

Fatigue

Problem

Cancer-related fatigue is defined as “a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning” (National Comprehensive Cancer Network [NCCN], 2008, p. FT-1).

Incidence

Fatigue is the most common symptom reported by patients with cancer during treatment. An estimated 80%–100% of people with cancer experience fatigue (Lawrence, Kupelnick, Miller, Devine, & Lau, 2004; Prue, Rankin, Allen, Gracey, & Cramp, 2006; Servaes, Verhagen, & Bleijenberg, 2002). Fatigue may be related directly to the cancer or its treatment and may continue for years after treatment is completed (Wang, 2008). Fatigue may occur as an isolated symptom or as one element in a cluster of symptoms such as pain, depression, sleep disturbance, and anemia (NCCN, 2008).

Assessment

Because fatigue is a subjective experience, it is best assessed by patient self-report. A detailed assessment of risk and contributing factors (see Table 11-1) and information obtained from a clinical measurement tool are essential for monitoring fatigue.

Clinical Measurement Tools

No matter what tool is used to measure fatigue, it should obtain comparable data at different points in time. This is essential in determining the effects of nursing interventions on the person’s fatigue experience. The following clinical measurement tools for fatigue are presented in Table 11-2.

Table 11-1. Fatigue Assessment Guide

Assessment	Yes	No
Physical Symptoms		
Shortness of breath		
Heart palpitations		
General lack of energy		
Risk and Contributing Factors		
Anemia		
Hypothyroidism		
Hypogonadism		
Adrenal insufficiency		
Cardiomyopathy		
Pulmonary dysfunction		
Fluid and electrolyte imbalances		
Nausea		
Pain		
Depressed mood		
Emotional distress		
Sleep disturbances		
Sedation secondary to specific classes of medications		
<i>Note.</i> Based on information from National Comprehensive Cancer Network, 2008; Newton, 2008.		

1. Brief Fatigue Inventory (BFI) (see Figure 11-1)
2. Numeric Rating Scale (e.g., Oncology Nursing Society [ONS] Fatigue Scale [see Figure 11-2])
3. Revised Piper Fatigue Scale

References

- Beck, S.L. (2004). *Measuring oncology-nursing sensitive patient outcomes: Evidence-based summary*. Retrieved April 17, 2008, from <http://www.ons.org/outcomes/measurements/fatigue.shtml>
- Butt, Z., Wagner, L.I., Beaumont, J.L., Paice, J.A., Peterman, A.H., Shevrin, D., et al. (2008). Use of a single-item screening tool to detect clinically significant fatigue, pain, distress, and anorexia in ambulatory cancer practice. *Journal of Pain and Symptom Management*, 35(1), 20–30.

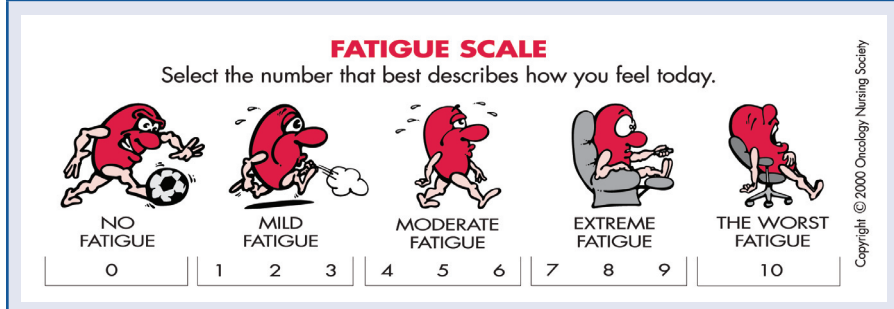
Table 11-2. Clinical Measurement Tools for Fatigue

Name of Tool	Number of Items	Domains	Reliability and Validity	Populations	Clinical Utility
Brief Fatigue Inventory	9	Severity and impact of fatigue	Adequate reliability and validity established	Variety of cancer diagnoses, chronic cancer-related pain	Rapidly identifies patients with clinically significant fatigue
Numeric Rating Scale (e.g., Oncology Nursing Society Fatigue Scale)	1	Intensity	Less reliable than multiple-item fatigue measures. Established reliability and validity for fatigue screening.	Solid tumors	Easy to use
Revised Piper Fatigue Scale	22 plus 5 additional open-ended items	Behavioral/ severity, affective, sensory, cognitive/ mood	Adequate reliability and validity established	Variety of cancer diagnoses	Somewhat long for clinical use

Note. Based on information from Beck, 2004; Butt et al., 2008; Lee et al., 1991.

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Figure 11-2. Numeric Rating Scale



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Case Study

W.H. was a 53-year-old female diagnosed with stage T2 N0 MX invasive ductal breast cancer (grade III 2.5 × 2.5 × 2.3 cm tumor, estrogen receptor/progesterone receptor negative, HER2/neu negative). W.H.'s oncologist recommended AC-T (four cycles of doxorubicin/cyclophosphamide every three weeks followed by four cycles of paclitaxel every three weeks). W.H. was married and worked full-time managing a business. During chemotherapy teaching, W.H. mentioned how important it was for her to be able to continue working, stating that it would help her to “stay focused on something besides cancer.” She also said that she did not have many hobbies and had always thrived on the intensity of her career, stating, “I’m kind of a control freak.”

The topic of fatigue was covered during W.H.'s teaching about potential side effects from chemotherapy. Recognizing W.H.'s concern about having enough energy to continue working, W.H. and her nurse consulted the ONS Putting Evidence Into Practice (PEP) resource on fatigue to facilitate discussion about interventions that are effective in both preventing and treating fatigue during cancer treatment. After noting that multiple randomized controlled trials have shown exercise to be effective in limiting and managing fatigue, W.H. was quick to mention that she had never been one to exercise on a regular basis. Reading further, she learned that “exercise” can be something as simple as walking several times per week and said that she definitely was willing to give that a try.

Together, W.H. and her nurse also reviewed the interventions listed on the ONS PEP resource on fatigue that are likely to be effective. W.H. was not interested in learning relaxation techniques (“I can’t see myself doing that”) but said she would think about scheduling regular massages and trying to “slow down” at work. The nurse explained to W.H. the importance of screening for other factors that may be contributing to fatigue (interventions cited in the *Likely to Be Effective* section of the ONS PEP resource) and explained that this was a standard part of the nursing

assessment at each visit in addition to measuring the intensity and impact of fatigue by completing the BFI.

W.H. found that working the day after receiving chemotherapy was difficult because of the delayed nausea, so she scheduled her chemotherapy for Thursdays, taking Fridays off. W.H. was proud of herself for taking this step (working less) in caring for herself. She also was walking at lunch with a friend several times per week and felt that the exercise helped her to reenergize.

Upon completion of the four cycles of doxorubicin and cyclophosphamide, W.H. admitted that she really struggles at work the week following her chemotherapy. She mentioned that she had a friend who “got a shot” during her chemotherapy to help with her fatigue. W.H.’s hemoglobin was 10.1 g/dl and her hematocrit was 29.4 g/dl. After reviewing the ONS PEP resource on fatigue, the nurse discussed with W.H. the risks and benefits of using erythropoiesis-stimulating agents (ESAs). The nurse facilitated further discussion with the patient and her oncologist during the visit.

Ultimately, W.H. was able to complete her treatment without further significant drop in hemoglobin and without adding an ESA. Her scores on the BFI remained at the mild fatigue level (1–3) throughout treatment except for the weeks after treatment, when her fatigue was at a moderate level (4–6). The patient and nurse continued to monitor the level of fatigue and its consequences for functioning as the patient completed her treatment and began the recovery process. The nurse provided anticipatory guidance that fatigue may persist for several months after the conclusion of treatment and continued to offer suggestions and reinforcement of the patient’s efforts to adopt effective self-management behaviors.

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What interventions are effective in preventing and treating fatigue?

Recommended for Practice

Interventions for which effectiveness has been demonstrated by strong evidence from rigorously conducted studies, meta-analyses, or systematic reviews and for which expectation of harms is small compared with the benefits

EXERCISE

Fourteen meta-analyses or systematic reviews (Conn, Hafdahl, Porock, McDaniel, & Nielsen, 2006; Courneya & Friedenreich, 1999; Cramp & Daniel, 2008; Galvao & Newton, 2005; Jacobsen, Donovan, Vadaparampil, & Small, 2007; Knols, Aaronson, Uebelhart, Fransen, & Aufdemkampe, 2005; Labourey, 2007; Markes, Brockow, & Resch, 2006; McNeely et al., 2006; Oldervoll, Kaasa, Hjermstad, Lund, & Loge, 2004; Schmitz et al., 2005; Stevinson, Lawlor, & Fox, 2004; Stricker, Drake, Hoyer, & Mock, 2004; Thorsen, Courneya, Stevinson, & Fossa, 2008) support the benefits of exercise in the management of fatigue during and following cancer treatment in patients with breast cancer, prostate cancer, and mixed solid tumors and in recipients of hematopoietic stem cell transplantation. Although positive results for the outcome of fatigue have not been observed consistently across studies, and effect sizes were very small and in some cases were not statistically significant (Conn et al.; Jacobsen et al.; Markes et al.), the general pattern of results in 28 randomized controlled trials (RCTs) (N = 2,083 participants) indicates that exercising several times per week (including walking, cycling, swimming, resistance exercise, or a combination of aerobic and resistance exercise) can be effective in reducing fatigue during and following cancer treatment. Most of the studies reviewed suffer from methodologic shortcomings, and meta-analysis is limited by the fact that there is heterogeneity in the exercise characteristics and intervention dose, as well as diverse measures of outcomes and variation in the timing of outcome assessment. Moreover, few studies required that study participants have a clinically significant level of fatigue. As a result, the possibility exists that many participants were experiencing little or no fatigue at the time of study entry, thus limiting the ability to detect intervention effects. Much more research is needed to systematically assess the safety of exercise (both aerobic exercise and strength training) (Humpel & Iverson, 2005) and to tailor the type, intensity, frequency, and duration of physical exercise to different tumor types and stages of

the disease and treatments. Further research is needed using larger samples, attention control groups (a feature of study design that tests the hypothesis that improvements in fatigue occurred not because of the intervention but rather are the result of the expectancy of improvement or as a result of the attention received during the course of the treatment), and blinding of the outcome assessor. The study design also should control for exercise motivation and preferences as well as participant adherence.

Likely to Be Effective

Interventions for which effectiveness has been demonstrated by supportive evidence from a single rigorously conducted controlled trial, consistent supportive evidence from well-designed controlled trials using small samples, or guidelines developed from evidence and supported by expert opinion

SCREENING FOR POTENTIAL ETIOLOGIC FACTORS AND MANAGING AS APPROPRIATE

There is expert consensus that patients with fatigue be screened for potentially treatable etiologic factors contributing to fatigue (National Comprehensive Cancer Network [NCCN], 2008) and managed as indicated. These treatable etiologic factors include concurrent distressing symptoms, including pain, nausea, and depression; hypothyroidism, hypogonadism, cardiomyopathy, adrenal insufficiency, pulmonary dysfunction, anemia, sleep disturbance, fluid and electrolyte imbalances, and emotional distress; and sedation secondary to specific classes of medications (e.g., opiates, antidepressants, antiemetics, antihistamines) or due to drug-drug interactions.

ENERGY CONSERVATION AND ACTIVITY MANAGEMENT

A nurse-delivered intervention focused on energy conservation and activity management (ECAM) was found to have a modest but significant effect in a large, multisite RCT in patients (predominantly with breast cancer) initiating chemotherapy or radiation (Barsevick et al., 2004). A pilot study by the same investigators showed a trend for ECAM to be superior using a historical control group (Barsevick, Whitmer, Sweeney, & Nail, 2002).

EDUCATION/INFORMATION PROVISION

A meta-analysis (Jacobsen et al., 2007), seven RCTs (Fawzy, 1995; Fillion et al., 2008; Gaston-Johansson et al., 2000; Given et al., 2002; Kim, Roscoe, & Morrow, 2002; Ream, Richardson, & Alexander-Dann, 2006; Yates et al., 2005), a matched-pairs controlled trial (Vilela et al., 2006), and two single-arm studies (Allison et al., 2004; Lindemalm, Strang, & Lekander, 2005) in patients with mixed solid and hematologic malignancies across all phases of the disease support a conclusion that educational interventions (including teaching, counseling, support, anticipatory guidance about fatigue patterns, coping skills training, and coaching) play a role in supporting positive coping in patients with fatigue and in reducing fatigue levels. In addition, the NCCN consensus panel guidelines recommend that patients and families be provided with anticipatory guidance about patterns of fatigue and recommendations for self-management, especially when beginning fatigue-inducing treatments (NCCN, 2008). These multifaceted psychoeducational interventions vary in content and delivery method. Thus, concluding which specific elements of such interventions are therapeutic is difficult. Moreover, six RCTs have demonstrated no statistically significant effect of psychoeducational interventions on fatigue outcomes. However, these trials in relatively small and heterogeneous samples may have been underpowered, and none of the studies used level of fatigue as a

criterion of eligibility (Arving et al., 2007; Berglund et al., 2007; Brown et al., 2006; Godino, Jodar, Duran, Martinez, & Schiaffino, 2006; Rummans et al., 2006; Williams & Schreier, 2005). Overall, study results support a conclusion that patients welcome psychoeducative interventions related to fatigue and that they can apply the skills to improve their self-management of fatigue. The potency of these interventions is modest, and they are not effective for all patients.

MEASURES TO OPTIMIZE SLEEP QUALITY

Seven studies (Berger et al., 2002, 2003; Davidson, Waisberg, Brundage, & MacLean, 2001; Dirksen & Epstein, 2008; Espie et al., 2008; Quesnel, Savard, Simard, Ivers, & Morin, 2003; Savard, Simard, Ivers, & Morin, 2005), including three RCTs, support the conclusion that a multicomponent cognitive-behavioral therapy (CBT) intervention designed to optimize sleep quality improves fatigue outcomes. The CBT intervention, delivered individually or in a group, generally included relaxation training, along with sleep consolidation strategies (avoiding long or late afternoon naps, limiting time in bed to actual sleep time), stimulus control therapy (go to bed only when sleepy, use bed/bedroom for sleep and sexual activities only, designate a consistent time to lie down and get up, avoid caffeine and stimulating activity in the evening), and strategies to reduce cognitive-emotional arousal (keep at least an hour to relax before going to bed and establish a pre-sleep routine to be used every night).

RELAXATION

Three RCTs (Cohen & Fried, 2007; Decker, Cline-Elsen, & Gallagher, 1992; Kim & Kim, 2005) found progressive muscle relaxation training, relaxation breathing and yoga-like positioning, and relaxation training with guided imagery delivered in a series of sessions to be effective in lowering fatigue scores. Although a meta-analysis of the effectiveness of relaxation training in reducing treatment-related symptoms in acute nonsurgical cancer treatment did not identify a statistically significant effect of relaxation on fatigue in pooled analyses, those results must be interpreted cautiously because only two of the three aforementioned studies described were included (Luebbert, Dahme, & Hasenbring, 2001).

MASSAGE, HEALING TOUCH, POLARITY THERAPY, AND HAPTOTHERAPY

Single studies provide evidence that massage and healing touch (combined in some studies with centering, breathing, and relaxing music) may be effective in reducing fatigue (Ahles et al., 1999; Cassileth & Vickers, 2004; Currin & Meister, 2008; Post-White et al., 2003). A controlled pilot study in a small sample of 15 women receiving radiation therapy for breast cancer (Roscoe, Matteson, Mustian, Padmanaban, & Morrow, 2005) demonstrated that polarity therapy (an intervention hypothesized to promote healing, relaxation, and well-being by unblocking and balancing energy flow and reestablishing homeostasis within the human energy field) also may be effective in reducing fatigue. On the other hand, in a small controlled trial, five sessions of haptotherapy (a form of complementary therapy that uses a massage-like touch together with an expressive-supportive conversation to help patients connect with feelings and improve coping) delivered over several weeks to patients undergoing outpatient chemotherapy did not result in improvement in fatigue (Van Den Berg, Visser, Schoolmeesters, Edelman, & Borne, 2006). A systematic review concluded that the mixed study results seen with therapeutic modalities that incorporate massage and healing touch may be due, in part, to methodologic limitations, including insufficient statistical power, nonrandomized designs, nonblinded outcomes assessment, and failure to account for participant attrition in statistical analysis (Myers, Walton, Bratsman, Wilson, & Small, 2008).

Benefits Balanced With Harms

Interventions for which clinicians and patients should weigh the beneficial and harmful effects according to individual circumstances and priorities

CORRECTION OF ANEMIA WITH ERYTHROPOIESIS-STIMULATING AGENTS

Data from eight meta-analyses or systematic reviews (Bohlius et al., 2006; Bokemeyer et al., 2007; Kimel, Leidy, Mannix, & Dixon, 2008; Mikhael, Melosky, Cripps, Rayson, & Kouroukis, 2007; Minton, Richardson, Sharpe, Hotopf, & Stone, 2008; Minton, Stone, Richardson, Sharpe, & Hotopf, 2008; Rizzo et al., 2008; Wilson et al., 2007) suggest that patients receiving erythropoiesis-stimulating agents (ESAs) to correct anemia less than 10 g/dl may experience increased vigor and diminished fatigue. Only limited evidence exists that ESAs improve fatigue when anemia is less severe. Although some data suggest that a target hemoglobin level of 11–12 g/dl will produce the greatest gains in fatigue and other quality-of-life outcomes (Stasi et al., 2005), better quality evidence is needed to unequivocally support the use of ESAs solely as an intervention to improve patient reported outcomes such as fatigue (Bottomley, Thomas, Van Steen, Flechtner, & Djulbegovic, 2002; Littlewood, Cella, & Nortier, 2002). Although both epoetin and darbepoetin 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 increased risk of thrombotic events, hypertension, and concerns that ESAs may support or extend tumor growth in patients with head and neck cancer, breast cancer, non-small cell lung cancer, or cervical cancer. Particular caution should be exercised in the use of ESAs at higher doses, with dosing to target a hemoglobin \geq 12 g/dl, and with protracted ESA treatment (Aapro, Scherhag, & Burger, 2008; Bennett et al., 2008; Melosky, 2008). ESAs may not be indicated to treat anemia associated with malignancy or the anemia of cancer in patients with solid or nonmyeloid hematologic malignancies (e.g., myeloma, chronic lymphocytic leukemia, non-Hodgkin lymphoma), or in patients at increased risk for thromboembolic complications (Rizzo et al., 2008). National clinical practice guidelines (NCCN, 2009; Rodgers, 2006) and the guidance of the U.S. Food and Drug Administration should be used to direct the management of patients receiving ESAs, including decisions about patient monitoring, treatment thresholds, dose reductions, treatment discontinuation, and the use of supplemental iron.

Effectiveness Not Established

Interventions for which insufficient or conflicting data or data of inadequate quality currently exist, with no clear indication of harm

STRUCTURED REHABILITATION

Three single-arm trials (Korstjens, Mesters, van der Peet, Gijzen, & van den Borne, 2006; Strauss-Blasche, Gnad, Ekmekcioglu, Hladschik, & Marktl, 2005; van Weert et al., 2006), a small RCT (Heim, v d Malsburg, & Niklas, 2007), and a systematic review (van Weert et al., 2008) suggest that structured rehabilitation programs result in statistically significant and sustained improvements in fatigue, particularly in patients who have completed treatment and are in the survivorship phase. The rehabilitation interventions studied were multicomponent

interventions composed of a structured combination of intensive exercise, physical training, sports, psychoeducation, and physical modalities such as massage, mud packs, and manual lymph drainage. In some studies, these therapies were delivered over the course of a several-week inpatient rehabilitation hospital stay.

INDIVIDUAL AND GROUP PSYCHOTHERAPY

Improved fatigue outcomes resulting from individual or group psychotherapy have been demonstrated in two RCTs (Boesen et al., 2005; Fawzy et al., 1990). The addition of exercise to a group psychotherapy intervention (either stress management and relaxation training or expressive-supportive psychotherapy) was found to improve fatigue outcomes when compared to group psychotherapy alone (Courneya et al., 2003). Difficulty in disentangling the effect of the diverse components in these programs limits the conclusions that can be drawn, and in a multicenter RCT of supportive group psychotherapy in 158 women with metastatic breast cancer (Goodwin et al., 2001), a psychotherapy intervention did not result in a significant improvement in fatigue.

COGNITIVE-BEHAVIORAL THERAPY FOR FATIGUE

Two RCTs of CBT have been conducted in small heterogeneous samples, with mixed effects on the outcome of fatigue. In one RCT (N = 60 patients completing a course of chemotherapy), there was a trend toward greater improvement in fatigue over time in the group receiving CBT ($p = 0.09$) (Armes, Chalder, Addington-Hall, Richardson, & Hotopf, 2007). In another randomized trial of CBT in 112 fatigued cancer survivors, participants in the intervention group experienced clinically and statistically significant benefits in fatigue severity compared to the wait-list control group (Gielissen, Verhagen, Witjes, & Bleijenberg, 2006).

COGNITIVE-BEHAVIORAL THERAPY FOR CONCURRENT SYMPTOMS

Three RCTs and a small case series analysis have examined fatigue outcomes associated with CBT for concurrent symptoms such as pain or depression. Although outcomes of an RCT of CBT for cancer pain in 131 patients demonstrated improvement in the outcomes of pain, the differences in fatigue were not statistically significant (Dalton, Keefe, Carlson, & Youngblood, 2004). However, two RCTs (N = 200 patients with cancer with major depressive disorder [Strong et al., 2008] and N = 45 women with metastatic breast cancer [Savard et al., 2006]) and a small case series (N = 6 women with metastatic breast cancer [Levesque, Savard, Simard, Gauthier, & Ivers, 2004]) demonstrated that a CBT intervention for depression also resulted in statistically significant improvements in fatigue ($p < 0.01$).

EXPRESSIVE WRITING

A pilot study compared an expressive writing intervention (four weekly sessions in which participants wrote about their deepest thoughts and feelings) with a writing intervention where participants wrote about neutral issues related to health. No differences in fatigue were reported between the two groups, although post-intervention, the group that had received the expressive writing intervention reported greater vigor (de Moor et al., 2002).

HYPNOSIS

The effects of a 15-minute presurgery hypnosis session compared with nondirective empathic listening (attentional control) were examined in an RCT in 200 women undergoing excisional breast biopsy or lumpectomy. Patients in the hypnosis group reported significantly less fatigue ($p < 0.001$) (Montgomery et al., 2007) when discharged from the same-day surgery center. Despite the sample size and the inclusion of an attention control group, conclusions are limited by the fact that outcome assessors were not blinded to group assignment.

PAROXETINE

Four trials have examined the effectiveness of paroxetine in treating fatigue during and following cancer treatment, with mixed findings. In two large, multicenter, double-blinded, placebo-controlled RCTs (Morrow et al., 2003; Roscoe, Morrow, et al., 2005), paroxetine 20 mg PO daily did not have an effect on fatigue, although improvements in depression and overall mood were noted in the paroxetine treatment group. A recent meta-analysis pooling these results concluded that paroxetine has no benefit over placebo in the treatment of cancer-related fatigue (Minton, Richardson, et al., 2008; Minton, Stone, et al., 2008). However, two small trials have shown a trend toward a possible benefit for paroxetine in treating fatigue in women with hot flashes ($N = 13$) (Weitzner, Moncello, Jacobsen, & Minton, 2002) and patients receiving interferon alfa ($N = 18$) (Capuron et al., 2002).

METHYLPHENIDATE

Five prospective, open-label, single-arm trials with small samples and three placebo-controlled, double-blind RCTs have examined the use of methylphenidate (patient-controlled dosing or upward titration from 10 mg/day to 30 mg/day) in reducing fatigue. All five single-arm studies (Bruera, Driver, et al., 2003; Hanna et al., 2006; Sarhill et al., 2001; Schwartz, Thompson, & Masood, 2002; Sugawara et al., 2002) reported improvements in fatigue as a result of methylphenidate, although in one study (Sarhill et al.), more than half of the patients experienced side effects such as insomnia, agitation, anorexia, nausea and vomiting, or dry mouth, and in another study (Hanna et al.), 19% of patients withdrew because of adverse events. In the RCTs (Bruera et al., 2006; Butler et al., 2007; Mar Fan et al., 2007), methylphenidate had no effect on fatigue outcomes, although studies were generally underpowered. A meta-analysis combining the results of the Bruera et al. (2006) RCT with study results from another investigator that have been reported only in abstract form concluded that methylphenidate treatment compared with placebo was associated with a small but statistically significant ($Z = 1.96$; $p = 0.05$) reduction in cancer-related fatigue (Minton, Richardson, et al., 2008; Minton, Stone, et al., 2008).

DONEPEZIL

Donepezil 5 mg every morning has been evaluated in a double-blind, placebo-controlled RCT ($N = 142$) (Bruera et al., 2007) and in two uncontrolled, open-label trials (Bruera, Strasser, Shen, et al., 2003; Shaw et al., 2006). In both open-label trials, statistically significant improvements were reported in fatigue outcomes. However, in the RCT, fatigue outcomes were not significantly different between the donepezil-treated and placebo-control groups. Conclusions are limited by the paucity of RCTs, and this, together with small samples and short length of treatment, make it difficult to gauge conclusively the effects of donepezil on fatigue outcomes or its tolerability.

BUPROPION SUSTAINED-RELEASE

Bupropion-sustained release at a dose of 100–300 mg/day demonstrated preliminary efficacy in improving fatigue outcomes in two small, open-label, uncontrolled trials in 15 patients with various cancer diagnoses who were experiencing fatigue or depression with marked fatigue (Cullum, Wojciechowski, Pelletier, & Simpson, 2004) and 21 patients with mostly primary brain tumors, breast cancer, or a hematologic malignancy (Moss, Simpson, Pelletier, & Forsyth, 2005). Controlled studies are necessary to establish the efficacy of this intervention in a more homogeneous sample of patients with cancer and to determine whether this effect of bupropion is separate from its action as an antidepressant.

MODAFINIL

In a case report, the use of modafinil (at a dose of 100 mg QD or BID) was associated with improvements in daytime wakefulness and normalization of the sleep-wake cycle in two older adult patients with advanced cancer (Caraceni & Simonetti, 2004). No side effects were reported. In another case report, an older adult with postoperative lethargy and listlessness after resection of an intraventricular subependymoma experienced improved wakefulness and responsiveness after five days of treatment with modafinil 400 mg daily. The use of modafinil (at a dose of 100–400 mg in a daily or divided dose) also is supported by an expert opinion report (Cox & Pappagallo, 2001); however, controlled trials are needed.

VENLAFAXINE

A randomized, doubled-blinded, placebo-controlled crossover trial with 57 breast cancer survivors receiving venlafaxine 37.5 mg and 22 breast cancer survivors receiving 75 mg venlafaxine found no improvement in fatigue overall at either dose of venlafaxine (Carpenter et al., 2007). However, a subgroup of 15 women with a $\geq 50\%$ decrease in physiologic hot flashes experienced significant improvement in fatigue ($p = 0.007$). The side effects included dry mouth and constipation, and at 12-month follow-up, most study participants had discontinued venlafaxine treatment.

SERTRALINE

When the effects of sertraline on fatigue were studied in an RCT of 189 patients with advanced cancer, sertraline did not have a significant effect on fatigue in the absence of major depression (Stockler et al., 2007). Although the outcome of fatigue was not examined, a single-arm trial has suggested that sertraline improved anxiety, depression, and overall quality of life in depressed patients with cancer (Torta, Siri, & Caldera, 2008). RCTs examining whether sertraline improves fatigue outcomes in depressed patients with cancer are indicated.

TARGETED ANTI-CYTOKINE THERAPY

Two small pilot studies have examined the effects on fatigue of targeted anti-cytokine therapy with either infliximab or etanercept. In a small single-arm trial of infliximab 5 mg/kg, 9 of the 14 participants had improvements in their fatigue severity score (Tookman, Jones, Dewitte, & Lodge, 2008). However, treatment with infliximab was associated with five serious adverse events, including two serious infections attributed by the investigators as possibly related to treatment with infliximab. The effect on fatigue of etanercept 25 mg administered twice weekly in patients with advanced malignancy receiving docetaxel 43 mg/m² weekly was studied in a small cohort ($N = 12$). Patients receiving docetaxel plus etanercept reported

significantly less fatigue than those patients receiving docetaxel alone (Monk et al., 2006). Small sample sizes, nonrandom group assignment, and the absence of a placebo control arm limit the conclusions that can be drawn.

REIKI

A small ($N = 16$), counterbalanced, crossover trial in patients who had recently completed treatment showed no benefit of Reiki on fatigue outcomes (Tsang, Carlson, & Olson, 2007). However, the small, heterogeneous sample and the fact that interaction and order effects were not examined limit the conclusions that can be drawn.

YOGA

Two RCTs and a single-arm pilot study have examined the effects of yoga on fatigue outcomes. In the small ($N = 38$) RCT comparing the effects of a seven-week yoga program to a wait-list control, no significant differences in fatigue were reported; however, the design did not control for the possible confounding effects of chemotherapy treatment (Cohen, Warneke, Fouladi, Rodriguez, & Chaoul-Reich, 2004). Additionally, in the single-arm trial ($N = 13$) of an eight-week yoga intervention, the intervention had no significant effect on fatigue, although a trend existed for increased yoga practice to be associated with decreased fatigue ($p < 0.07$) (Carson et al., 2007). Similarly, a 12-week yoga intervention also had no impact on fatigue in an RCT ($N = 128$) (Moadel et al., 2007). However, intervention group participants who were highly adherent with the yoga intervention experienced significant improvements in fatigue compared with those intervention group participants who were less adherent.

MINDFULNESS-BASED STRESS REDUCTION

The effects of mindfulness-based stress reduction on fatigue outcomes have been examined in four trials, with mixed results. An RCT comparing mindfulness-based stress reduction with a wait-list control (Specia, Carlson, Goodey, & Angen, 2000) and two single-arm studies (Carlson, Specia, Patel, & Goodey, 2003; Kieviet-Stijnen, Visser, Garssen, & Hudig, 2008), all with small samples, demonstrated no statistically significant effects on fatigue. However, another single-arm trial of a mindfulness-based stress reduction intervention in 63 participants with mixed tumors noted improvements in stress, mood disturbance, sleep quality, and fatigue (Carlson & Garland, 2005).

ACUPUNCTURE

In two RCTs (Gadsby, Franks, Jarvis, & Dewhurst, 1997; Molassiotis, Sylt, & Diggins, 2007) and a single-arm pilot study (Vickers, Straus, Fearon, & Cassileth, 2004), all with small samples, patients receiving traditional Chinese acupuncture or acupuncture-like transcutaneous electrical nerve stimulation tended to report less fatigue. Improvements may not be sustained once acupuncture is discontinued (Molassiotis et al.).

ART, MUSIC, OR ANIMAL-ASSISTED THERAPY

Art therapy (Bar-Sela, Atid, Danos, Gabay, & Epelbaum, 2007), music therapy (Bozcuk et al., 2006; Burns et al., 2008; Clark et al., 2006), and animal-assisted therapy (Johnson, Meadows, Haubner, & Sevedge, 2008) each have been studied in one or more small trials, and none has demonstrated positive effects on the outcome of fatigue. Studies were generally underpowered because of small sample sizes, and the interventions themselves may have been

insufficiently potent. Nonrandom treatment assignment and the use of pre/post-test study designs rather than a comparison group further limit the conclusions that can be drawn.

DISTRACTION—VIRTUAL REALITY IMMERSION

A distractive intervention, virtual reality immersion (VRI), has been investigated in three randomized crossover trials (Schneider, Ellis, Coombs, Shonkwiler, & Folsom, 2003; Schneider & Hood, 2007; Schneider, Prince-Paul, Allen, Silverman, & Talaba, 2004), an RCT (Oyama, Kaneda, Katsumata, Akechi, & Ohsuga, 2000), and a single-arm pilot study (Oyama, Ohsuga, Tatsuno, & Katsumata, 1999). All but one (Schneider & Hood) of the trials studied fewer than 20 participants, and across studies, the results have been mixed. In one of the three randomized crossover trials, the patients who received the VRI intervention demonstrated a trend toward lower fatigue scores, although the differences did not reach statistical significance (Schneider et al.); however, in the largest crossover trial (N = 127) (Schneider & Hood), VRI had no effect on fatigue. Adequately powered RCTs are needed to further explore these preliminary results.

LEVOCARNITINE SUPPLEMENTATION

Four small, open-label, single-arm trials in patients with mixed advanced solid tumors receiving chemotherapy provide preliminary support for the safety and efficacy of levocarnitine supplementation in treating fatigue in nonanemic patients with cancer who have low serum carnitine levels (Cruciani et al., 2004, 2006; Gramignano et al., 2006; Graziano et al., 2002). Although the conclusions that can be drawn are limited by small sample sizes, non-randomized study designs, and the absence of double-blinded controls, the results suggest that levocarnitine supplementation should be further studied as a possible intervention for fatigue in patients with cancer.

VITAMIN SUPPLEMENTATION

High-dose vitamin C supplementation has shown beneficial effects ($p < 0.01$) on fatigue in a single-arm, open-label trial in 39 terminally ill patients with advanced malignancies (Yeom, Jung, & Song, 2007). However, the sample was small (N = 39), and the study design did not provide for a comparison group or blinding. In a double-blind, crossover, placebo-controlled RCT in 40 women receiving a six-week course of breast irradiation, the use of a daily multivitamin was associated with worsened fatigue outcomes (de Souza Fêde et al., 2007). The investigators speculate that some of the ingredients in the multivitamin formula may have induced worsening fatigue. Moreover, confounds may have been introduced owing to the small sample size and the fact that the evaluation period in the study was extremely short, with a crossover at the midpoint of radiation therapy.

ADENOSINE 5' TRIPHOSPHATE INFUSION

A randomized, open-label study of 30-hour IV infusions of adenosine 5' triphosphate (ATP) administered every two to four weeks for 10 doses was conducted in 28 patients with advanced non-small cell lung cancer (Agteresch, Dagnelie, van der Gaast, Stijnen, & Wilson, 2000). Researchers reported a significant effect on fatigue, as measured by a single item on the Rotterdam Symptom Checklist. Mild infusional side effects such as chest discomfort and flushing resolved by slowing the rate of infusion. Conclusions are limited by the open-label design, the small sample size, and the fact that the investigators did not control for concomitant administration of corticosteroids to manage other disease-related symptoms such as cerebral edema, nausea, and dyspnea. The impact of continuous infusion therapy on quality of life was not assessed.

LECTIN-STANDARDIZED MISTLETOE EXTRACT

In two large retrospective cohort studies in women with breast cancer (Beuth, Schneider, & Schierholz, 2008; Schumacher et al., 2003), compared to those who were not using any complementary pharmacologic therapy or nutritional supplement, the administration of lectin-standardized mistletoe extract was associated with a significant reduction in fatigue, both while on postoperative treatment and during the post-treatment follow-up. Mistletoe extract was safe overall, with reported side effects of predominantly local and self-limited skin reactions such as erythema or itching. The fact that fatigue outcomes were collected via chart review rather than systematically by patient self-report limits the conclusions that can be drawn from these studies.

ESSIAC

A retrospective cohort study of 510 patients with breast cancer, with 32 (6.2%) reporting that they were using the herbal treatment Essiac to treat their breast cancer, found no significant differences in fatigue between those who were using Essiac and those who were not (Zick et al., 2006). The group using Essiac tended to be younger and with more advanced stages of breast cancer; however, this study did not control for these potential confounds.

CHINESE MEDICINAL HERBS

A Cochrane review of the effects of Chinese medicinal herbs on treatment side effects in women with breast cancer identified one study reporting a small but statistically significant improvement in fatigue in women receiving chemotherapy for breast cancer who also were receiving Chinese medicinal herbs compared to those women who did not receive this supplement (Zhang, Liu, Li, He, & Tripathy, 2007).

OMEGA-3 FATTY ACID SUPPLEMENTATION

Two single-arm, open-label trials (Cerchietti, Navigante, & Castro, 2007; Read et al., 2007) and one placebo-controlled RCT (Bruera, Strasser, Palmer, et al., 2003) examining the effects of supplementation with omega-3 fatty acids have shown preliminary evidence to suggest beneficial effects on fatigue outcomes, although overall, omega-3 fatty acid supplementation may not be well tolerated because of dysgeusia and oily diarrhea. In the studies where omega-3 fatty acids have been combined with other agents, disentangling the effects of specific agents on cancer-related fatigue and the side-effects profile is impossible. Additional research to establish the maximum tolerated dose of omega-3 fatty acid supplementation in patients with satisfactory performance status and limited gastrointestinal symptoms at baseline may be indicated as an initial step in further development of this therapy.

COMBINATION THERAPY: DIETARY SUPPLEMENTS AND LIPID REPLACEMENT/ ANTIOXIDANT SUPPLEMENTATION

Single studies in small, heterogeneous samples offer preliminary evidence that a dietary supplement such as soy protein (Jensen & Hesselov, 1997), enteral food supplementation (Cerchietti et al., 2004), lipid replacement/antioxidant combination (Colodny et al., 2000), or a combination of polyphenols, antioxidants, vitamins, alpha-lipoic acid, and carbocysteine (alone or in combination with one or more pharmacologic agents such as celecoxib, medroxy progesterone acetate, l-carnitine, or thalidomide) (Mantovani et al., 2006, 2008) may be effective in

reducing fatigue. Small sample sizes, nonrandomized, uncontrolled study designs, and the failure to control for baseline differences in fatigue between the study and comparison groups limit definitive conclusions. Moreover, with these combination therapies, disentangling the relative effects of a specific agent on the outcome of cancer-related fatigue and the overall tolerability of the regimen is impossible.

COMBINATION THERAPY: AROMATHERAPY, FOOT SOAK, AND REFLEXOLOGY

An open-label pilot study of a combination of an aromatherapy foot soak with lavender for 3 minutes and reflexology for 10 minutes with jojoba oil and lavender in 20 patients at the end of life found significant decreases in fatigue one and four hours after the treatment (Kohara et al., 2004).

Effectiveness Unlikely

Interventions for which lack of effectiveness has been demonstrated by negative evidence from a single rigorously conducted controlled trial, consistent negative evidence from well-designed controlled trials using small samples, or guidelines developed from evidence and supported by expert opinion

There are no interventions as of May 2008.

Not Recommended for Practice

Interventions for which lack of effectiveness or harmfulness has been demonstrated by strong evidence from rigorously conducted studies, meta-analyses, or systematic reviews, or interventions where the costs, burden, or harms associated with the intervention exceed anticipated benefit

There are no interventions as of May 2008.

Expert Opinion

Low-risk interventions that are (1) consistent with sound clinical practice, (2) suggested by an expert in a peer-reviewed publication (journal or book chapter), and (3) for which limited evidence exists. An expert is an individual with peer-reviewed journal publications in the domain of interest.

Although empirical evidence is limited, experts recommend that the following interventions be considered for patients experiencing fatigue during and following cancer treatment (Ahlberg, Ekman, Gaston-Johansson, & Mock, 2003; Bower et al., 2005; Cimprich, 1993; Cimprich & Ronis, 2003; Davis, Khoshknabi, & Yue, 2006; Iop, Manfredi, & Bonura, 2004; Lawrence, Kupelnick, Miller, Devine, & Lau, 2004; Levy, 2008; Mock, 2004; Mock et al., 2007; Mock & Olsen, 2003; Morrow, Shelke, Roscoe, Hickok, & Mustian, 2005; Mustian et al., 2007; Nail, 2002; NCCN, 2008; Radbruch et al., 2008; Shafqat et al., 2005; Sood & Moynihan, 2005; Stone & Minton, 2008).

- Work with patients and family caregivers to improve assessment of fatigue and identify management strategies.

- Promote open communication among patients, family members, and the caregiving team to facilitate discussions about the experience of fatigue and its effects on daily life.
- Consider attention-restoring activities, such as exposure to natural environments, and pleasant distractions such as music.
- Encourage a balanced diet with adequate intake of fluid, electrolytes, calories, protein, carbohydrates, fat, vitamins, and minerals.
- Consider treatment with low-dose corticosteroids.

Definitions of the interventions are available at www.ons.org/outcomes.

Literature search completed through May 2008.

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