Putting Evidence Into Practice: An Update of Evidence-Based Interventions for Cancer-Related Fatigue During and Following Treatment

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Cancer-related fatigue (CRF) has deleterious effects on physical, social, cognitive, and vocational functioning, and causes emotional and spiritual distress for patients and their families; however, it remains under-recognized and undertreated. This article critically reviews and integrates the available empirical evidence supporting the efficacy of pharmacologic and nonpharmacologic treatment approaches to CRF, highlighting new evidence since 2007 and 2009 Putting Evidence Into Practice publications. Interventions that are recommended for practice or likely to be effective in improving fatigue outcomes include exercise; screening for treatable risk factors; management of concurrent symptoms; yoga; structured rehabilitation; Wisconsin ginseng; cognitive-behavioral therapies for insomnia, pain, and depression; mindfulness-based stress reduction; and psychoeducational interventions such as anticipatory guidance, psychosocial support, and energy conservation and activity management. This information can be applied to improve the management of CRF; inform health policy and program development; shape the design of clinical trials of new therapies for CRF; and drive basic and translational research.

The National Comprehensive Cancer Network ([NCCN], 2014) defined cancer-related fatigue (CRF) as an unusual, persistent, and subjective sense of tiredness that is not proportional to recent activity and interferes with usual functioning. The clinical expression of CRF may include generalized weakness, diminished mental concentration, insomnia or hypersomnia, and emotional reactivity (de Raaf, de Klerk, & van der Rijt, 2013; Goedendorp, Gielissen, Verhagen, & Bleijenberg, 2009). Depending on how fatigue is defined and measured, prevalence estimates across the cancer continuum range from 25%-99% (Campos, Hassan, Riechelmann, & Del Giglio, 2011; Dhruba et al., 2013; Hummel & Iversen, 2010; Langston, Armes, Levy, Tiley, & Ream, 2013; Neefjes, van der Vorst, Blauwhoff-Busker, & Verheul, 2013; Peters, Goedendorp, Verhagen, van der Graaf, & Bleijenberg, 2013; Van Lancker et al., 2014; Weis, 2011). Building on the framework of previously published Putting Evidence Into Practice summaries (Mitchell & Beck, 2009; Mitchell, Beck, Hood, Moore, & Tanner, 2007), this article critically appraises the strength and quality of the evidence regarding the safety and efficacy of pharmacologic and nonpharmacologic interventions to ameliorate CRF during and following cancer and its treatment, and at the end of life. Although the recommendations provided represent the best available evidence, clinical judgment and individual circumstances should determine appropriate interventions for specific patients.
Methods

Computerized searches of PubMed and CINAHL® were performed using the search terms listed in Figure 1. Database searches were performed by a medical librarian in consultation with study team members. Citations published from January 1990 through March 2014 were retrieved, and articles meeting the inclusion criteria listed in Figure 2 were summarized and critically appraised by a team of RNs, advanced practice nurses, and nurse scientists. Tables of evidence were prepared, and major and minor study design flaws were identified using the taxonomy proposed by Hadorn, Baker, Hodges, and Hicks (1996). After the evidence supporting each intervention had been critically examined, the collective weight of the evidence for each identified intervention was classified using evidence quality, magnitude of the outcome (effect size), safety, and concurrence of the evidence among studies. The Oncology Nursing Society’s weight-of-evidence categories were adapted by Mitchell and Friese (2009) from other published schema (Atkins et al., 2004; Lohr, 2004).

Results

Figure 3 lists the fatigue interventions for which evidence exists from one or more empirical studies, classifying them based on the collective strength of the evidence about their efficacy and safety. Several interventions for fatigue identified in the literature were supported by expert opinion only (NCCN, 2014).

Recommended for Practice

Exercise/physical activity has been confirmed as effective in the management of CRF in more than 40 meta-analyses or systematic reviews of randomized, controlled trials (RCTs); more than 20 of the reviews have been published since 2010 (Braam et al., 2013; Brown et al., 2011; Cramer, Lauche, Klose, Dobos, & Langhorst, 2014; Cramp & Byron-Daniel, 2012; Crandall, Maguire, Campbell, & Kearney, 2014; Eickmeyer, Gamble, Shahpar, & Do, 2012; Focht et al., 2013; Fong et al., 2012; Keogh & MacLeod, 2012; McMillan & Newhouse, 2011; Mishra, Scherer, Geigle, et al., 2012; Mishra, Scherer, Snyder, et al., 2012; Mustian, Sprod, Janelsins, Peppone, & Mohile, 2012; Paramanandam & Dunn, 2014; Payne, Wiffen, & Martin, 2012; Persoon et al., 2013; Puetz & Herring, 2012; Speck, Courneya, Mößle, Duval, & Schmitz, 2010; Strasser, Steindorf, Wiskemann, & Ulrich, 2013; Tomlinson, Diorio, Beyene, & Sung, 2014; van Haren et al., 2013; Velthus, Agassildenburg, Aufderkampe, & Wittink, 2010; Wolin, Ruiz, Tuchman, & Lucia, 2010; Zou, Yang, He, Sun, & Xu, 2014). Populations in which effectiveness has been demonstrated include patients with breast, colon, and prostate cancers; patients undergoing treatment with radiation, chemotherapy, or hematopoietic stem cell transplantation; young adults with cancer; and survivors who have been treated for a solid tumor or a hematologic malignancy. In their meta-analysis, Puetz and Herring (2012) noted that exercise exerts a palliative effect on fatigue during active treatment and provides a rehabilitative effect following treatment. Limitations of the current evidence base remain that effect sizes are generally small, and positive results for the outcome of CRF have not been observed consistently across studies (Cramp & Byron-Daniel, 2012; Eickmeyer et al., 2012; Mustian et al., 2012). The exercise modalities that have been examined differ in content (walking, cycling, swimming, resistive exercise, or combined exercise), as well as frequency, duration, intensity, and degree of supervision (i.e., fully supervised groups versus self-directed exercise). Knowledge about the type, intensity, and duration of physical exercise most beneficial in reducing fatigue at different stages of disease and treatment is still emerging (Puetz & Herring, 2012), and more research is needed to systematically assess the safety, tolerability, and efficacy of aerobic exercise and strength training in cancer subpopulations, such as those with lung cancer (Brown et al., 2011; Paramanandam & Dunn, 2014), and across the cancer-control continuum (Wolin, Schwartz, Matthews, Courneya, & Schmitz, 2012).

Likely to Be Effective

Psychoeducational interventions, including those delivered via the Internet, have been tested in more than a dozen RCTs or quasieperimental studies and continue to demonstrate positive effects on fatigue outcomes (Allison et al., 2004; Badger et al., 2011; Björneklett et al., 2012; Boesen et al., 2005; Brown et al., 2006; Chan, Richardson, & Richardson, 2011; Dolbeault et al., 2009; Donnelly et al., 2011; Fawzy et al., 1990; Fillion et al., 2008; Given et al., 2002; Godino, Jodar, Durán, Martinez, & Schiaffino, 2006; Goedendorp et al., 2010; Johnston et al., 2011; Kim, Roscoe, & Morrow, 2002; Mollaolu & Erdan, 2014; Ream, Richardson, & Alexander-Dann, 2006; Reif, de Vries, Petermann, & Görrès, 2013; Schöllberg et al., 2014; Vilela et al., 2006; Wangnum et al., 2013; Yates et al., 2005; Yesilbalkan, Karadakovan, & Göker, 2009; Yun et al., 2012). In addition, several systematic reviews have concluded that psychoeducational interventions are efficacious for CRF management (Duijts, Faber, Oldenburg, van Beurden, & Aaronson, 2011; Fors et al., 2011; Goedendorp et al., 2009; Jacobsen, Donovan, & Schiaffino, 2006; Goedendorp et al., 2010; Johnston et al., 2008; Given et al., 2002; Godino, Jodar, Durán, Martinez, & Schiaffino, 2006; Goedendorp et al., 2010; Johnston et al., 2011; Kim, Roscoe, & Morrow, 2002; Mollaolu & Erdan, 2014; Ream, Richardson, & Alexander-Dann, 2006; Reif, de Vries, Petermann, & Görrès, 2013; Schöllberg et al., 2014; Vilela et al., 2006; Wangnum et al., 2013; Yates et al., 2005; Yesilbalkan, Karadakovan, & Göker, 2009; Yun et al., 2012). In addition, several systematic reviews have concluded that psychoeducational interventions are efficacious for CRF management (Duijts, Faber, Oldenburg, van Beurden, & Aaronson, 2011; Fors et al., 2011; Goedendorp et al., 2009; Jacobsen, Donovan, & Schiaffino, 2006; Goedendorp et al., 2010; Johnston et al., 2008; Given et al., 2002; Godino, Jodar, Durán, Martinez, & Schiaffino, 2006; Goedendorp et al., 2010; Johnston et al., 2011; Kim, Roscoe, & Morrow, 2002; Mollaolu & Erdan, 2014; Ream, Richardson, & Alexander-Dann, 2006; Reif, de Vries, Petermann, & Görrès, 2013; Schöllberg et al., 2014; Vilela et al., 2006; Wangnum et al., 2013; Yates et al., 2005; Yesilbalkan, Karadakovan, & Göker, 2009; Yun et al., 2012). In addition, several systematic reviews have concluded that psychoeducational interventions are efficacious for CRF management (Duijts, Faber, Oldenburg, van Beurden, & Aaronson, 2011; Fors et al., 2011; Goedendorp et al., 2009; Jacobsen, Donovan, & Schiaffino, 2006; Goedendorp et al., 2010; Johnston et al., 2008; Given et al., 2002; Godino, Jodar, Durán, Martinez, & Schiaffino, 2006; Goedendorp et al., 2010; Johnston et al., 2011; Kim, Roscoe, & Morrow, 2002; Mollaolu & Erdan, 2014; Ream, Richardson, & Alexander-Dann, 2006; Reif, de Vries, Petermann, & Görrès, 2013; Schöllberg et al., 2014; Vilela et al., 2006; Wangnum et al., 2013; Yates et al., 2005; Yesilbalkan, Karadakovan, & Göker, 2009; Yun et al., 2012). In addition, several systematic reviews have concluded that psychoeducational interventions are efficacious for CRF management (Duijts, Faber, Oldenburg, van Beurden, & Aaronson, 2011; Fors et al., 2011; Goedendorp et al., 2009).
English-language published reports of quantitative studies, systematic reviews, or meta-analyses related to cancer-related fatigue interventions that met all of the following criteria were selected for review.

1. Article was a full report (not an abstract) of an empirical study of a pharmacologic or nonpharmacologic intervention administered explicitly to manage or treat fatigue.

2. Fatigue was (a) measured using either an instrument designed explicitly to measure the construct of fatigue or measured using a fatigue subscale of a quality of life or other instrument, and (b) the scores on the fatigue measure or the fatigue subscale were reported in the results.

3. Fatigue reduction, either as an isolated outcome or as a component of a symptom cluster, was the intended purpose of the intervention.

4. Fatigue was identified explicitly as a primary, secondary, or exploratory endpoint, and the rationale for the intervention was reduction of symptoms, not treatment of the underlying malignancy.

5. Study participants were adult patients with cancer who were anywhere in the postdiagnosis trajectory, including during active treatment (i.e., surgery, chemotherapy, biotherapy, molecularly targeted therapy, or hematopoietic stem cell transplantation), post-treatment follow-up, survivorship, or at the end of life.

Note: For intervention categories in which a meta-analysis was available, only those papers not included in the meta-analysis were selected for review.

FIGURE 2. Inclusion Criteria

Vadaparampil, & Small, 2007; Kangas, Bovbjerg, & Montgomery, 2008; Larkin, Lopez, & Aromataris, 2013). At the same time, some trials of psychoeducational interventions failed to demonstrate an effect on CRF; however, the interventions favorably affected other outcomes that may relate to CRF, including psychological symptoms, activity levels, or sleep quality (Armes, Chalder, Addington-Hall, Richardson, & Hotopf, 2007; Goodwin et al., 2001; Purcell, Fleming, Burmeister, Bennett, & Haines, 2011). Psychoeducational interventions typically incorporate anticipatory guidance about patterns of fatigue and tailored recommendations for self-management of fatigue, including increased activity, exercise, measures to address sleep dysregulation, coaching and emotional support to enhance motivation, self-care and active coping, and praise and encouragement to promote self-efficacy and goal-setting and augment feelings of control. Many of the effective psychoeducational interventions also included components of energy conservation and activity management. Although energy conservation and activity management delivered as a single intervention had beneficial effects on fatigue outcomes in one RCT (Barsevick et al., 2004), a second RCT by the same investigators did not confirm a benefit for fatigue (Barsevick et al., 2010). The investigators speculated that statistical power and effect size were diminished by floor effects and low intervention potency.

Progressive muscle relaxation and/or relaxation breathing with or without imagery or distraction delivered in a series of sessions has been shown in six small RCTs to improve CRF in outpatients undergoing radiotherapy (Decker, Cline-Elsen, & Gallagher, 1992), allogeneic hematopoietic stem cell transplantation recipients (Kim & Kim, 2005), women with early-stage breast cancer (Cohen & Fried, 2007), patients who undergo breast cancer surgery (Garssen et al., 2013), women receiving adjuvant chemotherapy for breast cancer (Demiralp, Oflaz, & Komurcu, 2010), and patients with solid tumors who have pain, sleep disturbance, and fatigue (Kwekkeboom et al., 2012). Although relaxation techniques are often combined when delivered in clinical practice, isolating the effects of these intervention components complicates the interpretation of trial results. Two randomized trials comparing the effects of relaxation versus progressive resistance training on CRF outcomes are in progress (Potthoff et al., 2013; Schmidt et al., 2013).

Four RCTs and a recent systematic review provide continued evidence that cognitive-behavioral interventions for sleep delivered individually, in a group setting, or via the Internet also produce beneficial effects on CRF outcomes (Mitchell & Epstein, 2008; Espie et al., 2008; Fleming, Randell, Harvey, & Espie, 2014; Garland et al., 2014; Ritterband et al., 2012). The interventions include relaxation training along with sleep-consolidation strategies (i.e., avoiding long or late afternoon naps, limiting time in bed to actual sleep time), stimulus control therapy (i.e., going to bed only when sleepy, using the bed or bedroom for sleep and sexual activities only, consistently going to bed and getting up at the same time, and avoiding caffeine and stimulating activity in the evening), and strategies to reduce cognitive-emotional arousal (i.e., sitting aside at least an hour to relax before going to bed and establishing a pre-sleep routine to be used every night). To date, the effect on fatigue outcomes of pharmacologic therapies designed to treat insomnia have had very little systematic study (Zee & Ancoli-Israel, 2009).

Since the last evidence update was published (Mitchell & Beck, 2009), several additional interventions, including yoga, structured multidimensional rehabilitation, and Wisconsin ginseng, are now supported by sufficiently robust evidence to conclude that they are likely to be effective for CRF.

Yoga practices significantly improved fatigue outcomes in two RCTs in breast cancer survivors (Bower, Garet, & Sternlieb, 2011; Kiecolt-Glaser et al., 2014) and women undergoing breast cancer radiation therapy (Chandwani et al., 2014). Evidence from other small trials suggests that yoga may have beneficial effects in reducing fatigue in other populations (Bower et al., 2011; Carson, Carson, Porter, Keefe, & Seewaldt, 2009; Carson et al., 2007; Cohen, Warneke, Fouladi, Rodriguez, & Chaul-Reich, 2004; Dhruva et al., 2012; Moadel et al., 2007). However, five systematic reviews concluded that the effectiveness of yoga on fatigue outcomes has not been consistently established across a wide range of cancer populations or at all points in the cancer continuum (Buffart et al., 2012; Felbel, Meerpol, Monsel, Engert, & Skoetz, 2014; Harder, Parlour, & Jenkins, 2012; Sadja & Mills, 2013; Zhang, Yang, Tian, & Wang, 2012). In addition, they noted a high risk of bias across studies with respect to sampling, inconsistent methods, short duration of follow-up, and non-blinding of participants and outcome assessors.

Structured multidimensional rehabilitation interventions have been evaluated in several single-arm, quasixperimental, or preference trials (Berthussen et al., 2012; Chasen & Bhargava, 2010; Chasen, Feldstain, Gravelle, Macdonald, & Pereira, 2013; Cuesta-Vargas, Buchan, & Arroyo-Morales, 2014; Gagnon et al., 2013; Hanssens et al., 2011; Kröz et al., 2013; Kummer, Catuogno, Perseus, Bloch, & Baumann, 2013; Lee, Lim, Yoo, & Kim, 2011; Lindemalm, Strang, & Lekander, 2005; Rabin, Pinto, Dunsiger, Nash, & Trask, 2009; Riesenberg &
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Lübbe, 2010; Strauss-Blasche, Gnad, Ekmeckioglu, Hladschik, & Markt, 2005; Swenson et al., 2014; van Weert et al., 2006; Windsor, Potter, McAdam, & McCowan, 2009). In addition, 11 RCTs examined these interventions in patients with a range of solid tumors, including those with advanced disease (Adamsen et al., 2006, 2009; Andersen et al., 2013; Cantarero-Villanueva et al., 2012; Cheville et al., 2010; Heim, Malsburg, & Niklas, 2007; Jensen et al., 2014; Korstjens, Mesters, van der Peet, Gijsen, & van den Borne, 2006; Li et al., 2013; van Weert et al., 2010; Wangnum et al., 2013). The interventions studied a structured combination of several components, including physical training, psychoeducation, and approaches such as nutritional counseling, mud packs, massage, relaxation, and manual lymph drainage. In some studies, the therapies were delivered over the course of several weeks during an inpatient hospital stay. Across trials, the multicomponent interventions consistently demonstrated beneficial effects on fatigue outcomes as well as other patient-centered outcomes, including physical function, mood, and nutritional status (Egan et al., 2013; Scott et al., 2013). At the same time, several trials of multicomponent rehabilitative interventions did not improve fatigue outcomes (Cheville et al., 2010; Culos-Reed et al., 2010; Gagnon et al., 2013; Gjerset et al., 2011; Hawkes et al., 2013; Pinto, Papandonatos, Goldstein, Marcus, & Farrell, 2013; Windsor et al., 2009). Interpretation of the studies is complicated by high rates of attrition, low statistical power, design flaws, and measurement of outcomes, such as vigor, other than fatigue. Group psychotherapy combined with exercise and a multimodal mind-body program combined with exercise have also been shown to improve fatigue in patients with solid tumors undergoing active treatment and during long-term follow-up (Courneya et al., 2003; Spahn et al., 2013), and a meta-analysis concluded that exercise in combination with behavioral or psychosocial interventions improves fatigue in patients with and survivors of breast cancer (Duijts et al., 2011). Disentangling the effects of intervention components and accounting for the effects of individual tailoring of many of the rehabilitation interventions makes unbiased interpretation of trial results challenging.

Wisconsin ginseng (an eight-week course of 2,000 mg daily) was effective in improving fatigue outcomes in cancer survivors and was well tolerated in a large double-blind, placebo-controlled trial (Barton et al., 2013).

Meditation, mindfulness-based stress reduction (MBSR), and cognitive-behavioral stress management have been shown to improve fatigue severity and fatigue-related daytime interference in five RCTs during and following treatment for breast cancer (Hoffman et al., 2012; Kim, Kim, Ahn, Seo, & Kim, 2013; Lengacher et al., 2009, 2012; Vargas et al., 2013) and in two RCTs and a single-arm trial of patients with mixed tumor sites (Carlson & Garland, 2005; Speca, Carlson, Goody, & Angen, 2000; van der Lee & Garssen, 2012). Secondary analyses suggest that the improvement in fatigue outcomes in those receiving the MBSR intervention may be greatest in those with fatigue-related biomarker abnormalities at study baseline (Reich et al., 2014). However, two RCTs (Milbury et al., 2013; Rissansen, Arving, Ahlgren, & Nordin, 2014) and two single-arm trials in patients with mixed solid tumors (Carlson, Speca, Patet, & Goody, 2003; Kievet-Stijnen, Visser, Garssen, & Hudig, 2008) showed inconsistent effects on fatigue outcomes. The absence

**Effectiveness Established**
- Exercise

**Likely to Be Effective**
- Psychoeducational interventions
- Progressive muscle relaxation and/or relaxation breathing with or without imagery or distraction
- Cognitive-behavioral therapy for sleep
- Yoga
- Structured multidimensional rehabilitation
- Wisconsin ginseng
- Meditation, mindfulness-based stress reduction, and cognitive-behavioral stress management
- Management of concurrent symptoms
- Cognitive-behavioral therapy for fatigue, depression, and pain with or without hypnosis

**Benefits Balanced With Harms**
- Erythropoiesis-stimulating agents
- Dexamethasone

**Effectiveness Not Established**
- Paroxetine, sertraline, venlafaxine, donepezil, buproprion sustained release, methylphenidate, modafinil, etanercept, infliximab
- Acupuncture, acupressure, self-acupressure
- Nutritional supplements and herbal remedies: levocarnitine, lectin-standardized mistletoe, megestrol acetate, omega-3 fatty acid supplementation, PG2 (a partially purified extract of Astragalus membranaceus), protein supplementation, gauran, Chinese medicinal herbs, essiac, valerian mistletoe extract
- Morning exposure to bright light
- Qigong, tai chi
- Massage, biofield therapies (Reiki, therapeutic touch, haptotherapy, polarity therapy)
- Expressive writing, art, music, dance, or animal-assisted therapy, exposure to nature, distraction (virtual reality immersion)
- Combination therapy: high-dose vitamin C, multiple vitamin, omega-3 fatty acid supplementation
- Combination therapy: aromatherapy, foot soak, and reflexology
- Combination therapy: medroxyprogesterone, celecoxib, and enteral supplementation

**Supported by Expert Opinion**
- Work with patient and family to improve assessment of fatigue and identify management strategies.
- Promote open communication between patient, family, and caregiving team to facilitate discussions about the experience of fatigue and its effects on daily life.
- Screen for the presence of treatable etiologic or contributing factors, including hypothyroidism, hypogonadism, adrenal insufficiency, cardiomyopathy, pulmonary dysfunction, concurrent distressing symptoms (pain, nausea, depression), emotional distress, sleep disturbances, anemia, nutritional compromise, fluid and electrolyte imbalances, and inactivity/physical deconditioning.
- Current medications (including over-the-counter medications and herbal supplements) should be reviewed to identify any agents or medications interactions that may contribute to worsening fatigue (e.g., opiates, antidepressants, antiemetics, antihistamines).
- Consider attention-restoring activities, such as exposure to natural environments and pleasant distractions (e.g., music).
- Encourage a balanced diet with adequate intake of fluid, calories, protein, carbohydrates, fat, vitamins, and minerals.

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**FIGURE 3. Evidence-Based Interventions for Fatigue During and Following Cancer**
of a comparison group in the single-arm studies and the inclusion of heterogeneous meditative techniques confound the interpretation of the studies.

Management of concurrent symptoms, including pain, shortness of breath, insomnia, and depression, improved fatigue outcomes in an RCT of an advanced practice nurse intervention that incorporated systematic symptom monitoring and management (de Raaf, de Klerk, Timman, et al., 2013). A palliative care clinic consultation to address concurrent symptoms also improved CRF outcomes in a single-arm cohort study (Yennurajalingam et al., 2010).

Cognitive-behavioral therapy interventions for fatigue, depression, and pain, and cognitive-behavioral therapy combined with hypnosis have demonstrated favorable effects on fatigue outcomes. Six RCTs confirmed that cognitive-behavioral therapy interventions alleviate CRF among patients with cancer and a major depressive disorder (Strong et al., 2008), survivors with fatigue (Gielissen, Wiborg, Verhagen, Knoop, & Bleijenberg, 2012), patients with mixed tumor types undergoing cancer treatment (Goedendorp et al., 2010), severely fatigued survivors with mixed tumor types (Gielissen, Verhagen, Witjes, & Bleijenberg, 2006), severely fatigued survivors with mixed tumor types (Prinsen et al., 2013), and women with metastatic breast cancer who were depressed (Savard et al., 2006). In addition, cognitive-behavioral therapy interventions were found to alleviate CRF in a single-arm trial among depressed cancer survivors (Brothers, Yang, Strunk, & Andersen, 2011) and a systematic review (Kwekkeboom, Cherwin, Lee, & Wanta, 2010). Two RCTs of cognitive-behavioral therapy plus hypnosis in women with breast cancer showed a reduction in fatigue severity during and sustained improvements following radiation therapy treatment (Montgomery et al., 2009, 2014). Hypnosis alone was found to improve fatigue outcomes in women undergoing excisional breast biopsy or lumpectomy in an RCT with an attentional control (Montgomery et al., 2007). A systematic review concluded that cognitive-behavioral therapy plus hypnosis and hypnosis alone are supported by sparse but promising evidence of efficacy (Cramer, Lauche, Paul, et al., 2014). However, in one RCT of cognitive-behavioral therapy tailored to symptom profiles, statistically significant differences in fatigue were not seen, but the intervention improved pain outcomes (Dalton, Keefe, Carlson, & Youngblood, 2004).

Benefits Balanced With Harms

The use of erythropoiesis-stimulating agents (ESAs) to correct anemia may increase vigor and reduce CRF (Bohlius, Tonia, & Schwarzer, 2011; Eton & Cella, 2011; Tonia & Bohlius, 2011). However, little evidence exists that ESAs improve fatigue when anemia is less severe (Bohlius et al., 2014; Grant et al., 2013). A target hemoglobin level of 11–12 g/dl was associated with the greatest reduction in CRF and improvement in other quality-of-life outcomes (Eton & Cella, 2011). Although ESAs are generally well tolerated, the use of these agents specifically for the management of fatigue must be considered in light of safety issues, including an elevated risk for thromboembolic complications and decreased survival, particularly when ESAs are used in patients with cancer who are not receiving chemotherapy (Bohlius et al., 2013; Bormanis et al., 2013; Boulamaane et al., 2013; Gao, Ma, & Lu, 2013; Tonia et al., 2012; Tonia, Schwarzer, & Bohlius, 2013; Wauters & Vansteenkiste, 2012). National clinical practice guidelines (Lichtin, 2011; NCCN, 2015; Rizzo et al., 2010) and the recommendations of the U.S. Food and Drug Administration (2013) should guide decisions about treatment initiation, discontinuation, monitoring, and management in patients receiving ESAs.

Low-dose dexamethasone (4 mg BID for two weeks) improved CRF in patients with advanced cancer in a small randomized placebo-controlled trial (Yennurajalingam et al., 2013). Although adverse events were comparable in the dexamethasone and placebo groups, the limited follow-up and study attrition make drawing definitive conclusions difficult about the safety of dexamethasone treatment (Franco, William, Poon, & Azad, 2014; Yamane, Ochi, Yamagishi, & Takigawa, 2014; Yennurajalingam & Bruera, 2014). Systemic corticosteroids may have prominent adverse effects in particular subpopulations such as those at the end of life (Matsuo & Yomiya, 2015).

Effectiveness Not Established

More than 15 pharmacologic agents and nutritional supplements have been tested, either alone or as part of a combination therapy, for their effectiveness in improving CRF outcomes. Several systematic reviews summarized the results of trials evaluating pharmacologic agents for CRF management (Breitbart & Alici, 2008, 2010; Breitbart & Alici-Evcimen, 2007; Gong et al., 2014; Minton, Richardson, Sharpe, Hotopf, & Stone, 2008, 2010, 2011; Peuckmann, Elsner, Krumm, Trottenberg, & Radbruch, 2010).

Paroxetine may exert beneficial effects on fatigue in women with hot flashes (Weitzner, Moncello, Jacobsen, & Minton, 2002) and patients receiving interferon (Capuron et al., 2002); however, two large randomized, double-blind placebo-controlled trials failed to demonstrate an effect of paroxetine on fatigue outcomes (Morrow et al., 2003; Roscoe, Morrow, et al., 2005). Little evidence exists that the antidepressants bupropion (Cullum, Wojciechowski, Pelletier, & Simpson, 2004; Moss, Simpson, Pelletier, & Forsyth, 2006), sertraline (Stockler et al., 2007), or venlafaxine are effective in treating CRF, but treatment with venlafaxine did improve fatigue in the subgroup of participants who also experienced a significant reduction in the severity and interference caused by hot flashes (Carpenter et al., 2007).

Modafinil is a novel psychostimulant that, in single or divided daily doses of 100–400 mg, seems to be well tolerated and has shown some evidence of efficacy in improving CRF in open-label trials (Blackhall, Petroni, Shu, Baum, & Farace, 2009; Spathis et al., 2009) and in one placebo-controlled trial (Jean-Pierre et al., 2010). However, in three RCTs, the effects of modafinil on fatigue endpoints did not exceed those of the placebo (Boele et al., 2013; Hoeve et al., 2014; Spathis et al., 2014).

Methylphenidate, or the D-isomer form of methylphenidate, administered using varying doses and schedules, reduced CRF in several trials (Kerr et al., 2012; Lower et al., 2009; Roth et al., 2010), but other studies have not confirmed this benefit (Bruera et al., 2006, 2013; Escalante et al., 2014; Moraska et al., 2010). Despite the conclusions of a number of systematic reviews that preliminary evidence supports the use of psychostimulants to...
treat CRF (Breitbart & Alici, 2010; Gong et al., 2014; Minton et al., 2011; Portela, Rubiales, & Centeno, 2011), given mixed evidence for efficacy and the potential for side effects that may include dry mouth, hypertension, anorexia, and anxiety, the use of psycho-stimulants to treat CRF outside the context of a clinical trial has been discouraged until stronger evidence of efficacy is available (Barton, 2014; Rudy, Barton, & Loprinzi, 2014).

Donepezil, a reversible acetylcholinesterase inhibitor, exhibited a positive effect on CRF in two open-label trials when given at a dose of 5–10 mg per day (Brueera et al., 2003; Shaw et al., 2006); however, a subsequent randomized, double-blinded, placebo-controlled trial did not demonstrate an improvement in fatigue outcomes over placebo (Brueera et al., 2007).

Similarly, a blinded, placebo-controlled trial of testosterone replacement in a small sample of men with advanced cancer did not improve fatigue endpoints (Del Fabbro et al., 2013).

Additional studies are needed to confirm the observation that thyrotropin-releasing hormone improved fatigue outcomes in a small, pilot, randomized, placebo-controlled crossover study in eight patients with cancer who also had significant fatigue (Kamath, Feinn, & Winokur, 2012).

Two small single-arm pilot studies have examined the effects on fatigue of targeted anticytokine therapy with infliximab or etanercept (Monk et al., 2006; Tookman, Jones, DeWitte, & Lodge, 2008). Small sample sizes and the lack of randomization or a control arm limit conclusions.

Acupuncture, acupressure, and self-acupuncture have been examined in several RCTs, and six meta-analyses or systematic reviews examining the evidence have been published (Chien, Liu, & Hsu, 2013; Finnegan-John, Molassiotis, Richardson, & Ream, 2013; Garcia et al., 2013; He, Wang, & Li, 2013; Johnston et al., 2011; Molassiotis et al., 2012, 2013; O’Regan & Filshire, 2010; Posadzki et al., 2013; Smith, Carmady, Thornton, Perz, & Ussher, 2013; Towler, Molassiotis, & Brearley, 2013; Zeng, Luo, Xie, Huang, & Cheng, 2014). A number of the RCTs showed a positive effect on CRF outcomes, and the evidence suggests that acupuncture, acupressure, and self-acupuncture are feasible, well accepted, and safe. However, interpretation of the study outcomes is complicated because many of the trials have high risk of bias resulting from design flaws such as short duration of follow-up, single acupuncturists, and nonblinding of outcome assessors. Although the authors of the reviews and meta-analyses captured different studies in their analyses, used different review methodologies, and have drawn somewhat conflicting conclusions (Azad & John, 2013; Ernst & Posadzki, 2013; Molassiotis, 2013a, 2013b; Molassiotis & Richardson, 2013), all have urged additional study using rigorous trial designs.

Nutritional supplements and herbal remedies have been evaluated for their effects on fatigue outcomes as single interventions or as part of a multicomponent regimen include vitamin supplements (de Souza Fede et al., 2007; Yeom, Jung, & Song, 2007), multicomponent nutritional supplementation (Baldwin & Weekes, 2012; Macciò et al., 2012; Mantovani et al., 2006), coenzyme Q10 (Lesser et al., 2013), levocarnitine (Cruciani et al., 2004, 2006, 2009, 2012; Gramignano et al., 2006; Graziano et al., 2002; Mantovani et al., 2008), lectin-standardized mistletoe (Schumacher et al., 2003), megestrol acetate alone or in combination with omega-3 fatty acid supplementation (Brueera et al., 1998; Mantovani, 2010), PG2 (Chen et al., 2012), protein supplementa-

tion in combination with nutritional counseling (Jensen & Hessov, 1997), gaurana (da Costa Miranda et al., 2009; del Giglio et al., 2013; de Oliveira Campos et al., 2011), Chinese herbal medicine (Su, Wang, Grant, & Liu, 2014), essiac (Zick et al., 2006), and valerian (Barton et al., 2011). Improvements in fatigue endpoints were inconsistent, and results must be interpreted with caution because of the potential for bias given the preponderance of open-label, nonrandomized study designs; small samples; and testing of multiple secondary endpoints.

Morning exposure to bright light has been shown in a small RCT to prevent deterioration in CRF during chemotherapy for breast cancer (Ancoli-Israel et al., 2012), potentially by protecting recipients from circadian rhythm desynchronization during cancer treatment (Neikrug et al., 2012). A secondary analysis confirmed that improvements in quality of life also seen in response to bright light therapy were mediated by its effects on fatigue (Jeste et al., 2013). Similar findings have also been noted in a small RCT of light therapy in cancer survivors with mixed diagnoses (Redd et al., 2014).

Qi gong has shown beneficial effects on fatigue outcomes in three randomized clinical trials (Campo et al., 2014; Chen et al., 2013; Oh et al., 2010), and tai chi improved fatigue in a small single-arm trial (Galantino, Callens, Cardena, Piela, & Mao, 2013); however, a meta-analysis by Zeng et al. (2014) concluded that study results should be interpreted cautiously because of heterogeneous study quality and risk of bias.

Massage and biofield therapies such Reiki, healing touch, polarity therapy, or baptotherapy showed mixed evidence of fatigue reduction in RCTs or quasiexperimental studies (Aghabati, Mohammadi, & Pour Esmaiel, 2010; Ahles et al., 1999; Currin & Meister, 2008; Fernández-Lao et al., 2012; FitzHenry et al., 2014; Karagozoglu & Kalve, 2013; Khiewkvern, Promthet, Sukprasert, Eu mphipitpong, & Brashaw, 2013; Lutgendorf et al., 2010; Mehling et al., 2012; Mustian et al., 2011; Post-White et al., 2003; Roscoe, Matteson, Mustian, Padmanaban, & Morrow, 2005; Tsang, Carlson, & Olson, 2007; van den Berg, Visser, Schoolmeesters, Edelman, & van den Borne, 2006). The modalities have been examined as single interventions and as part of a multicomponent intervention, combined with aromatherapy or core muscle exercises. However, methodologic limitations, including short length of follow-up, small sample sizes, and the absence of sham or active control conditions, and the mixed efficacy results, permit only tentative conclusions. Several systematic reviews have concluded that, although preliminary evidence supports the efficacy of massage and biofield therapies (Ernst, 2009; Jain & Mills, 2010; Myers, Walton, Bratsman, Wilson, & Small, 2008; Pan, Yang, Wang, Zhang, & Liang, 2013), continued testing and refinement in methodologically rigorous trials are needed (Hammerschlag et al., 2012; Visser et al., 2011).

Preliminary evidence suggests that the following complementary approaches may be promising in the treatment of CRF: expressive writing (de Moor et al., 2002; Lu, Zheng, Young, Kagawa-Singer, & Loh, 2012; Milbury et al., 2014; Mosher et al., 2012); biofeedback (Alvarez, Meyer, Granoff, & Lundy, 2013); cranial stimulation (Lyon, Schubert, & Taylor, 2010); art, music, dance, or animal-assisted therapy (Archer, Buxton, & Sheffield, 2014; Bar-Sela, Atid, Danos, Gabay, & Epelbaum, 2007; Bozcek et al., 2006; Bradt, Dileo, Grocke, & Magill, 2011; Clark et al., 2006; Johnson, Meadows, Haubner, & Sevedge, 2008; Sturm, Baak, 2014).
Fatigue is a common problem for patients during and often for many months following cancer treatment. It is one of the most common side effects of treatment and can be difficult to describe to others. The symptoms of fatigue are different than “feeling tired.” Fatigue can begin suddenly, it can be all-consuming, naps may not help, and fatigue can be physically and emotionally draining on the patient as well as the family. Fatigue may be accompanied by a generalized weakness, a sensation of limb heaviness, decreased ability to concentrate, sleeplessness, and/or irritability. People sometimes think that they are just being lazy or depressed, but fatigue can limit the ability to do everyday activities and enjoy life.

Many factors can contribute to cancer-related fatigue. A few simple tests, including a blood count to check for anemia or infection, thyroid function tests, and a physical examination, will help your healthcare provider to eliminate some immediately treatable causes for fatigue and make a diagnosis. Fatigue can be managed with a plan tailored to you and to the factors contributing to fatigue in your situation, such as muscle weakness or deconditioning, emotional distress, impaired sleep quality, or the side effects of sedating medications. Studies show that there are effective ways to manage cancer-related fatigue. They include the following.

**Exercise**
- With permission from your healthcare team, begin a program of physical activity such as walking, stretching, and cycling. Begin with 5–10 minutes twice daily, and increase the time by 1 minute per day. Do not be tempted to overdo exercise but, rather, strive for consistency.
- A moderate amount of exercise may actually help improve your energy level. Find a friend to walk with; he or she can encourage you to get out when you’re tempted to stay in. An exercise trainer or physical therapist can also help with strengthening and building muscles and improving flexibility and balance.

- Consider a referral to a physical or occupational therapist, exercise physiologist, or physiatrist to develop and advance your exercise program. Rehabilitation programs may improve fatigue outcomes.

**Gain Information About Fatigue and Its Management**
- Learn more about your fatigue and talk to your family about ways they can be supportive.
- Differentiate facets of the fatigue experience (fatigue, tiredness, weakness, cognitive slowing) and discuss with your healthcare team.
- Keep a journal or diary of activities, fatigue severity, associated feelings/symptoms, and the effectiveness of self-management strategies.

**Improve Sleep Quality**
- Try to get undisturbed sleep. Go to bed at a regular time each day and follow a regular routine. The routine will begin to serve as a signal to your body that it’s time for sleep.
- If you wake up at night because of pain or other symptoms, ask your team if your medication schedule can be adjusted to allow several hours of sleep at night.
- Substitute napping with other activities. Taking a daytime nap is almost a guarantee that you will have trouble sleeping at night. Try replacing a nap with relaxing activities like meditation, progressive muscle relaxation, or yoga. These activities can also help you avoid sleep troubles by reducing the anxiety and stress that also play a part in sleep difficulties.

**Energy Conservation and Activity Management**
Energy conservation means looking at your daily routines to find ways to reduce the amount of effort needed to perform certain tasks, eliminating other tasks, and alternating rest periods with activities throughout the day to prevent bursts of activity and discourage physical inactivity. Although not every technique will work for you, these are suggestions that you can consider.
• Set priorities to reduce or eliminate tasks that are less important. Redefine “necessary” and sort out the really important activities from those that can wait.
• Schedule a daily routine to ensure pacing of activities and balance of rest and activity.
• Delegate or use labor-saving devices.
• Schedule activities for times of peak energy and mental concentration.
• Forgo jobs that need not be done every day, such as making beds.
• Ask your team about an occupational therapy evaluation to teach you energy-saving strategies.
• Keep a list of tasks that need to be done near your phone. When a neighbor, family member or friend asks what they can do to help, ask them!

Seek Help in Managing Stress, Concurrent Distressing Symptoms, and the Ups and Downs of the Cancer Experience
• Maintain open communication with your family and healthcare team about fatigue and its effects on daily life.
• Ask your nurse or doctor if your fatigue or other symptoms, such as pain or depression that contribute to your fatigue may be helped with medication. In addition to exploring the newest medical treatments for fatigue and other symptoms, you’ll make your team aware of the severity of your tiredness.
• Consider participating in counseling or support groups.

Other approaches that are supported by evidence that could be considered for the treatment of fatigue include Wisconsin ginseng, yoga, and mindfulness-based stress reduction.

Approaches that have been evaluated but do not have enough research to recommend them include wakefulness-promoting agents such as modafinil or methylphenidate, acupuncture, massage, bright light therapy, and biofield therapies such as Reiki, therapeutic touch, qigong, or tai chi. In specific clinical circumstances, these approaches may still be helpful.

Implications for Practice and Research

This review of the evidence for fatigue management during and following cancer treatment can be used by clinicians to broaden their therapeutic armamentarium and to develop individually tailored multimodal approaches to CRF management. Findings can be applied in the delivery of evidence-based supportive care, updating of evidence-based management guidelines (Bower et al., 2014; Howell et al., 2013), and national quality reporting programs as part of a learning healthcare system, as recommended by the Institute of Medicine (2013). This evidence review can also be used to guide clinical program development and to support health policy initiatives that improve access to and reimbursement for research-tested interventions for CRF, including access to comprehensive rehabilitation services and the delivery of supportive care interventions by advanced practice nurses.
The analysis of the evidence suggests a number of implications for further CRF research. Many of the interventions for fatigue have had only limited study, often in uncontrolled pilot studies or single-site RCTs. Promising interventions, such as massage, biofield therapies, qigong, morning exposure to bright light, and acupuncture should receive continued study and refinement in rigorously designed, multisite trials. Interventions that are recommended for practice or likely to be effective, including exercise, psychoeducational interventions, and cognitive-behavioral therapies for sleep, fatigue, and concurrent symptoms, should be manualized to strengthen intervention fidelity and optimize widespread implementation and testing in pragmatic trials conducted in diverse community-based settings. Also indicated are RCTs to further evaluate therapies such as psychostimulants, MBSR, meditation, acupuncture, and energy conservation and activity management, where results have been mixed. Few RCTs include participants experiencing CRF in the context of multiple chronic conditions (Wright, Hammer, & Melkus, 2014) or those with advanced disease; as a result, research evidence is limited to support the feasibility, acceptability, and effectiveness of fatigue interventions for these specific subpopulations. This is particularly important because some evidence indicates that intervention programs that are lengthy or incorporate frequent treatment sessions may exacerbate fatigue in some patient populations, including those receiving radiation therapy (Brown et al., 2006) or those with advanced cancers (Dalton et al., 2004).

The limitations in drawing definitive conclusions about the effectiveness of several interventions suggest implications for the design of future CRF trials. Key study design decisions include whether a heterogeneous or homogeneous sample provides a better evaluation of efficacy (Sikorskii et al., 2014), whether fatigue-targeted criteria should be incorporated for study eligibility to enhance power (King, Ahn, Atienza, & Kraemer, 2008), and whether fatigue endpoint measures with well-established properties of precision and responsiveness such as the PROMIS Fatigue scale should be selected (Barsevick et al., 2013). Inclusion of congruent endpoints also enhances comparison of results across trials and permits formal meta-analysis. Intervention dose intensity and mechanism of action, treatment fidelity, patient preferences, and adequate statistical power are also important trial design considerations, particularly given that a number of the nonpharmacologic interventions incorporate individual tailoring (Ellis et al., 2012; Reich et al., 2014), include multiple components, and share an emphasis on progressive muscle relaxation, mindfulness, meditation, and controlled movement (Stan, Collins, Olsen, Croghan, & Pruthi, 2012).

Conclusion

As evidence-based treatment strategies for fatigue during and following cancer continue to evolve, clinicians are challenged to synthesize the evidence base and select the most effective strategies for intervention. The body of intervention research for CRF offers empirical and practical insights that clinicians can apply in their practices to achieve optimal management of this distressing symptom. This review also reveals gaps in the current knowledge and underscores the need for continued research to test and refine interventions that reduce fatigue and promote well-being in patients experiencing CRF.

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