Integrative Nonpharmacologic Behavioral Interventions for the Management of Cancer-Related Fatigue

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Key Words. Cancer • Fatigue • Behavioral medicine • Exercise • Nutrition

ABSTRACT
Cancer-related fatigue (CRF) is a debilitating, multifaceted biopsychosocial symptom experienced by the majority of cancer survivors during and after treatment. CRF begins after diagnosis and frequently persists long after treatments end, even when the cancer is in remission. The etiological pathopsychophysiology underlying CRF is multifactorial and not well delineated. Mechanisms may include abnormal accumulation of muscle metabolites, dysregulation of the homeostatic status of cytokines, irregularities in neuromuscular function, abnormal gene expression, inadequate ATP synthesis, serotonin dysregulation, abnormal vagal afferent nerve activation, as well as an array of psychosocial mechanisms, including self-efficacy, causal attributions, expectancy, coping, and social support. An important first step in the management of CRF is the identification and treatment of associated comorbidities, such as anemia, hypothyroidism, pain, emotional distress, insomnia, malnutrition, and other comorbid conditions. However, even effective clinical management of these conditions will not necessarily alleviate CRF for a significant proportion of cancer survivors. For these individuals, intervention with additional therapeutic modalities may be required. The National Comprehensive Cancer Network guidelines recommend that integrative nonpharmacologic behavioral interventions be implemented for the effective management of CRF. These types of interventions may include exercise, psychosocial support, stress management, energy conservation, nutritional therapy, sleep therapy, and restorative therapy. A growing body of scientific evidence supports the use of exercise and psychosocial interventions for the management of CRF. Research on these interventions has yielded positive outcomes in cancer survivors with different diagnoses undergoing a variety of cancer treatments. The data from trials investigating the efficacy of other types of integrative nonpharmacologic behavioral therapies for the management of CRF, though limited, are also encouraging. This article provides an overview of current research on the relative merits of integrative nonpharmacologic behavioral interventions for the effective clinical management of CRF and makes recommendations for future research. The Oncologist 2007; 12(suppl 1):52–67

Disclosure of potential conflicts of interest is found at the end of this article.

INTRODUCTION
Cancer treatments, such as surgery, chemotherapy, radiation therapy, and hormone therapy, cause suffering and distress that lead to impaired quality of life (QoL) for many cancer survivors. The most common problem reported by cancer survivors is cancer-related fatigue (CRF) [1–19]. Cancer survivors frequently report that CRF begins with diagnosis, worsens during the course of treatment, and per-
CRF often means that survivors must depend on others for home management, transportation, and even simple self-care activities, such as preparing food or bathing [1,2,16,32,48–50]. These changes in daily activity and self-sufficiency may be demoralizing and discouraging. Furthermore, CRF forces patients to engage in unwanted activities in an attempt to cope with their fatigue, such as lying down or taking naps [1,2,16,32,51]. Importantly, CRF is considered more distressing and has a greater negative impact on patients’ daily activities and QoL than other cancer-related symptoms, including vomiting, nausea, pain, and depression [1,2,16,32,52]. With the improvements and advances in cancer therapy seen in recent years, the impact of CRF is magnified because life expectancy has increased in cancer survivors [1,2,11,16,24,32,53–56].

**Current Approaches to the Treatment of CRF**

The etiology of CRF is complex and multidimensional. The causal contributions of numerous biopsychosocial domains hypothesized to influence CRF are poorly understood and encompass a vast array of potential contributing factors and dynamic psychophysiological pathways. These pos-
possible causes are outlined by Ryan and colleagues [57]. CRF remains underrecognized and undertreated because it is not clearly understood. Indeed, it was not until 1998 that CRF was acknowledged as an official diagnosis in the International Classification of Disease (ICD-10). Subsequently, in 2000, the National Comprehensive Cancer Network (NCCN) published the first set of guidelines synthesizing available research and clinical experience in oncology to provide recommendations for supportive patient care [58]. Since that time, the NCCN Fatigue Practice Guidelines have been updated annually to provide concise, up-to-date recommendations for the management of CRF based on the current understanding of the symptom and the development of new therapies [32].

The guidelines for the management of CRF currently proposed by the NCCN [32] suggest that clinicians frequently screen for CRF in patients with cancer and, when present, screen for possible contributing factors (e.g., pain, emotional distress, sleep disruption, anemia, nutrition), including comorbid conditions (e.g., infection, cardiac dysfunction, pulmonary dysfunction, renal dysfunction, hepatic dysfunction, neurologic dysfunction, endocrine dysfunction, hypothyroidism). Identifying CRF and its contributing factors does not mean the problem will be alleviated. Clinicians usually treat contributing factors via pharmacologic means (e.g., colony-stimulating factors, antidepressants, steroids, benzodiazepines, benzodiazepine-receptor agonists, thyroid hormones, and psychostimulants) and expect that the CRF will also be resolved [1,2,13,14,16,32]. Unfortunately, many patients with cancer continue to experience CRF even after successful clinical treatment of these contributing factors [1,2,16,32,59,60]. Additionally, clinicians often encourage patients experiencing CRF to rest and conserve energy, although CRF is not alleviated by periods of rest, as is the case with other types of fatigue [1,2,16,51]. Patients may also experience CRF in the absence of any clinically discernable contributing factors [1,2,8,9,12–14,16]. In instances where no specific causal factors can be identified or when the patient continues to have moderate-to-severe fatigue after addressing these factors, the NCCN guidelines [32] recommend that physicians consider both pharmacologic interventions and integrative nonpharmacologic behavioral interventions.

The NCCN guidelines recommend the use of a variety of integrative nonpharmacologic behavioral interventions, including exercise, psychosocial interventions, and other integrative therapies for the effective management of CRF. This article provides an overview of the scientific evidence for the efficacy of integrative nonpharmacologic behavioral interventions in the management of CRF and makes recommendations for future research.

**Exercise Interventions**
Physical activity is defined as any skeletal muscle movement that causes an increase in energy expenditure above a resting basal metabolic rate and encompasses a wide variety of lifestyle and occupational activities [61]. Exercise is more specifically defined as physical activity performed in a systematically dosed manner (e.g., a specific frequency, intensity, duration, and mode) with the intention of improving health-related outcomes, such as cardiovascular fitness,
muscular strength, body composition, depression, anxiety, sleep, cognition, and fatigue [61]. In the current article, the term exercise or physical exercise is used to describe any physical activity intervention designed and delivered with the intention of improving CRF.

Physical exercise is an integrative nonpharmacologic behavioral intervention that shows great promise in mitigating the acute CRF experienced by cancer patients during treatment, as well as the persistent CRF they experience after treatments are complete. Galvao and Newton [62], Knols and colleagues [63], Stevinson and colleagues [64], Schmidtz and colleagues [65], and McNeely and colleagues [66] recently summarized the evidence from over 45 studies, reported in 64 published papers [67–130], demonstrating positive benefits from physical exercise interventions implemented with cancer survivors during and after treatment. Eight additional published studies [131–138], not included in these reviews, also demonstrated positive effects from physical exercise interventions during and after treatments for cancer. The main outcomes examined included CRF, emotional distress (e.g., depression, anxiety), QoL, aerobic capacity, muscular strength, flexibility, body composition, functional capacity, and immunological parameters. Twelve of these studies assessed CRF as a primary or secondary outcome and employed a randomized, controlled clinical trial experimental design. The current article restricts discussion of studies involving exercise interventions to these 12 randomized controlled clinical trials (Table 1) [74,81,89,104–107,117,124,128,131,132].

Collectively, the results of these 12 studies provide preliminary evidence that exercise is safe and well tolerated by cancer survivors with various cancer diagnoses. The studies also suggest the results are similar for patients throughout the cancer care continuum, postsurgery or post-transplant, as well as during and after chemotherapy, radiation therapy, and/or hormone therapy. One study also suggests that low-intensity seated exercise is safe and well tolerated even by women with metastatic breast cancer. Additionally, this research suggests that exercise interventions involving moderately intense (55%–75% of heart rate maximum) aerobic exercise (e.g., walking and cycling) ranging from 10–90 minutes in duration, 3–7 days/week are consistently effective at either reducing or halting the progression of CRF in cancer patients during and after treatment. Furthermore, one study showed that progressive resistance training (three times per week, 85%–90% of one-repetition maximum, progressively increasing sets and repetitions) was effective in reducing CRF in cancer patients receiving hormone therapy. Lastly, a recent meta-analysis by Schmitz and colleagues [65] suggests that the evidence for exercise as an effective therapy for managing CRF is indeed consistently positive, although the effect size (ES) is small (weighted mean ES = 0.13, 95% confidence interval [CI], −0.06 to 0.33 during treatment; weighted mean ES = 0.16, 95% CI, −0.23 to 0.54 post-treatment), indicating the need for developing more effective exercise interventions.

Although the extant exercise and cancer control literature provides consistent support for the efficacy of exercise interventions in managing CRF during and after treatment, this body of literature is preliminary. The studies have small sample sizes and lack consistency in the type and amounts of exercise used. These limitations make it impossible to apply the results effectively as specifically tailored exercise prescriptions that best meet the needs of the patient. There are also methodologic concerns. The measures used to assess CRF and control groups are inconsistent, making interpretations and conclusions across studies difficult. Appropriate statistical and follow-up analyses were not commonly used (e.g., intent-to-treat analyses in randomized controlled trials), making comparisons based on regimen and methods of exercise intervention difficult to ascertain [62–64].

Despite these limitations, this growing body of research provides consistent preliminary support for the safety of exercise interventions for cancer survivors across the entire cancer care continuum.

Psychosocial Interventions
During the last 20 years the body of knowledge regarding the benefits of psychosocial interventions for cancer survivors has grown substantially. Psychosocial interventions include activities such as support interventions (either individually or in groups), education, stress management, coping strategy training, and behavioral interventions designed to assist survivors with managing their CRF. Psychosocial interventions may be particularly useful for cancer survivors in whom exercise is contraindicated, or as an adjunct to exercise programs. As with exercise interventions, a growing body of empiric data supports the use of psychosocial interventions for the management of CRF. Randomized, controlled clinical trials have examined a variety of psychosocial interventions in cancer survivors during and after treatment (Table 2) [139–153].

Taken together, the results of these studies suggest that psychosocial support therapy portends lower levels of CRF among patients undergoing treatment and cancer survivors with different cancer diagnoses. Additionally, this research suggests that psychosocial interventions are effective in helping to manage CRF whether delivered individually or in a group setting, orally or written, and, interestingly, by a licensed professional or a trained...
**Table 1. Randomized controlled trials investigating exercise for the management of cancer-related fatigue**

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of cancer</th>
<th>Treatment</th>
<th>n</th>
<th>Type of exercise</th>
<th>Instrument used to assess fatigue</th>
<th>Effects on fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mock et al. [104]</td>
<td>Breast cancer stage I–II, predominantly stage II</td>
<td>CT</td>
<td>14</td>
<td>Home-based self-paced walking program 4–5 times/wk for 10–45 minutes and support therapy for 4–6 months versus usual care for controls</td>
<td>100-mm SAS</td>
<td>Fatigue symptom intensity (SAS) was lower among the exercise group compared with controls</td>
</tr>
<tr>
<td>Mock et al. [106]</td>
<td>Breast cancer stage I–II, predominantly stage I</td>
<td>RT</td>
<td>46</td>
<td>Home-based self-paced walking program 4–5 times/wk for 20–30 minutes for 6 wks versus usual care for controls</td>
<td>100-mm SAS and modified PFS</td>
<td>Fatigue symptom intensity (SAS) was lower among the exercise group compared with controls; fatigue (PFS) was lower among individuals in the exercise group compared with controls</td>
</tr>
<tr>
<td>Dimeo et al. [89]</td>
<td>Mixed solid tumor or lymphoma</td>
<td>Post high-dose CT and autologous peripheral blood stem cell transplant</td>
<td>59</td>
<td>Supervised bed ergometer for 15 minutes at ≥50% cardiac reserve during hospitalization (~2 days/wk) versus usual care for controls</td>
<td>Fatigue subscale of the POMS questionnaire</td>
<td>No significant increase in fatigue from admission to discharge in exercise group (p = .28) compared with control group who experienced significant increase in fatigue (p = .02)</td>
</tr>
<tr>
<td>Mock et al. [105]</td>
<td>Breast cancer stage I–III, predominantly stages I and II</td>
<td>CT or RT</td>
<td>50</td>
<td>Home-based self-paced walking program for 10–30 min 5–6 times/wk for 6 wks in RT patients and 4–6 months for CT patients</td>
<td>Modified PFS, a 0–10-point daily rating scale and the fatigue subscale of the POMS questionnaire</td>
<td>Fatigue (PFS) was lower among individuals classified as high walkers compared with individuals classified as low walkers from pretest to post-test; a daily ratings (VAS) of fatigue were lower for the high walkers compared with the low walkers; fatigue (POMS) decreased among high walkers compared with an increase in fatigue among low walkers</td>
</tr>
<tr>
<td>Segal et al. [124]</td>
<td>Prostate cancer</td>
<td>Androgen-deprivation therapy</td>
<td>155</td>
<td>Supervised resistance training program 3 times/wk for 12 wks versus usual care for controls</td>
<td>FACT-F</td>
<td>Fatigue improved significantly more among patients in the exercise group compared with patients in the control group (p = .002 for difference in change scores between groups)</td>
</tr>
<tr>
<td>Courneya et al. [81]</td>
<td>Colorectal cancer</td>
<td>Surgery during previous 3 months, some undergoing CT or RT and some not</td>
<td>102</td>
<td>Home-based walking or patient preference (swimming, cycling) exercise program 3–5 times/wk at 65%–75% maximum heart rate for 20–30 minutes for 16 wks</td>
<td>FACT-F</td>
<td>Fatigue decreased among participants in the exercise group, while increasing among participants in the control group</td>
</tr>
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</table>

(Continued)
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<table>
<thead>
<tr>
<th>Author</th>
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</thead>
<tbody>
<tr>
<td>Dimeo et al. [131]</td>
<td>Lung or gastrointestinal tumors</td>
<td>Surgery during previous 3 months, some post-CT or post-RT. No ongoing RT or CT</td>
<td>69</td>
<td>Stationary biking for 30 minutes 5 times/wk or a progressive relaxation training program for 45 minutes 3 times/wk</td>
<td>EORTC QLQ-C30 version 2</td>
<td>Fatigue was significantly reduced in the exercise and relaxation groups ($p = .02$ and $p = .009$, respectively), with no significant differences between the two groups</td>
</tr>
<tr>
<td>Windsor et al. [128]</td>
<td>Prostate cancer</td>
<td>RT</td>
<td>66</td>
<td>Home-based walking for 30 minutes 3 days/wk at a target of 60%–70% maximum heart rate versus usual care for controls for 10 wks</td>
<td>BFI</td>
<td>Fatigue did not significantly increase among the exercise group during radiotherapy ($p = .203$); however, fatigue did significantly increase in the control group during radiotherapy ($p = .013$)</td>
</tr>
<tr>
<td>Headley et al. [132]</td>
<td>Metastatic breast cancer</td>
<td>CT</td>
<td>32</td>
<td>Home-based seated exercise program 3 times/wk</td>
<td>FACT-F</td>
<td>Fatigue scores increased significantly less among the exercise group compared with the control group ($p = .008$)</td>
</tr>
<tr>
<td>Pinto et al. [117]</td>
<td>Breast cancer</td>
<td>Post-treatment within 5 years of diagnosis</td>
<td>86</td>
<td>Home-based walking at a moderate intensity (55%–65% maximum heart rate) 2–5times/wk, for 10–30 minutes for 12 wks</td>
<td>VAS</td>
<td>Fatigue was significantly reduced among individuals in the exercise group compared with an increase in fatigue among the controls ($p = .001$)</td>
</tr>
<tr>
<td>Campbell et al. [74]</td>
<td>Breast cancer</td>
<td>CT or RT</td>
<td>22</td>
<td>Supervised mixed aerobic and resistance exercise 2times/wk for 10–20 minutes/session at 60%–75% of maximum heart rate for 12 wks</td>
<td>PFS</td>
<td>Fatigue decreased more among individuals in the exercise group compared with individuals in the control group</td>
</tr>
<tr>
<td>Mock et al. [107]</td>
<td>Breast cancer stages 0–III</td>
<td>CT or RT</td>
<td>119</td>
<td>Home-based walking for 15–30 min 5–6 times/wk at 50%–70% maximum heart rate for 6 wks for RT patients and 3–6 months for CT patients versus usual care for controls</td>
<td>PFS</td>
<td>Fatigue was significantly reduced among subjects fully complying with the exercise program ($p = .03$)</td>
</tr>
</tbody>
</table>

*Patients in the usual-care group were found to be actively exercising during the study period and the analysis was therefore changed to consider a dose–response perspective, with subjects split into high- and low-walk groups. Abbreviations: BFI, Brief Fatigue Inventory; CT, chemotherapy; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life questionnaire, version 2; FACT-F, Functional Assessment of Cancer Therapy–Fatigue; FACT-I, Functional Assessment of Chronic Illness Therapy–Fatigue, version IV; PFS, Piper Fatigue Scale; POMS, Profile of Mood States questionnaire; RT, radiotherapy; SAS, symptom assessment scale; VAS, visual analog scale.
nonprofessional. Furthermore, the benefits may continue for many months following cessation of the interventions [141]. However, interventions that are too lengthy and that require too many sessions during the time when patients are receiving treatments for their cancer, such as radiation, may in fact exacerbate CRF [153].

Unfortunately, the wide variety of psychosocial interventions and the lack of detailed descriptions of the interventions limit the ability to make a differential or overall assessment of the efficacy of psychosocial interventions. As is evident from Table 2, studies used varying combinations of psychosocial intervention techniques and investigated the effects on CRF using a wide range of assessment tools. Despite the diverse array of psychosocial interventions, in general, the results from these studies suggest that psychosocial interventions benefit patients with cancer both during and after the completion of treatments by improving CRF. However, further research is needed to delineate the optimal mode of delivery, as well as the optimal content for psychosocial interventions targeted at managing CRF.

**Other Integrative Interventions**

In an attempt to mitigate the unpleasantness of treatment side effects, including CRF, patients with cancer and survivors are increasingly turning to integrative nonpharmacologic behavioral interventions that have not typically been considered part of western European medicine [154–157]. The most common forms of integrative modalities used by cancer survivors across the U.S. include prayer, relaxation, and exercise [157]. A brief summary follows of the evidence for the merits of yoga, mindfulness-based stress reduction (MBSR), nutrition, sleep, polarity, and restorative therapies for managing CRF.

**Yoga**

One particular type of exercise intervention, collectively known as yoga, is based on Eastern traditions from India (i.e., classical, Advaita Vedanta, Tantra), Tibet (i.e., Tibetan), and China (i.e., Chi Kung, Tai Chi) [158,159]. The word yoga is derived from its Sanskrit root, “yuj,” which literally means “to yoke” or join together. In this case, yoga refers to a joining of the mind and the body. The earliest forms of yoga were firmly rooted in introspective and meditative practices based on Vedic, Upanishad, and Sutra texts. These early forms ultimately led to what is known today as classical yoga. The system of classical yoga, based largely on the yoga sutras, combines physical exercise with mindfulness, and is the most common style of yoga taught today in the West [158–160]. In an effort to alleviate side effects, such as CRF, and improve QoL, patients with cancer are turning to yoga with promising results.

Cohen [158] demonstrated no increase in CRF among 39 patients with lymphoma actively receiving treatment, or within 12 months post-treatment, who participated in a Tibetan yoga stress reduction program once a week for 7 weeks. The program included yoga postures, visualization, breathing, and mindfulness. Participants in the waitlist control demonstrated increases in CRF. This is the first published study to report the effect of yoga on CRF using a validated measure (Brief Fatigue Inventory). While results of the study are very encouraging and suggest that yoga may be a viable therapeutic intervention for improving CRF, the evidence remains preliminary. However, this study strongly suggests the need for appropriately powered, randomized controlled trials with CRF as a primary outcome in order to develop a scientific evidence base supporting the use of yoga for the clinical management of CRF [161,162].

**MBSR**

Mindfulness-based stress reduction (MBSR) is a multimodal program focused on improving well-being and health [163]. The most widely recognized MBSR program was developed by Kabat-Zinn [163] at the Massachusetts Medical Center. The program includes one 90-minute session per week for 8 weeks, along with a 3-hour silent retreat between weeks 6 and 7. The curriculum consists of three major components: (a) experiential practice of gentle Hatha yoga (including yoga stretches, poses, and breathing and meditation exercises) performed once a week during the 90-minute sessions and at home; (b) educational materials related to mindfulness, relaxation, meditation, and yoga; and (c) group processing and discussion.

Specia and colleagues [164] demonstrated greater reductions in CRF among 109 early- or late-stage cancer patients participating in an MBSR program compared with participants in a wait-list control group. Additionally, Carlson and colleagues [165,166] reported improvements in CRF from preintervention to postintervention among 59 patients with breast or prostate cancer participating in an 8-week MBSR program. Both intervention programs were modeled after the Massachusetts Medical Center program headed by Kabat-Zinn [163]. The yoga portion of the intervention included gentle Hatha yoga stretches and poses and breathing and meditation exercises performed once a week as part of the 90-minute class. These are the first two published studies to report on the effect of MBSR on CRF. Again, while results of these studies are positive and suggest that MBSR may be a useful therapeutic intervention for improving CRF, the evidence is preliminary. There is a need for appropriately powered, randomized controlled trials with CRF as a primary outcome to create an informed scientific evidence base upon which to base clinical care.
Table 2. Randomized controlled trials investigating psychosocial interventions for the management of cancer-related fatigue

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of cancer</th>
<th>Treatment</th>
<th>n</th>
<th>Type of intervention</th>
<th>Instrument used to assess fatigue</th>
<th>Effects on fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiegel et al. [139]</td>
<td>Breast cancer stage IV</td>
<td>CT</td>
<td>86</td>
<td>Weekly support group for 1 year aimed at improving mood, coping strategies, and self-esteem</td>
<td>POMS-Fatigue subscale</td>
<td>Significantly less fatigue reported by the experimental group (p &lt; .01)</td>
</tr>
<tr>
<td>Forster et al. [140]</td>
<td>Mixed cancers</td>
<td>RT</td>
<td>100</td>
<td>Individual psychotherapy delivered weekly for 10 wks</td>
<td></td>
<td>Significant improvement in experimental group 4 wks after RT compared with control group (p &lt; .01)</td>
</tr>
<tr>
<td>Fawzy et al. [141]</td>
<td>Postsurgical melanoma stages I and II</td>
<td>None</td>
<td>66</td>
<td>Structured psychiatric group intervention involving health education, problem-solving skills, stress management, and coping skills provided weekly for 6 wks</td>
<td>POMS-Fatigue subscale</td>
<td>Significant reduction in fatigue after 6 months (p &lt; .05)</td>
</tr>
<tr>
<td>Fawzy [142]</td>
<td>Postsurgical melanoma stages I and II</td>
<td>None</td>
<td>62</td>
<td>Psychoeducational nursing intervention involving health education, stress management, and coping skills provided via a manual and 3 hours of nurse teaching</td>
<td>POMS-Fatigue subscale</td>
<td>Significant reduction in fatigue after 3 months (p &lt; .05)</td>
</tr>
<tr>
<td>Gaston-Johansson et al. [143]</td>
<td>Breast cancer stages II–IV</td>
<td>ABMT</td>
<td>110</td>
<td>CCSP Fatigue severity measured on a 100-mm VAS</td>
<td></td>
<td>7 days after ABMT, the CCSP group experienced significantly less fatigue than the control group (p &lt; .05)</td>
</tr>
<tr>
<td>Given et al. [144]</td>
<td>Solid tumors and lymphoma</td>
<td>CT</td>
<td>113</td>
<td>Nurse-administered stress-management training program provided during 10 consultations over 18 wks</td>
<td>Symptom experience scale</td>
<td>More patients in the experimental group reported neither pain nor fatigue at the 20-wk observation compared with patients in the control group</td>
</tr>
<tr>
<td>Jacobsen et al. [145]</td>
<td>Mixed cancers</td>
<td>CT</td>
<td>411</td>
<td>PSMT or SSMT versus usual care</td>
<td>Fatigue measured as “vitality” on SF-36</td>
<td>SSMT resulted in a significant increase in vitality compared with usual care; PSMT did not result in improved vitality compared with usual care</td>
</tr>
<tr>
<td>Given et al. [146]</td>
<td>Solid tumors, predominantly breast (40%) and lung (34%)</td>
<td>CT</td>
<td>237</td>
<td>Individually tailored nurse-administered cognitive behavioral program provided during 10 patient visits to the oncology unit over a period of 20 wks</td>
<td>Fatigue severity measured on a 10-point VAS</td>
<td>46% of patients lowered fatigue severity below baseline threshold</td>
</tr>
<tr>
<td>Barasevick et al. [147]</td>
<td>Undergoing treatment for a variety of cancers, predominantly breast (71%)</td>
<td>RT, CT, or RT + CT</td>
<td>396</td>
<td>ECAM versus nutritional control (guidance on healthy eating) provided to patients during three telephone sessions</td>
<td>POMS-SF; SCFS-P; GFS</td>
<td>Fatigue was significantly lower over time in the ECAM group compared with the control group (p &lt; .01 for GFS; p &lt; .05 for SCFS-P; p &lt; .05 for POMS-SF)</td>
</tr>
</tbody>
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<table>
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<tr>
<th>Author</th>
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</thead>
<tbody>
<tr>
<td>Sherwood et al. [148]</td>
<td>Stages II and IV cancers or recurrent cancer</td>
<td>CT</td>
<td>124</td>
<td>Nurse-administered cognitive behavioral symptom management program provided in 5 contacts, both in person and by telephone, at 2-wk intervals over a period of 8 wks</td>
<td>Fatigue severity measured on an 11-point scale</td>
<td>Aggregate symptom severity, including fatigue, was reduced at 10 and 20 wks postintervention; differences between symptom severity scores for the control and intervention groups approached significance only in patients aged ≤60 years ($p = .057$)</td>
</tr>
<tr>
<td>Given et al. [149]</td>
<td>Chemotherapy-naive patients in the first or second cycle of chemotherapy for solid tumors</td>
<td>CT</td>
<td>237</td>
<td>Nurse-administered cognitive behavioral symptom management program provided in 10 contacts over a period of 20 wks</td>
<td>Fatigue severity measured on a 10-point scale</td>
<td>Significant reduction in fatigue severity at 20 wks for patients in the experimental group not experiencing neutropenia</td>
</tr>
<tr>
<td>Stanton et al. [150]</td>
<td>Postsurgical breast cancer</td>
<td>None</td>
<td>418</td>
<td>Standard print control group (CTL) received an NCI publication with general information about cancer survivorship; videotape intervention group (VID) received the same publication and an NCI videotape addressing re-entry challenges in four life domains; psychoeducational counseling intervention group (EDU) received the publication, the videotape, a recovery manual, and 2 individual sessions to discuss the materials</td>
<td>Fatigue measured as “vitality” on the SF-36</td>
<td>VID resulted in a significant increase in vitality compared with CTL at 6 months ($p = .018$)</td>
</tr>
<tr>
<td>Boesen et al. [151]</td>
<td>Postsurgical cutaneous malignant melanoma of T1–4, N1a–2a, M0</td>
<td>Not stated</td>
<td>241</td>
<td>Structured psychoeducational intervention involving health education, stress management, and coping skills provided weekly for 6 wks</td>
<td>POMS</td>
<td>Significantly larger decrease in fatigue for the intervention group compared with control group at the first follow-up, ranging from 1–60 days post intervention ($p = .04$)</td>
</tr>
<tr>
<td>Williams and Schreier [152]</td>
<td>Breast cancer</td>
<td>CT</td>
<td>71</td>
<td>Audiotape consisting of education about exercise and relaxation for symptom management to be played prior to treatment</td>
<td>Fatigue occurrence and severity measured on the Self-Care Diary</td>
<td>Incidence of fatigue was greater in the control group after the intervention, however, no significant differences were found between groups regarding fatigue</td>
</tr>
<tr>
<td>Brown et al. [153]</td>
<td>Mixed cancers, predominantly gastrointestinal (38%)</td>
<td>RT</td>
<td>115</td>
<td>Structured multidisciplinary intervention provided during 8 sessions over a 4-wk period aimed at improving quality of life, including exercise, discussion, and support</td>
<td>Fatigue item on the LASA; POMS-Fatigue and Vigor-Activity subscales; Fatigue item on Spielberger’s STAI; Fatigue item on the SDS</td>
<td>No significant differences in fatigue were found between groups at any time point except for the control group reporting less fatigue on the SDS at wk 8 ($p = .018$)</td>
</tr>
</tbody>
</table>

Abbreviations: ABMT, autologous bone marrow/peripheral blood stem cell transplantation; CCSP, comprehensive coping strategy program; CT, chemotherapy; ECAM, energy conservation and activity management; GFS, General Fatigue Subscale; LASA, Linear Analogue Self-Assessment; NCI, National Cancer Institute; POMS, Profile of Mood States; POMS-SF, Profile of Mood States—Short Form; PSMT, professionally administered stress management training; RT, radiotherapy; SCFS-P, Schwartz Cancer Fatigue Scale—Physical scale; SDS, Symptom Distress Scale; SF-36, Medical Outcomes Study Short-Form Health Survey (36-item); SSMT, patient self-administered stress management training; STAI, State-Trait Anxiety Inventory; VAS, visual analog scale.
Nutritional Therapy
Patients with cancer are at risk for malnutrition and other nutrition-related problems as a result of the cancer itself, the body’s response to the cancer, and the treatment prescribed. Many factors may contribute to malnutrition, including nausea, vomiting, mucositis, diarrhea, and malabsorption of food. Clinical manifestations of malnutrition include fatigue, anorexia, weight loss, and muscle wasting, resulting in poor patient outcomes, including a negative effect on recovery and survival. Importantly, malnutrition and other nutrition-related problems may contribute to the development and exacerbation of CRF. In a recent randomized controlled trial in 111 patients with colorectal cancer undergoing radiation therapy, Ravasco and colleagues [167] reported lower CRF among participants assigned to the individualized dietary counseling group and those assigned to the protein-supplement group compared with individuals in the ad libitum food intake group. Patients who received protein supplements did not experience the same reduction in CRF as those receiving dietary counseling who were consuming ordinary foods. The results from this trial are encouraging and they represent the first preliminary evidence that concurrent individualized dietary counseling, based on regular foods, is an effective means of improving patients’ nutritional intake and CRF. However, further research is needed to establish a solid scientific evidence base regarding the benefits of nutritional therapy on CRF.

Sleep Therapy
Although patients with CRF frequently report disruptions in their sleep patterns, the relationship between sleep patterns and CRF is not well understood [168,169]. Healthcare professionals frequently recommend rest and sleep for the management of CRF [168]. One approach that is recommended for the management of sleep disorders is improved sleep hygiene [170]. The rationale behind this approach is that the often self-perpetuating nature of sleep problems means they can be a continuing cause of fatigue. Patients who sleep poorly often extend their overall period of sleep by taking naps, going to bed earlier, or getting up later. This extended “sleep opportunity” can be problematic, however, if it exceeds the basal ability of the body to generate sleep. The resulting reduction in nocturnal sleep quality increases the likelihood that patients will feel fatigued during the day and the cycle continues to repeat itself. Sleep interventions provide patients with guidance on good sleep hygiene (e.g., encouraging patients to go to sleep at the same time each evening and to rise at a similar time every morning). Other sleep interventions limit the overall time spent in bed, the duration of daytime naps, and evening stimulation [171].

Support for the utility of sleep hygiene in the management of CRF is limited by the lack of randomized controlled investigations in this area, although some preliminary positive evidence exists from nonrandomized, noncontrolled studies. Graydon and colleagues [172] observed improvements in CRF among cancer survivors who practiced rest and sleep to manage their symptoms. However, a wide variety of sleep scores were measured among patients adopting similar strategies, suggesting involvement of other factors. More recently, Berger and colleagues [171] reported that a sleep-management intervention in patients undergoing breast cancer chemotherapy resulted in improvements in CRF during the first three chemotherapy cycles, but not during the fourth cycle. Additionally, Savard and colleagues [173] reported significant differences in CRF from pre- to postintervention among breast cancer survivors receiving cognitive behavioral therapy for insomnia compared with survivors in a wait-list control condition. While these results may seem promising, they do not provide sufficient evidence to support the efficacy of sleep therapy for mitigating CRF and further research is needed.

Polarity Therapy
Polarity therapy is an energy therapy, developed by Dr. Randolph Stone in 1947, that employs gentle human touch in an effort to balance the electrical energy fields of living organisms and, thus, portend a state of well-being and health [174]. This “energy therapy” is based in historical Greek, Indian, Egyptian, and Chinese medical traditions. Roscoe and colleagues [174] published the first randomized, controlled pilot study investigating the efficacy of polarity therapy for improving CRF. This study reported that breast cancer survivors receiving one 75-minute session or two 75-minute sessions (a week apart) of polarity therapy during the course of radiation therapy demonstrated significant reductions in CRF compared with survivors receiving standard radiation therapy alone [174]. These results are very encouraging, especially considering this is an integrative nonpharmacologic behavioral intervention that does not require substantial lifestyle change on the part of the cancer survivor. However, this is the only published study to investigate the efficacy of polarity therapy for improving CRF and the study was conducted with a very small sample (n = 15). As such, further randomized controlled trials are needed to establish the efficacy of polarity therapy for improving CRF and create a solid evidence base upon which to inform clinical practice.

Restorative Therapy
Decreased attention capacity, or attentional fatigue, represents one aspect of the sensory dimension of CRF that has been documented in patients with cancer [175]. The aim
of restorative therapy is to maintain or restore attentional capacity and decrease attentional fatigue, thereby decreasing CRF. This is accomplished through involvement in activities that engage patients’ fascination or have other restorative properties that improve attentional capacity. Though limited, existing data indicate that restorative therapy provides benefits for the sensory dimension of CRF in patients newly diagnosed with cancer and in patients with cancer after surgery. For example, Cimprich [176] observed improvements in attentional fatigue in a randomized controlled trial involving 32 women during the 3 months after surgery for stage I or II breast cancer. More recently, Cimprich and Ronis [177], in a randomized study of 157 women with newly diagnosed breast cancer, reported that regular exposure to the natural environment was demonstrated to improve attentional fatigue. Research in this field is preliminary and a number of questions remain unanswered, particularly, the relationship between and specific role of mental fatigue and somatic fatigue in CRF. Additionally, since the studies conducted by Cimprich and colleagues did not use standard multidimensional CRF measures, it is not possible to establish whether the improvements in attentional fatigue actually resulted in improvements in CRF or more specific benefits, such as increased ability to perform activities of daily living or social activities. Further rigorous research is needed to develop scientific knowledge regarding the efficacy of restorative therapy for the management of CRF.

RECOMMENDATIONS FOR FUTURE RESEARCH

Clearly, some progress has been made in establishing clear scientific evidence for the use of several integrative nonpharmacologic behavioral interventions for the clinical management of CRF, but a great deal of research is still needed. Future research on integrative nonpharmacologic behavioral interventions should focus on discerning: (a) what physical exercise dose (mode, frequency, intensity, duration) is most effective for treating CRF; (b) how the safe and effective physical exercise dose for treating CRF varies with different cancer diagnoses (e.g., solid tumors, leukemias, and lymphomas, varying stages 0–IV); (c) how the safe and effective physical exercise dose for treating CRF varies throughout the cancer care continuum from diagnosis to many years post-treatment; (d) what the negative side effects of physical exercise for cancer survivors are and at what time points and doses they occur (e.g., interference with chemotherapy, radiation, hormone therapy, immune compromise); (e) what the optimum delivery method is for a physical exercise intervention (e.g., home-based, community, Internet) to achieve acceptable levels of adherence and compliance to produce improvements in CRF; (f) what the specific content of psychosocial therapy should include; (g) what the optimal delivery method is for psychosocial therapy interventions (e.g., individual, group, oral, written, licensed psychologist, or nonlicensed professional); (h) which other promising integrative nonpharmacologic behavioral interventions, such as yoga, MBSR, nutrition, sleep, polarity, and restorative therapies, are effective in treating CRF; and (i) which intervention or combination of interventions provides the most effective means of treating CRF. Future research on integrative nonpharmacologic behavioral interventions for the management of CRF should also follow rigorous scientific research methodology. Clinical trials should follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines [178]; experimental designs and statistical analyses should include CRF as a primary study outcome; research programs promoting specific interventions should include and be clearly reported as phase I, phase II, phase III, and phase IV clinical trials; and statistical analyses should use intent-to-treat analyses, as appropriate.

CONCLUSION

In line with guidelines from the NCCN, integrative nonpharmacologic behavioral treatment should be implemented for the effective management of CRF. A wide range of these interventions is available, including physical exercise, psychosocial therapy, yoga, MBSR, and nutritional, sleep, polarity, and restorative therapies. Physical exercise and psychosocial therapeutic interventions currently have the strongest scientific evidence base to support their use. Unfortunately, the most effective exercise prescription or psychosocial therapy remains unclear and the effect sizes are small. This means that while oncologists can and should encourage their patients to exercise and participate in psychosocial therapy to improve their symptoms and side effects, they cannot provide specific exercise or psychosocial prescriptions for the effective treatment of CRF, and hence, even with exercise and psychosocial therapy, the improvements in CRF may be small. As a result, exercise and psychosocial interventions as part of clinical care for symptom and side-effect management in oncology are not as effective or efficient as they should be. There is also promising, but very limited, evidence to support the use of other integrative nonpharmacologic behavioral interventions for the management of CRF, including yoga, MBSR, and nutritional, sleep, polarity, and restorative therapies. However, the scientific evidence underlying these interventions is very preliminary and the use of these modalities as part of standard clinical care in oncology for the management of CRF is premature.
Integrative nonpharmacologic behavioral interventions are already sought and used by many patients with cancer to aid in the management of their cancer- and treatment-related symptoms and side effects, such as CRF. The scientific community must continue conducting and funding research to provide the detailed scientific evidence and resources necessary for oncologists to prescribe these types of integrative nonpharmacologic behavioral interventions effectively as part of standard care and to assist cancer survivors in choosing which intervention will best suit their needs. While much is still to be discovered, integrative nonpharmacologic behavioral interventions show great promise in the battle against CRF and its life-altering effects.

ACKNOWLEDGMENTS
The authors are recipients of National Cancer Institute grants IR25-CA102618-01A1 and 2U10CA037420-20 and American Cancer Society grant RSG01071-01-PBP. Publication of this article was supported by a grant from Cephalon, Inc., Frazer, PA.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST
G.R.M. has acted as a consultant for MGI Pharma and Cephalon.

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