

FEATURE ARTICLE

Putting Evidence Into Practice: Evidence-Based Interventions for Fatigue During and Following Cancer and Its Treatment

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Cancer-related fatigue has a significant impact on patients' physical and psychosocial functioning, symptom distress, and quality of life, yet it remains under-recognized and undertreated. The Oncology Nursing Society's Putting Evidence Into Practice initiative sought to improve patient outcomes relative to this important problem by critically examining and summarizing the evidence base for interventions to prevent and manage fatigue during and following treatment. This article critically reviews and summarizes the available empirical evidence regarding interventions for cancer-related fatigue. In addition to offering patients and clinicians a tool to facilitate effective management of the distressing symptom, this evidence-based review identifies gaps in knowledge and research opportunities.

Nursing-sensitive patient outcomes are outcomes that are attained through or are significantly impacted by nursing interventions. The interventions must be within the scope of nursing practice and integral to the processes of nursing care.

Editor's note. This article is the fourth in a series on the Oncology Nursing Society's Putting Evidence Into Practice project, in which best practices for patient care are presented.

Fatigue is a distressing and pervasive problem for patients undergoing cancer treatment, cancer survivors, and patients with cancer who are at the end of life. Strategies to reduce, manage, or eliminate fatigue can have a positive impact on several patient outcomes, including symptom distress; physical, role, and vocational functioning; psychological distress; family well-being; and health-related quality of life. This article describes the process and results of an initiative, called Oncology Nursing Society's Putting Evidence Into Practice (Gobel, Beck, & O'Leary, 2006), to examine and evaluate the current evidence base for interventions to prevent and manage fatigue during and following cancer and its treatment.

Methods

As the initial step, the project team adopted a definition of fatigue and surveyed the literature to develop a list of reported interventions for managing cancer-related fatigue (see Figure 1). Fatigue was defined as a persistent and subjective sense of tiredness that interferes with usual functioning (Mock, 2001). Systematic database searches were conducted to determine which of the identified interventions for fatigue had been evaluated empirically, and the empirical evidence was examined systematically and critically. Team members, in consultation with a medical

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Digital Object Identifier: 10.1188/07.CJON.99-113

- Exercise
- Pharmacotherapy: Psychostimulants
 - Paroxetine and other selective serotonin reuptake inhibitors
 - Methylphenidate (routine dosing schedule and patient-controlled dosing schedule)
 - Testosterone supplementation
 - Thyroid supplementation
 - Modafinil
 - Low-dose prednisone
- Energy conservation and activity management
- Elevation of hemoglobin
 - Transfusion of red blood cells
 - Erythropoietin
- Psychoeducational interventions
 - Preparatory information and anticipatory guidance
 - Teaching information
 - Cognitive-behavioral modification
 - Distraction
- Interventions to improve sleep quality
- Diet and nutrition
 - Dietary modification and dietary supplementation
 - Vitamin and micronutrient supplementation (e.g., l-carnitine)
 - Weight optimization (effect on serum cortisol levels)
 - Hydration
- Complementary or integrative techniques
 - Acupuncture
 - Aromatherapy
 - Healing Touch
 - Massage
 - Music therapy
 - Meditation
 - Expressive writing
- Management and control of concurrent distressing symptoms

Figure 1. Interventions for Fatigue Identified in a Preliminary Survey of the Literature

librarian, performed computerized searches of PubMed, CINAHL®, ProQuest Dissertations and Theses, Cochrane Collection, Database of Abstracts of Reviews of Effects, EMBASE, PsycINFO, and Health Source: Nursing/Academic Edition (via EBSCO) using the search terms listed in Figure 2. In some instances, terms were exploded so that all of the more narrow terms were searched simultaneously. The team searched and retrieved citations from 1990–November 2005. The abstract of each article was studied, and articles meeting the inclusion criteria listed in Figure 3 were identified for review. In addition, the reference lists of relevant articles were hand searched to identify additional references. Where available, meta-analyses were reviewed and the evidence summarized. For intervention categories in which a meta-analysis was published in the two years prior to November 2005, only articles published in the year preceding the publication date of the meta-analysis and those published after the meta-analysis was in print were selected for additional review.

Systematic Critical Examination of the Evidence

To promote a systematic examination of each study, reviewers used standardized worksheets and prepared tables of evidence,

organizing the tables by intervention category or subcategory. The ONS levels of evidence framework was used to rank each study in terms of the level of evidence (Ropka & Spencer-Cisek, 2001), and criteria proposed by Hadorn, Baker, Hodges, and Hicks (1996) were used to identify major and minor flaws in study design (Ropka & Spencer-Cisek). After the evidence supporting each intervention had been critically examined, the collective strength of the evidence for each identified intervention was assigned one of six weight-of-evidence categories. As described in Table 1, the categories incorporate three criteria: evidence quality, magnitude of the outcome (effect size), and concurrence of the evidence among studies. The evidence categories were adapted from other published schema (Atkins et al., 2004) to reflect the unique aspect of simultaneously evaluating both biological and behavioral interventions relative to oncology nursing sensitive outcomes (Lohr, 2004). The graded evidence summaries were used to develop several products designed to promote application of the evidence in clinical practice (Mitchell, Beck, Herrle Tanner, Hood, & Moore, 2005), including a resource card (see Appendix), a detailed summary of the evidence, and evidence tables that provide an in-depth analysis of each study examined. They are available at www.ons.org/outcomes/fatigue/shtml.

Interventions Effective for Preventing and Treating Cancer-Related Fatigue

Several interventions for fatigue identified in the literature were supported by expert opinion only (see Figure 4). Figure 5 lists the fatigue interventions for which evidence exists from one or more empirical studies, classifying the interventions based on the collective strength of the evidence concerning their efficacy and safety.

Recommended for practice: Exercise is the only intervention that was supported by a body of evidence of sufficient rigor to permit the team to recommend that it be considered for carefully screened patients with cancer experiencing fatigue.

Computerized database searches were performed using the following terms, with and without the additional search terms cancer, neoplasms, fatigue, and cancer-fatigue.

Fatigue	Aromatherapy
Cancer fatigue	Music therapy
Fatigue due to drug therapy	Healing Touch
Anemia	Meditation
Exercise movement techniques	Nutrition(al)
Exercise	Nutritional status
Exercise therapy	Diet
Aerobic exercises	Vitamins
Erythropoietin	Nutrition(al) supplements
Psychoeducation(al)	Individual drugs names (including paroxetine, methylphenidate, modafinil, bupropion, testosterone, corticosteroids)
Psychotherapy	Drug therapy
Complementary and alternative medicine	Psychostimulants
Acupuncture	Antidepressants
Yoga	
Massage	

Figure 2. Search Terms

All English-language published reports of quantitative studies related to fatigue interventions that met all of the following criteria were selected for review.

1. Full report (not an abstract) of an empirical study of a pharmacologic or nonpharmacologic intervention
2. Fatigue was a dependent variable, fatigue was measured using either an instrument designed to measure the construct or measured using a fatigue subscale of a quality-of-life or other instrument, and the scores on the fatigue measure or the fatigue subscale were reported in the results.
3. Study participants included pediatric or adult patients with cancer who were anywhere in the postdiagnosis trajectory, including active treatment (surgical oncology, medical oncology, biotherapy, radiotherapy), follow-up, or the end of life.

Figure 3. Inclusion Criteria

Two meta-analyses and five systematic reviews (Courneya & Friedenreich, 1999; Galvao & Newton, 2005; Knols, Aaronson, Uebelhart, Fransen, & Aufdemkampe, 2005; Oldervoll, Kaasa, Hjemstad, Lund, & Loge, 2004; Schmitz et al., 2005; Stevinson, Lawlor, & Fox, 2004; Stricker, Drake, Hoyer, & Mock, 2004) support the benefits of exercise in the management of fatigue during and following cancer treatment in patients with breast cancer or solid tumors and those undergoing hematopoietic stem cell transplantation. Although positive results for the outcome of fatigue have not always been observed consistently across studies, the general pattern of results in 34 controlled trials (including 27 randomized trials) indicates that exercise

can be effective in reducing fatigue in patients during and following cancer treatment. Various exercise modalities have been applied, differing in content (walking, cycling, swimming, resistive exercise, or combined exercise), frequency (ranging from two times per week to two times daily), intensity (with most programs at 50%–90% of the estimated maximal oxygen consumption heart rate), degree of supervision (fully supervised group versus self-directed exercise), and duration (from two weeks to one year). In some studies, the intervention group was compared with a group that received some form of physical training of a lesser intensity, frequency, or duration; in other studies, the comparison groups were on a waiting list, participated in a crossover, or did not receive any exercise program or advice. The specific beneficial effects of physical exercise may vary as a function of the stage of disease, the nature of the medical treatment, and patients' current lifestyle. The type, intensity, and duration of physical exercise that are most beneficial in reducing fatigue at different stages of disease and treatment are not known (Humpel & Iverson, 2005), and more research is needed to systematically assess the safety of exercise (aerobic exercise and strength training) in cancer subpopulations. Most of the studies reviewed have methodologic shortcomings, and further research using larger samples, attentional control groups, blinding of the outcome assessor and controlling for motivation, exercise preferences, and adherence of the participants in an exercise program is needed.

Likely to be effective: Several interventions were evaluated as likely to be effective in preventing and managing cancer-related fatigue. They included energy conservation and activity

Table 1. Putting Evidence Into Practice Weight-of-Evidence Classification Schema

WEIGHT-OF-EVIDENCE CATEGORY	DESCRIPTION	EXAMPLES
Recommended for practice	Effectiveness is demonstrated by strong evidence from rigorously designed studies, meta-analyses, or systematic reviews. Expected benefit exceeds expected harms.	At least two multisite, well-conducted, randomized, controlled trials (RCTs) with at least 100 subjects Panel of expert recommendation derived from explicit literature search strategy; includes thorough analysis, quality rating, and synthesis of evidence
Likely to be effective	Evidence is less well established than for those listed under recommended for practice.	One well-conducted RCT with fewer than 100 patients or at one or more study sites Guidelines developed by consensus or expert opinion without synthesis or quality rating
Benefits balanced with harms	Clinicians and patients should weigh the beneficial and harmful effects according to individual circumstances and priorities.	RCTs, meta-analyses, or systematic reviews with documented adverse effects in certain populations
Effectiveness not established	Data currently are insufficient or are of inadequate quality.	Well-conducted case control study or poorly controlled RCT Conflicting evidence or statistically insignificant results
Effectiveness unlikely	Lack of effectiveness is less well established than those listed under not recommended for practice.	Single RCT with at least 100 subjects that showed no benefit No benefit and unacceptable toxicities found in observational or experimental studies
Not recommended for practice	Ineffectiveness or harm clearly is demonstrated, or cost or burden exceeds potential benefit.	No benefit or excess costs or burden from at least two multisite, well-conducted RCTs with at least 100 subjects Discouraged by expert recommendation derived from explicit literature search strategy; includes thorough analysis, quality rating, and synthesis of evidence

Note. Based on information from Mitchell & Friese, n.d.

Although evidence is limited, experts recommend the following interventions for patients experiencing fatigue during and following cancer treatment.

- Work with patients and family caregivers to improve assessment of fatigue and to identify management strategies.
- Promote open communication among patients, families, 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, calories, protein, carbohydrates, fat, vitamins, and minerals.
- Administer low-dose corticosteroids.

Figure 4. Fatigue Interventions Supported by Expert Opinion

Note. Based on information from Ahlberg et al., 2003; Bower et al., 2005; Cimprich, 1993; Cimprich & Ronis, 2003; Iop et al., 2004; Kalman & Villani, 1997; Kumar et al., 2004; Lawrence et al., 2004; Mock, 2003, 2004; Mock & Olsen, 2003; Morrow et al., 2005; Nail, 2002, 2004; National Comprehensive Cancer Network, 2005; Shafiqat et al., 2005; Slatkin & Rhiner, 2003; Stark & Cimprich, 2003; Stasi et al., 2003; Wagner & Cella, 2004.

management, measures to optimize sleep quality, progressive muscle relaxation, massage and Healing Touch, and the provision of education and anticipatory guidance concerning fatigue during and following treatment. In addition, the National Comprehensive Cancer Network ([NCCN], 2005) expert consensus panel has recommended that patients with fatigue be screened for treatable etiologic factors, including concurrent distressing symptoms such as 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 caused by drug-drug interactions, and managed as indicated.

Energy conservation and activity management are teaching and coaching interventions for fatigue that emphasize the principles of balancing rest and activity through planning, priority setting, and delegation. In a large, multisite, randomized clinical trial with patients (most of whom had breast cancer) who were initiating treatment with radiation or chemotherapy, energy conservation and activity management were found to have a modest but statistically significant effect on fatigue (Barsevick, Dudley, Beck, Sweeney, Whitmer, & Nail, 2004). A pilot study conducted by those investigators showed a trend for energy conservation and activity management to be superior using a historical control group (Barsevick, Whitmer, Sweeney, & Nail, 2002).

Five studies (two feasibility studies [Berger et al., 2002, 2003], two small [N = 14 (Davidson, Waisberg, Brundage, & MacLean, 2001) and N = 10 (Quesnel, Savard, Simard, Ivers, & Morin, 2003)] single-arm trials, and one randomized, controlled trial (Savard, Simard, Ivers, & Morin, 2005)) provided preliminary support that a multicomponent, cognitive-behavioral intervention designed to optimize sleep quality also may improve fatigue. The cognitive-behavioral intervention generally included relaxation training,

sleep consolidation strategies (e.g., avoid long or late-afternoon naps, limit time in bed to actual sleep time), stimulus control therapy (e.g., go to bed only when sleepy, use bed and bedroom for sleep and sexual activities only, set 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 presleep routine to be used every night). Results support the feasibility of the intervention approach delivered individually or in a group setting to women undergoing adjuvant chemotherapy primarily for breast cancer.

Progressive muscle relaxation training and relaxation breathing plus yoga-like positioning have been studied in two small, randomized trials and were found to be effective in reducing fatigue. In the first study, participants (N = 34) received progressive muscle relaxation training coupled with supportive therapy and home practice of muscle relaxation. Participants in the intervention group reported significantly less fatigue than those in the control group (Decker, Cline-Elsen, & Gallagher, 1992). In another small (N = 35), randomized trial, patients who were undergoing hematopoietic stem cell transplantation received an intervention consisting of 30 minutes of relaxation breathing and yoga-like positioning. The intervention was administered daily for a six-week period, and control group participants received usual care. Although conclusions are limited by the

Recommended for Practice

- Exercise

Likely to Be Effective

- Screen for potential etiologic factors and manage as appropriate.
- Energy conservation and activity management
- Measures to optimize sleep quality
- Education or information provision
- Relaxation
- Massage and Healing Touch

Benefits Balanced With Harms

- Correction of anemia less than 10 g/dl

Effectiveness Not Yet Established

- Individual and group psychotherapy
- Expressive writing
- Paroxetine
- Methylphenidate
- Donepezil
- Bupropion sustained release
- Modafinil
- Yoga
- Acupuncture
- Distraction: virtual reality immersion
- Levocarnitine supplementation
- Adenosine 5'-triphosphate infusion
- Fish oil supplementation
- Combination therapy: aromatherapy, foot soak, and reflexology
- Combination therapy: medroxyprogesterone, celecoxib, and enteral food supplementation
- Combination therapy: soy protein supplementation and nutrition counseling following discharge from hospital

Figure 5. Interventions for Fatigue Supported by Empirical Studies

absence of an attentional control, the group that received the breathing and positioning intervention reported significantly lower fatigue scores ($p < 0.05$) on all subscales of the Piper Fatigue Scale (Kim & Kim, 2005).

A large, multisite, randomized trial with a crossover found that in patients receiving outpatient chemotherapy, weekly Healing Touch had a significant effect on fatigue ($p = 0.02$) and weekly Swedish massage with aromatherapy had a borderline significant effect ($p = 0.06$) compared to either a control group or a group that received a nursing presence intervention (a therapeutic technique designed to convey empathy and to create a mutual openness, understanding, comfort, and sense of peace between patients and clinicians) (Post-White et al., 2003). For all patients, the interventions also included centering (a wellness technique wherein the focus of attention is shifted to a place of quiet within oneself where one can feel integrated and focused), breathing, and relaxing music. The effect of the diverse components in this program could not be disentangled. In a pilot study with patients undergoing high-dose chemotherapy, upper-body Swedish massage as often as three times per week was associated with a significant decrease in fatigue pretransplantation and prior to discharge but not during the acute post-bone marrow transplantation phase (Ahles et al., 1999). Data from an uncontrolled clinical analysis of a massage treatment program found a 41% reduction in fatigue in a large inpatient and outpatient population (Cassileth & Vickers, 2004). A controlled pilot study demonstrated efficacy of polarity therapy (an intervention hypothesized to promote healing, relaxation, and well-being by unblocking and balancing energy flow and re-establishing homeostasis in the human energy field) in a small sample of 15 women receiving radiation therapy for breast cancer (Roscoe, Matteson, Mustian, Padmanaban, & Morrow, 2005).

Two randomized, controlled trials and two nonrandomized pilot studies suggested that educational interventions may have a role in supporting positive coping in patients with fatigue. A randomized trial evaluating a supportive intervention delivered by nurses tailored to managing pain and fatigue during chemotherapy was effective in reducing pain, fatigue, and total symptoms (Given et al., 2002). The trial was conducted in 113 patients with mixed diagnoses, and the intervention included teaching, counseling and support, coordination, and communication. In another randomized, controlled trial ($N = 152$), patients undergoing radiation therapy for prostate cancer were provided with an informational intervention at their first and fifth radiation treatments (Kim, Roscoe, & Morrow, 2002). The intervention was based on self-regulation theory and provided patients with specific, objective information about what to expect during their radiation treatments. The control group received general information at the same two time points. At the time of the final radiation treatment, patients in the informational intervention showed a trend toward less fatigue when compared to the control group, although the result was only marginally significant ($p < 0.10$). The effects of a psychoeducational intervention (coping skills training designed to enhance personal control and promote emotional and instrumental coping responses) in patients with head and neck cancer ($N = 50$) were assessed in a pilot study (Allison et al., 2004). Participants reported improvements in fatigue as a result of the intervention. In the other pilot study, a four-component tailored intervention (assessment and monitoring, education, coaching in

the management of fatigue, and provision of emotional support) was implemented in a case series of eight patients and was found to lessen self-reported fatigue (Ream, Richardson, & Alexander-Dann, 2002). Although they were limited by the small sample size and the absence of a control group, the two studies support a conclusion that patients welcome psychoeducational interventions related to fatigue and that they will apply the skills they learn in their daily lives in managing fatigue. In addition, the NCCN consensus panel guidelines (NCCN, 2005) advised that patients and families be provided with anticipatory guidance about patterns of fatigue and recommendations for self-management, especially when beginning fatigue-inducing treatments.

Benefits balanced with harms: Data from four systematic reviews (Bohlius et al., 2004; Bottomley, Thomas, van Steen, Flechtner, & Djulbegovic, 2002b; Cella, Dobrez, & Glaspy, 2003; Djulbegovic, 2005) suggested that patients receiving recombinant human erythropoietin less than 10 g/dl to correct anemia may experience increased vigor and diminished fatigue. However, only limited evidence suggests that erythropoietin improves fatigue when anemia is less severe. Data indicate that a target hemoglobin level of 11–12 g/dl will produce the greatest improvements in fatigue and other quality-of-life outcomes (Stasi et al., 2005). Although epoetin and darbepoetin generally are well tolerated, the use of the agents specifically for the management of fatigue must be considered in light of safety issues, including a small increased risk of thrombotic events, hypertension, and theoretical concerns that epoetin may support or extend tumor growth in certain disease sites (Glaspy, 2005; Stasi et al., 2005; Steensma & Loprinzi, 2005). Overall, better-quality evidence is needed to unequivocally support the use of recombinant human erythropoietin solely as an intervention to improve patient-reported outcomes such as fatigue (Bottomley et al., 2002a; Littlewood, Cella, & Nortier, 2002).

Effectiveness not established: Several pharmacologic agents that may have a role in the management of fatigue have been studied, although none has demonstrated sufficiently strong evidence to establish their effectiveness. Four trials studying the use of paroxetine in treating fatigue during and following cancer treatment have produced mixed findings. In two large, multicenter, randomized, double-blinded, placebo-controlled trials in more than 400 patients with solid tumors receiving cyclic chemotherapy (not concurrent with radiotherapy or interferon) (Morrow et al., 2003) and 94 patients with breast cancer receiving at least four cycles of chemotherapy (Roscoe, Morrow, et al., 2005), paroxetine 20 mg by mouth daily did not have an effect on fatigue, although improvements in depression and overall mood were noted in the treatment group. 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 alpha ($N = 18$) (Capuron et al., 2002). Four prospective, open-label, single-arm trials with small samples have examined the use of methylphenidate in reducing fatigue (Bruera, Driver, et al., 2003; Sarhill et al., 2001; Schwartz, Thompson, & Masood, 2002; Sugawara et al., 2002). All four studies reported improvements in fatigue in most of their participants as a result of the methylphenidate intervention, although in one study (Sarhill et al.), more than half of the patients experienced side effects such as insomnia, agitation, anorexia, nausea and vomiting, and

dry mouth. Donepezil 5 mg every morning was evaluated in an uncontrolled, open-label trial in 27 patients with a variety of tumor sites who were receiving narcotics at a median oral morphine-equivalent daily dose of 180 mg per day (range = 30–600 mg) (Bruera, Strasser, Shen, et al., 2003). Fatigue improved significantly following a seven-day course of treatment. However, dose-limiting side effects were observed in approximately 25% of the sample, and the study was limited by its single-arm design and small sample size. In addition, the short length of treatment and minimal follow-up make conclusive assessment of the anticipated incidence and severity of donepezil side effects difficult. Randomized, controlled trials in larger samples are needed to evaluate the efficacy and toxicity profile of donepezil in limiting fatigue. Bupropion sustained release at a dose of 100–150 mg per day also was evaluated in an uncontrolled, open-label trial in 15 patients with various cancer diagnoses who were experiencing fatigue or depression with marked fatigue (Cullum, Wojciechowski, Pelletier, & Simpson, 2004). The rating for fatigue improvement was made by a clinician not directly involved in the trial, but the report did not specify whether that rater was blinded to the treatment condition. Thirteen of the 15 participants reported improvement in their fatigue, with eight participants rating their fatigue level as much improved. In all patients, the improvement occurred in two to four weeks. Controlled studies are necessary to establish the efficacy of this intervention in a more homogeneous sample of patients with cancer, and to determine whether the effect of bupropion is separate from its action as an antidepressant. In a case report regarding the use of modafinil (at a dose of 100 mg once or twice daily), improvements in daytime wakefulness and normalization of the sleep-wake cycle were reported in two older adult patients with advanced cancer (Caraceni & Simonetti, 2004). No side effects were reported. The potential usefulness of modafinil (at a dose of 100–400 mg in a daily or divided dose) in treating fatigue also is supported by an expert opinion report (Cox & Pappagallo, 2001).

Individual and group psychotherapy also was studied as an intervention for fatigue in patients with cancer, with mixed results. A multicenter, randomized, controlled trial of supportive group psychotherapy in women with metastatic breast cancer (N = 158) did not show positive benefit for fatigue, although a benefit of psychotherapy was noted for psychological symptoms and pain (Goodwin et al., 2001). By contrast, participants with stage I or II melanoma who were treated with surgery (N = 131 and N = 38) and participated in one of two randomized trials of six weekly group psychotherapy sessions reported significantly less fatigue two months postintervention than a control group that did not receive such treatment (Boesen et al., 2005; Fawzy et al., 1990). Psychotherapy also had some benefit in alleviating fatigue in a small case series of women with metastatic breast cancer (N = 6) (Levesque, Savard, Simard, Gauthier, & Ivers, 2004). The addition of exercise to a group psychotherapy intervention (either stress management and relaxation training or expressive-supportive psychotherapy) improved outcomes related to fatigue when compared to group psychotherapy intervention alone or a comparison group (Courneya et al., 2003). A multicomponent, supportive care intervention that included exercise, relaxation, education, and peer support produced statistically significant improvements in fatigue immediately

following the intervention, although the improvements were not sustained at three- and six-month follow-up (Lindemalm, Strang, & Lekander, 2005).

A distractive intervention, virtual reality immersion (VRI), was investigated in two randomized, crossover trials (Schneider, Ellis, Coombs, Shonkwiler, & Folsom, 2003; Schneider, Prince-Paul, Allen, Silverman, & Talaba, 2004) and one randomized, controlled trial (Oyama, Kaneda, Katsumata, Akechi, & Ohsuga, 2000), each with small samples (16–20 participants) consisting of patients mostly with solid tumors. When compared to treatment cycles in which no VRI intervention was given, a statistically significant decrease in fatigue was found immediately following a chemotherapy treatment during which the women received a VRI intervention; two days after treatment, a trend toward lower fatigue scores existed, although the differences did not reach statistical significance (Schneider et al., 2003). In the second crossover study led by the same principal investigator, fatigue scores tended to be lower when participants received the VRI intervention, although the results did not achieve statistical significance (Schneider et al., 2004). In the only randomized, controlled trial, no significant differences existed between the intervention and control groups when the VRI intervention was given for the first time; however, when the intervention was repeated with a subsequent cycle of chemotherapy, significant differences between the intervention and control groups in their report of fatigue and tiredness were observed. Whether the findings are attributable to carryover effects from the first VRI intervention, as the authors concluded, or simply to differential effects of repeated testing is unknown (Oyama et al., 2000).

Complementary therapies such as yoga, acupuncture, and expressive writing, as well as an intervention combining aromatherapy, lavender foot soak, and reflexology, have been evaluated in pilot studies with small samples. The studies were open label or uncontrolled and sample sizes were extremely small, which made drawing conclusions about efficacy difficult. Despite the limitations, study results suggest that such complementary therapies have potential in the treatment of fatigue in patients with cancer. Of note, the studies evaluating acupuncture, expressive writing, and the combined aromatherapy, foot soak, and reflexology intervention included patients with advanced cancer and at the end of life. If found to be effective in larger randomized, controlled trials, the approaches may offer treatment options for patients with advanced cancer and those at the end of life for whom other fatigue interventions such as exercise may not be feasible.

Several nutritional supplements have been explored, either as single agents or as part of combination therapy. The safety and potential efficacy of levocarnitine supplementation in treating fatigue in patients with cancer who have low serum carnitine levels were suggested by two small, open-label trials. In a phase I study of 13 patients with low serum carnitine levels, researchers confirmed that an oral dose of 1,750 mg of levocarnitine per day is tolerated without adverse effects and produced statistically significant beneficial effects on fatigue after only one week of therapy (Cruciani et al., 2004). A larger, phase II study of levocarnitine supplementation was conducted in patients with lower serum carnitine levels and fatigue who were receiving ifosfamide and cisplatin palliative chemotherapy (a therapy known to cause urinary loss of

carnitine) (Graziano et al., 2002). Fifty nonanemic patients were supplemented with oral levocarnitine at a dose of 4,000 mg daily for seven days. Ninety percent of patients reported improvements in fatigue after one week of levocarnitine, and the differences in fatigue scores from baseline to the first week of chemotherapy and levocarnitine treatment were statistically significantly improved. The improvements were sustained for two weeks after discontinuing levocarnitine supplementation. Although interpretation of the results is limited by the small sample size; the open-label, nonrandomized design; and the absence of a double-blinded control group, the studies suggest that levocarnitine supplementation should be explored further in randomized trials, and such studies are ongoing (see protocol summary at www.cancer.gov/clinicaltrials/ECOG-E4Z02).

A placebo-controlled, randomized trial of a 1,000 mg fish oil supplement (180 mg eicosapentaenoic acid, 120 mg docosahexaenoic acid, and 1 mg vitamin E) was evaluated in 91 adult patients with locally recurrent or metastatic cancer. Patients in the treatment group showed a trend toward less fatigue; however, the therapy was not well tolerated and only 30 of the 46 patients randomized to the fish oil supplement were able to complete a course of treatment (Bruera, Strasser, Palmer, et al., 2003). Dosing required more than 15 capsules per day and resulted in belching, dysgeusia, and oily diarrhea. A phase I trial to establish the maximum tolerated dose of fish oil in patients with satisfactory performance status and limited gastrointestinal symptoms at baseline may be indicated as an initial step in further development of the therapy.

A randomized, open-label trial of 30-hour IV infusions of adenosine 5'-triphosphate 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). Investigators reported a significant effect on fatigue, as measured by single items on the Rotterdam Symptom checklist. Mild infusional side effects (Common Toxicity Criteria for Adverse Events grade I-II) included chest discomfort (15%), urge to take a deep breath (10%), flushing (5%), nausea (5%), light-headedness (3%), dyspnea (3%), headache (2%), sweating (2%), mood alteration or anxiety (2%), and palpitations (1%). The side effects consistently resolved when the rate of adenosine 5'-triphosphate infusion was slowed. Study results are limited by the open-label design and small sample size and by the fact that study procedures did not control for the concomitant administration of corticosteroids to manage other disease-related symptoms such as cerebral edema, nausea, and dyspnea. Also of potential concern is the impact of continuous infusion therapy on quality of life.

The effects on fatigue of a combination of medroxyprogesterone (500 mg twice daily), celecoxib (200 mg twice daily), and an enteral diet supplement (designed to provide maximal caloric load in the smallest volume and lowest osmolarity, with a carbohydrate-protein-fat composition equivalent to 20% of the resting basal metabolic rate) was evaluated in a single-arm study of 15 adults with stage IIIb or IV adenocarcinoma of the lungs (Cerchietti et al., 2004). A significant difference was found in pretreatment and post-treatment fatigue ($p = 0.009$), although results are limited by the uncontrolled study design and small sample size.

Following elective colorectal surgery (69% for cancer), 32 patients (22 of whom had cancer) were assigned randomly to four months of soy protein supplementation in combination with nutritional counseling or usual postdischarge follow-up (Jensen & Hesselov, 1997). Although the intervention group consumed significantly more protein than the control group and gained weight and body mass, both groups had similar fatigue scores at hospital discharge and at the conclusion of the intervention follow-up period. Results suggested that for patients with small to moderate weight loss associated with colorectal surgery, improvements in weight and body mass are not associated with corollary improvements in fatigue or functional status.

Implications for Practice and Research

Clinicians can use the present review of the evidence base supporting interventions for managing fatigue during and following cancer treatment to identify interventions that have the potential to be effective, thereby broadening their therapeutic armamentarium. The evidence base suggests that approaches such as exercise, screening for treatable risk factors, energy conservation and activity management, progressive muscle relaxation, and education and anticipatory guidance are likely to be effective in ameliorating fatigue. Anticipating which interventions are likely to be effective can assist clinicians in the design of a multicomponent fatigue treatment approach. Clinicians also can use the review to examine their own practices, identifying intervention strategies such as complementary therapies that may be recommended only infrequently for fatigue but still hold the potential to be effective.

In addition, the review suggests a number of implications for further research. First, many of the interventions for fatigue have had only limited study, often in uncontrolled or pilot studies. Randomized clinical trials of the therapies for fatigue that have shown promise are needed urgently. Also indicated are randomized trials that further evaluate therapies such as methylphenidate, where mixed results have been found. In all trials, clinicians need to make thoughtful decisions about whether a heterogeneous or homogeneous patient sample (in terms of gender, disease site and stage, and modality of current treatment) would provide the better evaluation of efficacy. Clinicians also need to examine the efficacy of interventions for patients experiencing fatigue at the end of life. This is a population that currently has limited therapeutic options for fatigue, and studies indicate that fatigue clearly causes significant distress for that group of patients and their families (Lindqvist, Widmark, & Rasmussen, 2004). Continued research also is needed to identify effective interventions for specific dimensions of the fatigue experience such as cognitive slowing, daytime sleepiness, and asthenia.

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 cancer-related fatigue offers empirical and practical insights that clinicians can apply in their practice to achieve optimal management of the distressing symptom. When risks are low, trying an

intervention and evaluating its efficacy in a particular patient may be useful. The review also identifies the gaps in knowledge and underscores the need for continued research to identify, test, and refine interventions that reduce fatigue and promote functional well-being in patients experiencing this symptom.

The authors gratefully acknowledge the contributions of ONS staff members, including Gail Mallory, PhD, RN, CNA, Mark Vrabel, MLS, AHIP, Linda Eaton, RN, MSN, AOCN®, and Kelly Egnovich, and the thoughtful commentary provided by the outcomes project field reviewers and the anonymous reviewers of this article.

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Putting Evidence Into Practice information on three other nursing-sensitive patient outcomes—sleep-wake disturbances, nausea and vomiting, and prevention of infection—also is available online at www.ons.org/outcomes.

Appendix. Putting Evidence Into Practice Card on Preventing and Treating Fatigue

What Interventions Are Effective in Preventing and Treating Fatigue During and Following Cancer and Its Treatment?

RECOMMENDED FOR PRACTICE

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

Exercise

- Evidence at the highest level¹⁻⁷ supports the benefit of exercise in the management of fatigue during and following cancer treatment in patients with breast cancer, patients with solid tumors, and those undergoing hematopoietic stem cell transplantation. Although positive results for the outcome of fatigue have not always been observed consistently across studies, the general pattern of results indicates that exercising (including walking, cycling, swimming, resistive exercise, or combined exercise) several times per week can be effective in reducing fatigue in patients during and following cancer treatment. More research is needed to systematically assess the safety of exercise (both aerobic exercise and strength training) and to tailor the intensity, frequency, duration, and type of exercise prescribed for different oncology subpopulations.

LIKELY TO BE EFFECTIVE

Interventions for which the evidence is less well established than for those listed under "Recommended for Practice"

Screening for potential etiologic factors and management as appropriate

- Experts⁸ recommend that patients with fatigue be screened and managed as indicated for treatable etiologic factors, including concurrent distressing symptoms such as pain, nausea, and depression; hypothyroidism; hypogonadism; cardiomyopathy; adrenal insufficiency; pulmonary dysfunction; anemia; sleep disturbance; fluid and electrolyte imbalances; emotional distress; and sedation secondary to specific classes of medications (e.g., opiates, antidepressants, antiemetics, antihistamines) or caused by drug-drug interactions.

Energy conservation and activity management

- A nurse-delivered intervention focused on energy conservation and activity management (a multicomponent intervention designed to help patients to develop skills in planning, delegating, setting priorities, pacing, resting, and planning high-energy-use activities at times of peak energy) demonstrated a modest but significant effect in a large, multisite, randomized clinical trial with patients (most of whom had breast cancer) beginning chemotherapy or radiation.⁹

Education/information provision

- Studies suggest that educational interventions (including teaching, counseling, support, anticipatory guidance about fatigue patterns, coping skills training, and coaching) in the self-management of fatigue have a role in supporting positive coping in patients with fatigue and in reducing fatigue levels.¹⁰⁻¹⁵

Measures to optimize sleep quality

- Evidence suggests that a multicomponent, cognitive-behavioral intervention designed to optimize sleep quality also improves fatigue. The cognitive-behavioral intervention, delivered individually or in a group, generally includes relaxation training, along with sleep consolidation strategies (avoiding long or late afternoon naps, limiting time in bed to actual sleep time), stimulus control therapy (going to bed only when sleepy, using bed/bedroom for sleep and sexual activities only, setting consistent time to lie down and get up, avoiding caffeine and stimulating activity in the evening), and strategies to reduce cognitive-emotional arousal (allowing at least an hour to relax before going to bed and establishing a presleep routine to be used every night).¹⁶⁻²⁰

Relaxation

- Two small randomized controlled studies found progressive muscle relaxation training or relaxation breathing and yoga-like positioning delivered in a series of sessions to patients with cancer to be effective in lowering fatigue scores.^{21,22}

Massage and healing touch

- Single studies provide evidence that weekly healing touch or weekly Swedish massage with aromatherapy may be effective in reducing fatigue, particularly in patients receiving high-dose chemotherapy.^{23,24} Data from an uncontrolled clinical analysis of a massage treatment program found a 40.7% reduction in fatigue in a large inpatient and outpatient oncology population.²⁵ A controlled pilot study demonstrated efficacy of 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) in improving fatigue in a small sample of 15 women receiving radiation therapy for breast cancer.²⁶

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

- Several systematic reviews²⁷⁻³⁰ suggest that patients receiving recombinant human erythropoietin to correct anemia less than 10 g/dl may experience increased vigor and diminished fatigue. 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.²⁵ Although both epoetin and darbepoetin generally are well tolerated, the use of these agents specifically for the management of fatigue must be considered in light of safety issues, including a small increased risk of thrombotic events and hypertension and theoretical concerns that epoetin may support or extend tumor growth in certain tumor types.³¹⁻³³

EFFECTIVENESS NOT ESTABLISHED

Interventions for which insufficient data or data of inadequate quality currently exist

Individual and group psychotherapy

- Although a multicenter randomized trial of supportive group psychotherapy in women with metastatic breast cancer did not show specific benefit in terms of fatigue,³⁴ other smaller studies suggest that patients who participate in individual or group psychotherapy experience improved outcomes relative to fatigue.³⁵⁻³⁷

Expressive writing

- A pilot study of an expressive writing intervention (four weekly sessions in which participants either wrote about their deepest thoughts and feelings or about neutral issues related to health) found no differences in fatigue between the two groups; however, postintervention, the group who had received the expressive writing intervention reported greater vigor.³⁸

Paroxetine

- The evidence concerning the effectiveness of paroxetine in treating fatigue during and following cancer treatment is mixed. In two large randomized trials,^{39,40} paroxetine 20 mg po daily did not have an effect on fatigue, although improvements in depression and overall mood occurred in the paroxetine treatment group. However, two small trials showed a possible benefit of paroxetine in treating fatigue in women with hot flashes⁴¹ and in patients receiving interferon-alpha.⁴²

Methylphenidate

- Several small, open-label, single-arm trials have examined the use of methylphenidate in reducing fatigue.⁴³⁻⁴⁶ All reported improvements in fatigue in most of their participants as a result of the methylphenidate intervention, although in one study,⁴⁴ more than half of the patients experienced side effects such as insomnia, agitation, anorexia, nausea and vomiting, or dry mouth.

Donepezil

- An uncontrolled, open-label trial evaluated donepezil 5 mg every morning in patients who were receiving narcotics at a median oral morphine-equivalent daily dose of 180 mg/day.⁴⁷ Fatigue significantly improved following a seven-day course of donepezil, although several participants experienced side effects, including diarrhea. Randomized controlled trials are needed to evaluate the efficacy and toxicity profile of donepezil in limiting fatigue.

Modafinil

- In a case report regarding the use of modafinil (at a dose of 100 mg daily or twice daily), improvements in daytime wakefulness and normalization of the sleep-wake cycle occurred in two older adult patients with advanced cancer.⁴⁸

Bupropion sustained-release

- Researchers evaluated bupropion sustained-release at a dose of 100–150 mg/day in an uncontrolled, open-label trial in 15 patients with various cancer diagnoses who were experiencing fatigue or depression with marked fatigue,⁴⁹ and in a prospective case series of 21 patients, most of whom had a primary brain tumor, breast cancer, or a hematologic malignancy.⁵⁰ Most participants reported an improvement in their level of fatigue within two to four weeks of therapy; however, controlled trials are necessary to establish the efficacy of this intervention and to determine whether this effect of bupropion is separate from its action as an antidepressant.

Yoga

- A small study of the effects of a seven-week yoga program in adults with lymphoma receiving CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or similar therapy found no effect on fatigue.⁵¹

Acupuncture

- In two small studies, patients receiving acupuncture (traditional Chinese acupuncture or acupuncture-like transcutaneous electrical nerve stimulation) tended to report less fatigue in comparison to a control group.^{52,53}

Distraction: Virtual reality immersion

- A distractive intervention, virtual reality immersion, administered during chemotherapy treatment cycles has shown some preliminary evidence of effectiveness in reducing fatigue immediately following and for two days after treatment.⁵⁴⁻⁵⁷ Additional controlled trials with adequate statistical power to detect a difference between the treatment and control groups are needed to explore these preliminary results.

Levocarnitine supplementation

- Phase I–II trials provide preliminary evidence of the safety and potential efficacy of levocarnitine supplementation in improving fatigue in nonanemic patients with cancer who have low serum carnitine levels.^{58,59} These results suggest that levocarnitine supplementation should be studied further as a possible intervention for fatigue in patients with cancer.

Adenosine 5'-triphosphate infusion

- A randomized open-label study of 30-hour IV infusions of adenosine 5'-triphosphate administered every two to four weeks for 10 doses was conducted in 28 patients with advanced non-small cell lung cancer.⁶⁰ Infusion side effects occurring in a small number of participants included chest discomfort, flushing, and nausea. Side effects resolved by slowing the rate of infusion. Researchers reported a significant effect of the intervention on fatigue; however, the impact of repeated continuous infusions on quality of life was not examined. Study results also are limited by the open-label study design and small sample size and by the fact that study procedures did not control for the concomitant administration of corticosteroids to manage other disease-related symptoms such as cerebral edema, nausea, and dyspnea.

Omega-3 fatty acid supplementation

- A placebo-controlled randomized trial of a 1,000-mg omega-3 fatty acid supplement (180 mg eicosapentaenoic acid, 120 mg docosahexaenoic acid, and 1 mg vitamin E) in adult patients with locally recurrent or metastatic cancer showed a trend toward less fatigue. However, the therapy was not well tolerated, and only 30 of the 46 patients who were randomized to the fish oil supplement were able to complete a course of treatment.⁶¹ A phase I trial to establish the maximum tolerated dose of fish oil 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: Aromatherapy, foot soak, and reflexology

- An open-label pilot study of a combination of aromatherapy, foot soak with lavender for 30 minutes, and reflexology for 10 minutes in patients at the end of life found significant decreases in fatigue one and four hours after the treatment.⁶²

Combination therapy: Medroxyprogesterone, celecoxib, and enteral food supplementation

- A single-arm study evaluated the effects on fatigue of medroxyprogesterone (500 mg bid), celecoxib (200 mg bid), and enteral diet supplement (supplement designed to provide maximal caloric load in the smallest volume and lowest osmolarity, with a carbohydrate/protein/fat composition equivalent to 20% of the resting basal metabolic rate).⁶³ A significant difference occurred in pretreatment and post-

treatment fatigue, although the uncontrolled study design and small sample size limit interpretation of the results.

Combination therapy: Soy protein supplementation and nutrition counseling following discharge from hospital

- Following elective surgery for a colorectal malignancy, patients who were randomly assigned to four months of soy protein supplementation and nutrition counseling consumed significantly more protein than the control group receiving the usual care. However, both groups had similar fatigue scores at hospital discharge and at the conclusion of the intervention follow-up period.⁶⁴

EXPERT OPINION

Although limited evidence exists, experts^{8,65-82} recommend the following interventions in patients experiencing fatigue during and following cancer treatment.

- 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 a trial of low-dose corticosteroids.

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Definitions of the interventions and full citations: www.ons.org/outcomes
Literature search completed through December 2005.

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