatment of CRF. These agents include hematopoietics (for anemia), corticosteroids, and psychostimulants. Other therapeutic agents that are less well studied for CRF but are currently the focus of clinical trials include l-carnitine, modafinil, bupropion, and selective serotonin reuptake inhibitors such as paroxetine. The Oncologist 2007;12(suppl 1):43–51

Introduction
Fatigue is the most common symptom patients with cancer experience, with a prevalence rate that exceeds 60% in many studies [1]. Cancer-related fatigue (CRF) is often experienced with additional symptoms, including sleep disturbance, pain, and depression [2–4]. CRF may arise as a result of the cancer itself or it can be a frequently reported side effect of cancer treatment(s) such as chemotherapy, radiotherapy, surgery, and immunotherapy [1]. Typically, CRF is more severe than the usual fatigue experienced by healthy people in that it is associated with a higher level of distress, is disproportionate to the activity or exertion level, and is not relieved by sleep or rest [5–7]. CRF can compromise quality of life and a patient’s ability to function optimally on a daily basis. Many patients report that CRF is more distressing and has a greater impact on activities of daily living and quality of life than other cancer-related symptoms such as pain, nausea, and depression [8]. The U.S. National Institutes of Health has now identified treatment of CRF as a priority for advancing the care of cancer patients [9].

Rationale for Pharmacologic Management of Cancer-Related Fatigue
Perhaps because fatigue is often viewed as an inevitable, ubiquitous consequence of cancer and cancer treatment, pharmacologic intervention trials for its control were not seen until the 1980s [8,10,11]. Since then, awareness of the prevalence and impact of CRF has increased, as has interest in understanding the underlying pathophysiology. Owing to this growing awareness, research has begun to focus on identifying therapeutic interventions.

Although few studies have focused specifically on the etiology of fatigue, some evidence supports underlying metabolic, cytokine, neurophysiologic, and endocrine changes associated with CRF. These include potential roles for anemia, ATP, vagal afferents, and the interaction of the hypothalamic–pituitary–adrenal axis, cytokines, and circadian rhythm [6,7,12–15]. There are multiple potential predisposing/etiologic factors, including the cancer itself, treatment-related adverse effects, physiologic complications (i.e., anemia, infection, neuromuscular disorders,
metabolic disorders), impaired performance status, sleep disorders, and psychological comorbidities such as depression [1,16,17]. The etiology of CRF is discussed in greater detail in an accompanying paper in this issue [18].

Treating conditions that may contribute to CRF, such as anemia, metabolic disorders, pain, depression, and other noncancer comorbidities, can be a reasonable, clinically important first step in the management of CRF (Fig. 1) [19]. When fatigue persists despite the resolution of potential contributing factors, both nonpharmacologic and pharmacologic treatments should be considered. Nonpharmacologic therapies, such as exercise, nutritional and dietary assessment, and improved sleep hygiene, are discussed in an accompanying paper in this issue [20]. The current paper presents and discusses the results of a systematic review of clinical trials assessing pharmacologic options for treating CRF.

METHODS

We conducted a systematic review of the literature involving clinical trials in the United States, Canada, and Europe that assessed pharmacologic interventions for CRF. The inclusion criteria were as follows: clinical trial (published abstract or journal article), participants with cancer diagnosis/es, pharmacologic agent used as primary intervention in trial, and measurement of fatigue as outcome measure. Review articles were excluded, but reference lists were checked to identify other possible trials not identified by the search. The following databases were searched in October 2006 for studies published between 1966 and 2006: Ovid/MEDLINE®, CINAHL®, PubMed, Cochrane, and HealthSTAR. Additionally, we completed bibliographic searches of retrieved articles and contacted experts in the field to obtain other relevant data. Three individuals (the primary author [JC], a medical librarian, and an undergraduate student) independently searched the literature using the keywords: neoplasms, modafinil, erythropoietin, darbepoetin, bupropion, adrenal cortex hormones, paroxetine, methylphenidate, pemoline, carnitine, mirtazapine, fatigue; limits applied were: English language, clinical trial, randomized controlled trials. All search strategies were explicitly developed, executed, revised, saved, and compared by the search team.

The primary author reviewed titles and abstracts of all potentially relevant articles to determine whether they met the eligibility criteria for inclusion. Studies that met the eligibility criteria were retrieved and abstracted. The references cited in these studies were also reviewed to locate other potentially suitable studies not identified by the initial literature searches.

For identified articles that met the inclusion criteria, we extracted data from each eligible article and organized them into a table to allow comparison of the features of each trial such as the study population, design characteristics, primary results relevant to fatigue, assessment measures, adverse events, and attrition.

Figure 1. Treatable contributing factors for cancer-related fatigue. Based on National Comprehensive Cancer Network guidelines [19].
Results
We identified 32 clinical trials that met the inclusion criteria [21–53]. Results are presented in Table 1 and discussed below in order of frequency by drug class. Most of the clinical trials that we found (n = 19; 59%) were prospective, open-label designs; 13 (41%) were randomized controlled trials. Most trials (n = 24; 75%) included participants with several (mixed) cancer diagnoses. Study duration ranged from 7 days to 2 years, with most studies being of less than 4 months’ duration. Review of the study outcomes showed that therapeutic drug classes, such as hematopoietics, corticosteroids, psychostimulants, and antidepressants, may have a beneficial effect on CRF, as discussed below.

Hematopoietics
Anemia can occur in patients with cancer as a consequence of either disease-related processes or anticancer treatment [54]. Of the 32 trials identified by the search, 12 (38%) were clinical trials of epoetin alfa (Procrit®; Amgen Inc., Thousand Oaks, CA) and the longer-acting analog darbepoetin alfa (Aranesp®, Amgen). Of these 12, seven were randomized controlled clinical trials. Overall results provide evidence that these agents can decrease fatigue and improve quality of life in patients with cancer-related anemia [22–25,27,30,31,33,55–57]. Treatment with epoetin alfa or darbepoetin alfa one to three times per week for up to 6 months produced increases in hemoglobin concentrations of 1.8–2.6 g/dl [22,23,25]. Patients achieved significant improvements in energy level, activity level, and overall quality of life, and decreases in fatigue [24,25]. In these studies, the improvements in energy level and quality of life correlated with the increase in hemoglobin concentrations and were seen in patients with stable disease and in those who responded to chemotherapy.

Psychostimulants
Sleep disorders, including insomnia and excessive daytime sleepiness, are common in patients with cancer [58]. Psychostimulant medications, such as methylphenidate, could be effective in treating CRF, as they have been found to produce enhanced alertness, attention, and vigilance, and to reduce fatigue in patients with other chronic conditions, such as multiple sclerosis and HIV infection [59–61].

Methylphenidate (Ritalin®; Novartis Pharmaceuticals Corporation, East Hanover, NJ) is a central nervous system (CNS) stimulant that is structurally related to amphetamines. We found seven clinical trials (22%) of methylphenidate for the treatment of CRF. Although methylphenidate was shown to improve fatigue in these open-label studies in patients with cancer [36,40], its effect was not significantly different from that of placebo in a double-blind study [35]. However, a recent randomized placebo-controlled trial in nonanemic patients with cancer who had completed chemotherapy showed that dexamethasone (Focalin®, Novartis) was associated with significantly greater improvements in fatigue than placebo [37].

Given that relatively few randomized, placebo-controlled clinical trials have been conducted specifically to evaluate the use of psychostimulants in patients with CRF, adverse effects of psychostimulants, such as irritability, anorexia, insomnia, labile mood, nausea, and tachycardia, should be considered when making treatment decisions [1].

Antidepressants
Many patients with cancer also experience symptoms of depression. Estimates of the prevalence of major depressive disorder range from 5% to almost 50%, depending on the diagnostic methods used [1]. Bupropion (Wellbutrin-SR®; GlaxoSmithKline, Philadelphia) is an atypical antidepressant, unrelated to tricyclic antidepressants or selective serotonin reuptake inhibitors, that has been used to treat chronic fatigue syndrome and fatigue associated with multiple sclerosis [62–64]. We identified two studies (6% of total) of bupropion sustained-release (SR) in the treatment of CRF [42,43]. In these open-label case series, bupropion SR (100–300 mg/day) was associated with improvements in fatigue scores within 2–4 weeks of the start of treatment. Further placebo-controlled studies are necessary to establish the efficacy of bupropion in CRF.

We found two double-blinded, placebo-controlled randomized trials (6% of total) of the selective serotonin reuptake inhibitor paroxetine (Paxil®; GlaxoSmithKline) that showed this antidepressant improved depression but had no effect on fatigue in patients receiving chemotherapy [44,45], suggesting that the underlying causal mechanisms for depression and CRF are distinct.

Corticosteroids
We identified three (9% of total) clinical trials of glucocorticoids (one study of methylprednisolone, one of prednisone, and one of megestrol acetate). Two of these studies were randomized, double-blind, crossover studies [46,47]. Sample sizes were small (range, 37–84 per study). These studies reported improvements in symptoms, especially pain, and showed improved quality of life and reduced fatigue in patients with metastatic cancer [46,48]. For example, Bruner and colleagues demonstrated a significantly greater reduction in the severity of pain in patients with terminal cancer after 14 days of treatment with methylprednisolone compared with placebo [46]. The progestogen megestrol acetate was found to decrease fatigue and increase energy...
**Table 1. Clinical trials of drugs used in the treatment of cancer-related fatigue**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Publication</th>
<th>Cancer diagnosis</th>
<th>n</th>
<th>Study design</th>
<th>Duration of trial</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoetin alfa</td>
<td>Chang et al. [21]</td>
<td>Breast</td>
<td>354</td>
<td>Open-label clinical RCT; epoetin alfa, 40,000 U qw versus SOC</td>
<td>12 wks</td>
<td>FACT-An and FACT-An/Fatigue significantly improved in epoetin alfa group</td>
<td>Effective in QoL, reducing transfusions, and maintaining Hb level; 18% of epoetin and 17% of SOC patients dropped out; several adverse events higher in epoetin group</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Demetri et al. [22]</td>
<td>Mixed</td>
<td>2,370</td>
<td>Prospective, multicenter, open-label, nonrandomized study; epoetin alfa, 10,000 U tiw titrated to 20,000 U tiw as needed</td>
<td>Maximum 16 wks</td>
<td>Epoetin alfa associated with improved QoL; QoL correlated with improved Hb levels; epoetin alfa treatment correlated with fewer transfusions</td>
<td>Epoetin alfa effects were independent of tumor response</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Glaspy et al. [23]</td>
<td>Mixed</td>
<td>2,342</td>
<td>Prospective, multisite, open-label nonrandomized study; 150 U/kg tiw titrated to 300 U/kg tiw as needed</td>
<td>Maximum 16 wks</td>
<td>2,080 patients had evaluable data; 1,047 patients completed the 4 months of therapy; epoetin alfa associated with significant improvement in energy level, activity level, and overall QoL</td>
<td>Improvements correlated with magnitude of Hb increase</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Littlewood et al. [24]</td>
<td>Mixed</td>
<td>375</td>
<td>Multicenter (15 countries), placebo-controlled, double-blind RCT; epoetin alfa, 150–300 U/kg tiw</td>
<td>24 wks</td>
<td>Epoetin alfa reduced transfusion requirements and increased Hb versus placebo; QoL, energy, fatigue, ADL improved via FACT-An, CLAS</td>
<td>Epoetin alfa safe and well tolerated; raises question of relationship between improved Hb levels and survival (showed trend, though study not powered to definitively analyze for survival)</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Glaspy et al. [23]</td>
<td>Mixed</td>
<td>3,012</td>
<td>Open-label, nonrandomized study of epoetin alfa qw; epoetin alfa, 40,000 U qw titrated to 60,000 U qw as needed</td>
<td>Maximum 16 wks</td>
<td>Increased Hb levels, decreased transfusion requirements, improved QoL, improved fatigue</td>
<td>Prospective community-based trial; FACT-An scale used; LASA scale used for fatigue</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Reinhardt et al. [26]</td>
<td>Mixed</td>
<td>702</td>
<td>Prospective, open-label, multicenter study; epoetin alfa, 10,000 U tiw</td>
<td>8–18 wks</td>
<td>Patients in all groups reported improved fatigue</td>
<td>645 included in efficacy analyses; physicians tended to overestimate improvements in patients’ fatigue levels</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Fallowfield et al. [27]</td>
<td>Mixed</td>
<td>375</td>
<td>Multicenter (15 countries), placebo-controlled, double-blind RCT; epoetin alfa, 150–300 U/kg tiw</td>
<td>Maximum 28 wks</td>
<td>Epoetin alfa more effective than placebo in improving QoL; change in Hb correlated with change in QoL</td>
<td>FACT-An Fatigue subscale and FACT-G total used</td>
</tr>
<tr>
<td>Darbepoetin alfa</td>
<td>Bartsch et al. [28]</td>
<td>Mixed</td>
<td>75</td>
<td>Open-label prospective study; darbepoetin alfa, 150 µg qw titrated to 300 µg qw as needed</td>
<td>12 wks</td>
<td>Improved fatigue; well tolerated</td>
<td>Patients who were more anemic had greater response rates</td>
</tr>
<tr>
<td>Darbepoetin alfa</td>
<td>Vadhan-Raj et al. [29]</td>
<td>Mixed</td>
<td>1,173</td>
<td>Multicenter open-label prospective study to test 2-weekly dosing</td>
<td>16 wks</td>
<td>Fatigue improved by 26% (FACT-F)</td>
<td>Improvements in fatigue paralleled improvements in Hb</td>
</tr>
<tr>
<td>Darbepoetin alfa</td>
<td>Vansteen-kiste et al. [30]</td>
<td>Lung</td>
<td>320</td>
<td>Multicenter, placebo-controlled, double-blind RCT; initial dose darbepoetin alfa, 2.25 µg/kg/wk, titrated up to 4.5 µg/kg/wk as needed</td>
<td>12 wks</td>
<td>Patients receiving darbepoetin received fewer transfusions units of blood, had better improvement in fatigue</td>
<td>Primary outcome was transfusion requirement; FACT-Fatigue scale used</td>
</tr>
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<tbody>
<tr>
<td>Darbepoetin alfa</td>
<td>Hedenus et al. [31]; Littlewood et al. [32]</td>
<td>Lymphoma or myeloma</td>
<td>344</td>
<td>Multinational, placebo-controlled, double-blind RCT; darbepoetin alfa, 2.25 μg/kg/wk</td>
<td>12 wks</td>
<td>Improvements in Hb, fatigue, QoL</td>
<td>FACT-F used; analysis of ITT population</td>
</tr>
<tr>
<td>Epoetin beta (rHuEPO)</td>
<td>Osterborg et al. [33]</td>
<td>NHL, MM, CLL</td>
<td>349</td>
<td>RCT; epoetin beta, 150 IU/kg tiw</td>
<td>16 wks</td>
<td>QoL significantly improved in epoetin beta group, which correlated with improved Hb</td>
<td>Primary endpoint was transfusion or severe anemia-free survival; QoL was assessed by FACT; adverse events were similar between groups except for hypertension (more in epoetin group)</td>
</tr>
<tr>
<td>Darbepoetin alfa versus epoetin beta (rHuEPO)</td>
<td>Glaspy et al. [34]</td>
<td>Mixed</td>
<td>127</td>
<td>RCT; 4 groups with variable, staged up-titration of rHuEPO and darbepoetin alfa doses</td>
<td>12 wks</td>
<td>Hb concentration increased more in darbepoetin group; also early and maintained reduction in CRF</td>
<td></td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Bruera et al. [35]</td>
<td>Mixed</td>
<td>112</td>
<td>Double-blind, placebo-controlled RCT; methylphenidate, 5 mg daily, titrated to maximum 20 mg/day</td>
<td>7 days</td>
<td>Drug and placebo both decreased depression and fatigue</td>
<td>Fatigue assessed using FACIT-F and ESAS; daily phone calls by nurse to assess fatigue may have been useful intervention; 93% chose to continue medication</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Bruera et al. [36]</td>
<td>Mixed</td>
<td>31</td>
<td>Prospective, open-label study; methylphenidate, 5 mg/day, titrated to maximum 20 mg/day</td>
<td>7 days</td>
<td>Improved fatigue and functional well-being</td>
<td>FACT-F used to assess fatigue; 8 patients had side effects, but 93% chose to continue treatment</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Lower et al. [37]</td>
<td>Mixed; mostly breast and ovarian</td>
<td>152</td>
<td>Double-blind, placebo-controlled methylphenidate, 10–50 mg/day</td>
<td>2 mos</td>
<td>Fatigue (FACIT-F) significantly improved; memory (HSCS) improved</td>
<td>132 patients completed study; most frequent adverse reactions were headache (41%) and nausea (28%), most mild</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Sarhill et al. [38]</td>
<td>Mixed</td>
<td>11</td>
<td>Prospective open-label/case series; methylphenidate, 5 mg bid, titrated to 20–30 mg/day as needed</td>
<td>“Usually one week”, not specified</td>
<td>Rapid onset of benefit for sedation and pain</td>
<td>Response seen in variety of symptoms; well tolerated in these participants; no validated measure of fatigue used</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Homsi et al. [39]</td>
<td>Mixed</td>
<td>41</td>
<td>Prospective, open-label study; methylphenidate, 5 mg bid, titrated to 15 mg bid as needed</td>
<td>7 days</td>
<td>Decrease in severity of fatigue, anorexia, concentration, and sedation</td>
<td>30 patients completed study; 6 withdrew due to side effects; fatigue assessed by clinical interview</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Hanna et al. [40]</td>
<td>Breast</td>
<td>37</td>
<td>Prospective, open-label study; methylphenidate, 5 mg bid, titrated to 10 mg bid as needed</td>
<td>6 wks</td>
<td>54% (n = 20) responded with less fatigue (reduced BFI score)</td>
<td>BFI, FACT-F used to assess fatigue; 19% (n = 6) of patients withdrew due to adverse events</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Schwartz et al. [41]</td>
<td>Melanoma</td>
<td>12</td>
<td>Pilot study on effect of exercise and methylphenidate; comparison was historical control group; methylphenidate, 20 mg/day</td>
<td>Not stated</td>
<td>Fatigue and functional and cognitive status better for methylphenidate plus exercise group</td>
<td>Exercise and methylphenidate improved alfa-interferon-induced fatigue and cognitive function</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Cullum et al. [42]</td>
<td>Mixed</td>
<td>15</td>
<td>Prospective, open-label study; bupropion, 150 mg/day</td>
<td>2 years</td>
<td>13/15 saw improvement in fatigue, all within 2–4 weeks of treatment</td>
<td>Patients also had comorbid psychiatric diagnoses</td>
</tr>
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<tbody>
<tr>
<td>Bupropion</td>
<td>Moss et al. [43]</td>
<td>Mixed</td>
<td>21</td>
<td>Prospective open-label study; bupropion, 10–300 mg daily</td>
<td>4 wks</td>
<td>Significant improvement in depression</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Morrow et al. [44]</td>
<td>Mixed</td>
<td>549</td>
<td>Multicenter, double-blind, placebo-controlled RCT</td>
<td>2 mos</td>
<td>Depression decreased; no effect on fatigue</td>
<td>Community clinical oncology practices</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Roscoe et al. [45]</td>
<td>Breast</td>
<td>122</td>
<td>Double-blind, placebo-controlled RCT; paroxetine, 20 mg/day</td>
<td>2 mos</td>
<td>Depression decreased; no effect on fatigue</td>
<td>Suggests serotonin may not be primary mechanism of CRF; 11 women (6 paroxetine, 5 placebo) withdrew due to side effects</td>
</tr>
<tr>
<td>Corticosteroid (methylprednisolone)</td>
<td>Bruera et al. [46]</td>
<td>Mixed</td>
<td>40</td>
<td>Randomized, double-blind, crossover trial; corticosteroid, 16 mg bid</td>
<td>14 days</td>
<td>Mean intensity of pain improved; appetite and daily activity increased</td>
<td>Patients with terminal cancer; 9 patients did not complete the trial; significant placebo response observed</td>
</tr>
<tr>
<td>Corticosteroid (megestrol acetate)</td>
<td>Bruera et al. [47]</td>
<td>Mixed</td>
<td>84</td>
<td>Double-blind crossover study; corticosteroid, 160 mg tid</td>
<td>10 days</td>
<td>Improvements in fatigue (Piper Fatigue Scale), activity, appetite, and well-being</td>
<td>52 evaluable patients; improvement seen rapidly</td>
</tr>
<tr>
<td>Corticosteroid (prednisone)</td>
<td>Tannock et al. [48]</td>
<td>Metastatic prostate</td>
<td>37</td>
<td>Prospective, open-label study; corticosteroid, 7.5–10 mg/day</td>
<td>Not stated</td>
<td>38% had improvement in pain; pain improvement was associated with improvements in other dimensions (QoL, well-being)</td>
<td>Pain relief was primary benefit</td>
</tr>
<tr>
<td>l-carnitine</td>
<td>Gramignano et al. [49]</td>
<td>Mixed, stage III or IV</td>
<td>12</td>
<td>Prospective, open-label study; l-carnitine, 6 g/day</td>
<td>4 wks</td>
<td>Fatigue significantly decreased; QoL improved; nutritional measures improved</td>
<td>Participants had advanced tumors; fatigue measured by MFIS; small sample size</td>
</tr>
<tr>
<td>l-carnitine</td>
<td>Graziano et al. [50]</td>
<td>Mixed, stage IV solid tumors</td>
<td>50</td>
<td>Prospective open-label study; l-carnitine, 4 g/day</td>
<td>1 wk</td>
<td>Fatigue improved</td>
<td>FACT-F scale used; patients had normal BMIs and caloric intake</td>
</tr>
<tr>
<td>l-carnitine</td>
<td>Cruciani et al. [51]</td>
<td>Mixed</td>
<td>13</td>
<td>Open-label study; l-carnitine, 500–3,000 mg/day</td>
<td>1 wk</td>
<td>Fatigue improved in 90% (n = 45; p &lt; .001)</td>
<td>Low accrual rate (3%); open label means possible placebo effect</td>
</tr>
<tr>
<td>Modafinil</td>
<td>Kaleita et al. [52]</td>
<td>Brain</td>
<td>30</td>
<td>Prospective, open-label study; modafinil, 200–400 mg/day in divided doses</td>
<td>2 mos</td>
<td>Depression decreased; fatigue decreased</td>
<td>FSS and MFIS used; adverse reactions were noted, but no withdrawals</td>
</tr>
<tr>
<td>Modafinil</td>
<td>Morrow et al. [53]</td>
<td>Breast</td>
<td>51</td>
<td>Prospective, open-label study; modafinil, 200–300 mg/day in divided doses</td>
<td>1 mo</td>
<td>Fatigue severity improved; patients reported beneficial effects</td>
<td>3 women withdrew due to agitation, but treatment generally well tolerated</td>
</tr>
</tbody>
</table>

Abbreviations: ADL, activities of daily living; BFI, Brief Fatigue Inventory; bid, twice daily; BMI, body mass index; CLAS, Cancer Linear Analog Scale; CLL, chronic lymphocytic leukemia; CRF, cancer-related fatigue; ESAS, Edmonton Symptom Assessment System; FACT-F, Functional Assessment for Chronic Illness Therapy—Fatigue; FACT-An, Functional Assessment of Cancer Therapy—Anemia; FACT-F, Functional Assessment of Cancer Therapy—Fatigue; FACT-G, Functional Assessment of Cancer Treatment—General; FSS, Fatigue Severity Scale; Hb, hemoglobin; HSCS, High Sensitivity Cognitive Screen; ITT, intent to treat; LASA, Linear Analog Scale Assessment; MFIS, Modified Fatigue Impact Scale; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; QoL, quality of life; qw, once weekly; RCT, randomized controlled trial; rHuEPO, recombinant human erythropoietin; SOC, standard of care; tid, three times daily; tiw, three times a week.
levels, appetite, and feelings of well-being in patients with advanced cancer [47]. Studies of glucocorticoids were generally of short duration (10–14 days); however, given the clinical concerns of adverse effects with long-term corticosteroid therapy [59], studies with a longer duration may be warranted. Steroids may be most helpful to patients who are in the terminal phases of advanced cancer and have CRF.

L-carnitine
Chemotherapy can adversely affect the levels of L-carnitine, a micronutrient important for the processing of long-chain fatty acids and energy production in mammalian cells. We identified three studies (9% of total) of L-carnitine in the treatment of CRF [49–51]. These were all open-label prospective designs with 12–50 participants. Treatment with L-carnitine (500–600 mg/day) for a period of 1–4 weeks in patients with cancer but without significant anemia increased plasma free carnitine concentrations and significantly improved fatigue and quality-of-life measures. As with all open-label studies, future trials are needed with a blinded randomized design to verify these findings.

Modafinil
Modafinil (Provigil®; Cephalon, Frazer, PA), a CNS stimulant, improves wakefulness and has been approved by the U.S. Food and Drug Administration for the treatment of narcolepsy [65–67], obstructive sleep apnea [68], and shift-work sleep disorder [69]. Short-term clinical studies have shown improved wakefulness in patients with other conditions such as multiple sclerosis [70,71], major depression [72,73], and Parkinson’s disease [74,75].

We identified two prospective open-label studies of modafinil (6% of total) [52,53]. One study showed positive effects on fatigue that had persisted for an average of 2 years following breast cancer treatment [53]. For these patients, fatigue severity and other measures of quality of life were significantly improved following 1 month of treatment with modafinil. Another recent study of 30 patients with malignant and benign brain tumors who were treated with surgery, radiotherapy, and/or chemotherapy found that modafinil was associated with significant improvements in fatigue scores [52]. The most commonly reported adverse effects of modafinil treatment were headache, infection, nausea, nervousness, anxiety, and insomnia, all of which were generally mild. Randomized clinical trials of modafinil are under way to investigate its effect on CRF in patients receiving chemotherapy and those who have completed chemotherapy or radiation therapy.

CONCLUSIONS
Evaluation and treatment of CRF require a broad initial approach because of the multiple etiologies and possible contributing factors. Current therapeutic options include the assessment and treatment of any underlying causes (e.g., anemia, depression). Several pharmacologic approaches have the potential to provide relief for patients suffering from CRF. The most numerous rigorously designed clinical trials to date have been conducted with epoetin alfa and darbepoetin alfa; several studies have shown their efficacy in treating CRF in patients with anemia. Other classes of medications, such as psychostimulants and CNS stimulants, have shown promise in open-label prospective designs, but evidence is lacking from placebo-controlled randomized trials. Future research regarding pharmacologic treatment of fatigue needs to confirm the effects of promising open-label studies via a double-blind randomized design. In particular, the relative benefits and side-effect profiles should be evaluated via head-to-head randomized studies comparing different classes of medications, as well as medications as single agents versus medications in combination with promising behavioral and nonpharmacologic interventions, such as exercise.

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DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST
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