Cancer-related fatigue (CRF) is a disabling and distressing symptom that is highly prevalent across the cancer continuum from a patient’s diagnosis and treatment through survivorship and end of life. It has a multifactorial etiology and significant individual variability in its clinical expression, determinants, and sequelae. Despite the significance of CRF, it is often underdiagnosed, and management is frequently suboptimal. This review synthesizes the state of the science concerning the features, possible mechanisms, and predictors of CRF; offers recommendations for the evaluation of CRF; and appraises the strength of the evidence for a wide range of pharmacologic and nonpharmacologic interventions to prevent and manage fatigue during and after cancer and its treatment. There is evidence from methodologically rigorous controlled trials that exercise, psycho-educational interventions, and cognitive-behavioral therapy for insomnia are effective in the treatment of CRF, and a wide range of pharmacologic and nonpharmacologic interventions has shown initial promise in single-arm pilot studies with small, heterogeneous samples. Rigorously designed and adequately powered randomized trials are warranted to (1) determine the effectiveness of promising approaches and (2) identify the interventions that are most effective in treating CRF in specific subpopulations (eg, stem cell transplant recipients, older adults, patients with lung or colorectal cancers, survivors, and those at the end of life). Studies to elucidate the biologic expression profiles of CRF, to explicate the mechanisms through which particular interventions impact CRF, and to identify the mediators and moderators of fatigue outcomes will ultimately permit individually tailored approaches for the treatment of CRF.
Defining Features of CRF

Although many different definitions of CRF have been proposed, the National Comprehensive Cancer Network defines CRF as a distressing, persistent, and subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning [20]. On the basis of the 10th International Classification of Disease criteria for the diagnosis of CRF (Table 1) [1], CRF is of a markedly different quality and severity from ordinary fatigue, has an adverse impact on function, and is unrelated by rest or sleep [21]. For a clinician to make the diagnosis of CRF, fatigue must be persistent and be accompanied by associated symptoms such as an increasing need for rest, limb heaviness, diminished concentration, inertia, emotional lability, and postexertional malaise. The clinician must also be fairly certain that the underlying cause of CRF is cancer or its treatment.

The clinical expression of CRF is multidimensional, making evaluation of a patient who experiences fatigue challenging. An inherently subjective condition, fatigue may be experienced and reported differently by each patient. Qualitative studies of fatigue underscore the fact that CRF is unlike any other fatigue patients with cancer have experienced and suggest that its unpredictability and refractoriness to self-management strategies contribute to the distress associated with the condition [22,23]. Personality and coping style may also influence a patient’s experience of CRF [24].

Patients’ descriptions of CRF suggest it has both central and peripheral features, although the authors of at least one study [25] suggest that CRF appears to be predominantly a centrally mediated disorder. Some patients identify the main features of their fatigue as a loss of efficiency, mental fogginess, inertia, and sleep that is not restorative, whereas others describe an excessive need to rest, an inability to recover promptly from exertion, or muscle heaviness and weakness. Further research is needed to determine whether these represent variable features of fatigue, suggest the presence of fatigue subtypes, or are the cause or sequelae of fatigue [26,27]. Efforts continue to clarify the defining features of fatigue [28] and to distinguish CRF from syndromes that have overlapping symptoms, such as depression, cognitive dysfunction, or asthena [29-34], or that may share neurophysiologic mechanisms [35,36].

Incidence

Fatigue is one of the most commonly reported symptoms experienced by patients receiving treatment for cancer, and it often persists beyond the conclusion of active treatment [13,15,21,37-39]. Depending upon how CRF is defined and measured, prevalence estimates across the disease trajectory range from 25% to 99% [40]. In the results of a recent survey of more than 500 patients and nearly 100 clinicians, fatigue ranked as the most important symptom or concern across all cancer types [41]. The authors of longitudinal and comparative studies [7,38,39,42-45] indicate that fatigue also may be a significant problem for cancer survivors, with a significant proportion of survivors reporting fatigue scores greater than that of an age-matched general population. In the setting of advanced cancer, almost 60% of patients experience fatigue, with one-quarter reporting severe fatigue [46]. Fatigue may occur as an isolated symptom or as one component within a cluster of other symptoms, including depression, pain, sleep disturbance, and menopausal symptoms [47-52].

Etiology and Risk Factors

The etiology and risk factors for CRF are multifactorial. Although the relationship between fatigue and treatments

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**Table 1. International Classification of Diseases (10th edition) criteria for cancer-related fatigue**

A. Six (or more) of the following symptoms have been present every day or nearly every day during the same 2-week period in the past month, and at least one of the symptoms is (A1) significant fatigue.

A1. Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level

A2. Complaints of generalized weakness or limb heaviness

A3. Diminished concentration or attention

A4. Decreased motivation or interest to engage in usual activities

A5. Insomnia or hypersomnia

A6. Experience of sleep as unrefreshing or nonrestorative

A7. Perceived need to struggle to overcome inactivity

A8. Marked emotional reactivity (eg, sadness, frustration, irritability) to feeling fatigued

A9. Difficulty completing daily tasks attributed to feeling fatigued

A10. Perceived problems with short-term memory

A11. Postexertional malaise lasting several hours

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. There is evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer or cancer therapy.

D. The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delirium

Used with permission from Cello et al [1].
with radiation, chemotherapy, hematopoietic stem cell transplantation, hormonal, and biologic agents has been explored, few consistent relationships between fatigue and treatment-related variables, such as dose-intensity, radiation fractionation schedule, and time since treatment completion, have been observed [38]. Associations between the occurrence and severity of CRF and demographic variables, such as gender, age, marital status, and employment status, have not been consistently identified. The authors of various studies [25,40,53-66] suggest that fatigue may be related to anemia; myeloid suppression; mood disorder; concurrent symptoms such as pain or sleep disturbances; electrolyte disturbances; cardiopulmonary, hepatic, or renal dysfunction; hypothyroidism; hypogonadism; adrenal insufficiency; infection; malnutrition; deconditioning; skeletal muscle atrophy/weakness; and the adverse effects of medications, such as narcotics that act on the central nervous system. Accumulating evidence [67-84] also suggests that gene polymorphisms, altered circadian rhythm, immune dysregulation, abnormal cortisol secretion, proinflammatory cytokine activity, elevated body mass index, and metabolic syndrome may directly or indirectly contribute to CRF. In any one person, CRF likely involves the interaction of several physiologic and psychological mechanisms.

Psychophysiologic Models of CRF

Many different explanatory models of the psychophysiology of CRF have been proposed, and many use similar constructs. These conceptual models can be organized into 4 thematic groups: (1) energy balance/energy analysis, (2) fatigue as a stress response, (3) neuroendocrine-based regulatory fatigue, and (4) hybrid models.

Energy balance/energy analysis models depict energy as the major explanatory variable and suggest that an imbalance among energy intake, metabolism, and expenditure is the major etiologic factor in the development of fatigue. Examples of this thematic group of models include the Piper integrated fatigue model [85], the Irvine energy analysis model [86], the Winningham psychobiologic-entropy model [87], and Andrews et al’s model of altered skeletal muscle metabolism [88].

Fatigue as a stress response models posit that tiredness, fatigue, and exhaustion form an adaptational continuum of response to stress. Each state along this continuum from tiredness to exhaustion may be distinguished by different behavioral and symptom characteristics. Examples of models included in this thematic class include fatigue models proposed by Aistars [89], Rhoten [90], Glaus [91], and Olson et al [92,93].

Neuroendocrine-based regulatory fatigue models hypothesize that the multiple dimensions of fatigue are explained by dysregulation in the function of neuroimmunoendocrine-based regulatory systems, including the hypothalamic-pituitary axis, circadian rhythms, vagal afferent nerve activation, cytokine dysregulation, and neuroimmune system transmitter secretion and function [75]. Examples of models developed on the basis of neuroimmunoendocrine dysregulation include those that have been proposed by Miller et al [74], Lee et al [35], Payne [94], and Schubert et al [69].

More recently, 2 models that represent hybrid conceptual approaches have been proposed. On the basis of their earlier work, Olson et al [93] have recently proposed a model of CRF in which they propose that stressors associated with cancer and its treatment trigger declines in 4 systems—cognitive function, sleep quality, nutrition, and muscle endurance—and that these declines reduce one’s ability to adapt. Their model suggests that an understanding of the characteristics and etiologic mechanisms of CRF will emerge through study of the interactions among these 4 systems. Al Majid and Gray [95] have also recently proposed a hybrid model that incorporates the biological, psychological, and functional variables implicated in the induction of CRF, and they suggest the application of this model to elucidate the mechanisms by which exercise may ameliorate CRF. These 4 models may guide empirical evaluation and also clinical interventions to limit and manage fatigue and to reduce its deleterious impact on health-related quality of life. These models may also assist in defining the minimum data set for studies of CRF and in generating testable hypotheses for continued research into the problem of CRF.

Approaches to Measuring CRF

Several approaches to the measurement of CRF are available, including (1) single items that gauge fatigue severity; (2) instruments that were designed specifically to evaluate CRF from a multidimensional perspective; and (3) single items or subscales that measure relevant aspects of the fatigue experience that have been drawn from measures of quality of life, psychosocial adjustment, mood, or self-reported health status. Although the use of self-report measures to evaluate CRF predominates in the literature, applications of neurophysiologic and performance-based measurements of fatigue, including muscle force, endurance time, muscle reserve, neuromuscular-junction impulse propagation, and functional performance, are emerging [3,25,96-99]. This combined use of clinician-assessed and patient-reported outcome measures strengthens the evaluation of therapeutic response in clinical trials of new treatment approaches for fatigue and may contribute to an improved understanding of the central and peripheral mechanisms of CRF.

Screening patients with CRF is fundamental to improving fatigue management and is a key component of health-care quality. Although there is currently no consensus concerning the optimal method or frequency of screening for CRF in the clinical setting [100], the high prevalence of CRF supports routine screening for CRF at regular intervals throughout

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<table>
<thead>
<tr>
<th>Measure</th>
<th>Dimensions of Fatigue Evaluated</th>
<th>Scaling and Number of Items</th>
<th>Features</th>
</tr>
</thead>
</table>
| **Brief Fatigue Inventory** [114] | Severity and Impact of fatigue | 11-point Likert scale; 9 items | • Available in multiple languages  
• Cut points to define clinically relevant fatigue levels have been suggested [101,115,116]  
| **Fatigue numerical scale** [117] | Severity of fatigue | 100-mm linear analogue scale, 2 items |  
| **Cancer-related fatigue distress scale** [118] | Consequences of fatigue relative to physical, social, psychospiritual distress | 11-point Likert scale; 20 items | • Cut points to define clinically relevant fatigue levels have been suggested [119]  
| **Chalder fatigue scale** [119] | Fatigue severity, associated distress, self-efficacy for coping, and the extent to which fatigue was overwhelming, uncontrollable, unpredictable, and abnormal | 100-mm linear analogue scale; 7 items | • Minimal clinically important difference has been explored in patients with rheumatoid arthritis and system lupus erythematosus [121,122]  
| **Functional assessment of cancer therapy: fatigue** [123] | Physical, affective, and cognitive dimensions of fatigue and consequences for daily functioning | 5-point Likert scale; 13 items | • Available in multiple languages  
• Normal values for comparison with healthy and cancer samples available [21]  
• Cut points to define clinically relevant fatigue levels have been suggested [120]  
• Minimal clinically important difference has been examined in patients with cancer [124]  
| **Cancer fatigue scale** [117] | Physical, affective and cognitive dimensions of fatigue | 5-point Likert scale; 15 items | • Available in multiple languages  
| **Fatigue symptom inventory** [126,127] | Severity, frequency, daily pattern of fatigue, and its interference with quality of life. A single item provides information about possible diurnal variation in the daily experience of fatigue. | 11-point Likert scale; 14 items | • Cut points to define clinically relevant fatigue levels have been suggested [125]  
| **Fatigue severity scale** [129] | Single-item fatigue severity score and impact of fatigue on daily functioning | 7-point Likert scale for impact items; single-item 100 mm linear analogue scale for severity; 10 items | • Minimal clinically important difference has been explored in patients with rheumatoid arthritis and system lupus erythematosus [121,122]  
• Cut point for clinically relevant fatigue has been suggested [125]  
| **Fatigue scale, adolescent** [130] | Multiple dimensions of fatigue, including affective, behavioral, somatic and cognitive aspects of fatigue, and consequences for daily functioning | 5-point Likert scale; 14 items |  
| **Multidimensional fatigue symptom inventory** [131] | Multiple dimensions of fatigue, including global, somatic, cognitive, affective, and behavioral symptoms/manifestations of fatigue | 5-point Likert scale; 83 items | • A 30-item short form instrument has demonstrated acceptable psychometric properties [132]  
| **Multidimensional fatigue inventory** [133] | Multiple dimensions of fatigue: global experience, somatic symptoms, cognitive symptoms, affective symptoms and behavioral symptoms | 5-point Likert scale; 20 items | • Available in multiple languages  
• 15 item French-Canadian version has undergone psychometric testing [134]  
• Minimal clinically important difference has been explored in patients undergoing radiotherapy [135]  
(Table 2 continues)
treatment, initial posttreatment follow-up, long-term follow-up during survivorship, and at the end of life. There is accumulating evidence to suggest that brief measures to screen for fatigue are sensitive and that they can be applied efficiently in the clinic to identify individuals who would benefit from more systematic evaluation [101-108]. In selecting a measure for screening, consideration must be given to what response frame (ie, past 24 hours, past 7 days, past month) has the most clinical relevance for a specific patient population and will be least affected by biases of recall or by transient changes in CRF severity.

Although a brief measure may provide rapid assessment of general fatigue or serve as a screening tool, evidence suggests that such measures do not fully capture all the dimensions of fatigue [109]. More than 20 self-report measures (including single-item measures, multi-item unidimensional scales, and multidimensional inventories) have been developed to measure fatigue in patients with cancer (Table 2) [21,101,110-142]. Measures of symptoms, health, mood state, and psychosocial adjustment, such as the Medical Outcomes Study Short Form-36, Profile of Mood States, Rotterdam Symptom Checklist, Brief Symptom Inventory, and Symptom Distress Scale, also include single items that are used to measure fatigue or have subscales that reflect fatigue, vigor, or vitality.

There is consensus in the literature that fatigue is a multidimensional construct consisting of a sensory dimension (fatigue severity, persistence), a physiological dimension (eg, leg weakness, diminished mental concentration), an affective dimension (sadness, depression, fear), and a behavioral dimension (reduction in the performance of needed or valued activities). Multidimensional fatigue measures provide information about this full range of characteristics beyond fatigue presence and intensity. When selecting a measure of fatigue, it is important to keep in mind that other descriptors of fatigue, such as weakness, tiredness, or the absence of vigor or vitality, may not necessarily be equated with fatigue.

Psychometric considerations in the selection of a measure for clinical or research purposes include the measure’s reliability, validity, specificity, sensitivity to change, and recall period. Logistical issues such as respondent burden, translation into multiple languages, the complexity of scoring algorithms, and the availability of normative values and established thresholds of clinically important differences to aid interpretation may also shape decisions about instrument selection [34,59,113,143-146]. In addition, an optimal measure of fatigue for empirical or clinical purposes should demonstrate acceptable levels of sensitivity and specificity.

In the future, technological advances, such as item-banks, computerized-adapted testing, and other digital formats [147-150], will certainly contribute to improving the efficiency, precision, and ease of interpretation of screening measures for CRF. Ecological momentary assessment (a technique that elicits a repeated, real-time measurement of behaviors or experiences as they occur in the naturalistic setting of an individual’s day-to-day life) may overcome methodological limitations, including recall bias and the influence of current context on self-report of fatigue. Applications of this technique to assess fatigue outcomes in breast cancer survivors and in patients undergoing hematopoietic stem cell transplantation have recently been described [151,152].

**Evaluation of the Patient With CRF**

There is consensus that the evaluation of patients at risk for or experiencing CRF may be separated into 2 aspects: (1) routine, periodic screening to identify the presence of CRF and gauge its severity and (2) a detailed evaluation of the characteristics, consequences, and potential contributing factors for
patients with moderate-to-severe CRF [20]. The National Comprehensive Cancer Network guidelines [20] recommend that every patient be screened for the presence of fatigue. If present, fatigue should be assessed quantitatively on a 0 to 10 scale (0 = no fatigue and 10 = worst fatigue imaginable); those patients with a severity of more than 4 should be further evaluated by a history and physical examination.

A detailed history in patients with moderate or severe CRF includes the presence, intensity, and pervasiveness of fatigue; its course over time; the factors that exacerbate or relieve it; and its impact on functioning and level of distress. Clinicians can obtain valuable information about the consequences of CRF by exploring the effects of CRF on a patient’s self-esteem, mood, and his or her ability to perform activities of daily living, that is, fulfill important roles as a parent, spouse, and worker and relate to family and friends. Inquiring about the self-management interventions the patient has tried for fatigue and their effectiveness can be helpful in tailoring recommendations for fatigue management.

It is also important to consider etiologic factors or potentiating comorbidities that may amplify CRF (Table 3) [153,154]. Evaluation should include whether disease progression or recurrence could be among the causes of fatigue. The medication profile should be reviewed to identify specific classes of medications (including over-the-counter medications) with side-effect profiles that may intensify fatigue. Examples of such medications include opioid analgesics, sedative-hypnotic agents, benzodiazepines, and anxiolytics.

Table 3. Etiologic factors for cancer-related fatigue

- Advanced/metastatic disease or cancer recurrence
- Cancer treatment (chemotherapy, radiation, surgery, biologic agents, hormonal agents, molecularly targeted agents)
- Anemia
- Neutropenia
- Hypothyroidism
- Adrenal Insufficiency
- Hypogonadism
- Infection
- Malnutrition
- Depletion of vitamins B1, B6, and B12
- Electrolyte disturbances (calcium, magnesium, phosphorus)
- Cardiopulmonary, hepatic or renal dysfunction
- Sarcopenia, asthenia
- Inactivity, deconditioning
- Proinflammatory cytokine expression associated with generalized inflammation
- Medications with sedating side effects (eg, narcotics, anxiolytics, antiemetics, antidepressants), or medications with fatigue as part of the side effects profile (eg, beta-blockers) of medications
- Concurrent symptoms (eg, pain, dyspnea, nausea, diarrhea)
- Impaired sleep quality
- Psychological distress (depression, anxiety)

Based on information from Radbruch et al [153] and Cheville [154].

A number of antidepressant agents, antiemetics, antihistamines, and anticonvulsant agents also have the potential to produce daytime sleepiness and fatigue. Certain cardiac medications such as beta-blockers may contribute to fatigue by causing bradycardia, whereas corticosteroids may contribute to fatigue by disrupting sleep or generating proximal muscle weakness.

Interventions for CRF

Because fatigue typically has several different causes in any one patient, the treatment plan must be multidimensional and individually tailored. It is helpful to work with the patient and the family to improve the assessment of fatigue and identify management strategies. Open communication among the patient, family, and health-care team will facilitate discussion about the experience of fatigue and its effects on daily life. General supportive care recommendations for patients with fatigue include optimizing nutritional status and preventing weight loss [155], balancing rest with physical activity, and attention-restoring activities such as exposure to natural environments and pleasant distractions like music [20].

There have been more than 170 empiric studies of pharmacologic and nonpharmacologic interventions to reduce or manage CRF and several recent meta-analyses or systematic reviews of the topic [156-161]. For some interventions, there is strong and consistent evidence to support effectiveness, whereas for other interventions, only preliminary data are available. The results of studies in which the authors examined the impact of pharmacologic and nonpharmacologic interventions on fatigue outcomes during and after cancer and its treatment are summarized in Tables 4 [162-202] and 5 [203-285], and selected findings are discussed in the sections to follow.

Screen For and Manage, as Indicated, Mechanisms or Comorbidities Contributing to Fatigue.

There is expert consensus that patients with fatigue should be evaluated for potentially treatable etiologic factors contributing to fatigue [20] and managed as indicated. Examples of such etiologic factors include endocrinopathies, cardiopulmonary dysfunction, impaired sleep quality, medications with fatigue or sedation as side effects, deconditioning, asthenia, and sarcopenia, and concurrent symptoms such as pain, nausea, dyspnea, or depression [154,286,287].

Exercise. The findings from meta-analyses and systematic reviews of randomized trials [157,160,288-296] provide support for the benefits of exercise in the management of fatigue during and after cancer treatment for patients with breast cancer, solid tumors, or those undergoing hematopoietic stem cell transplantation. In these studies, effect sizes were generally small, and positive results for the outcome of fatigue were not observed consistently across studies. Al-
<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Design and Sample</th>
<th>Effect on Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP (adenosine 5'-triphosphate)</td>
<td>RCT, n = 58 patients with lung cancer (162)</td>
<td>Improvement</td>
</tr>
<tr>
<td>Bupropion sustained release</td>
<td>Two single-arm pilot studies, n = 36 patients with mixed tumors (163,164)</td>
<td>Improvement</td>
</tr>
<tr>
<td>Donepezil</td>
<td>Two single-arm open-label pilot studies and an RCT (n = 62) in patients with mixed tumors (165-167)</td>
<td>Improvement demonstrated in the 2 open-label pilot studies; no significant improvement in the RCT</td>
</tr>
<tr>
<td>Dexamphetamine</td>
<td>RCT (n = 50) patients with advanced cancer and receiving palliative care (168)</td>
<td>No improvement</td>
</tr>
<tr>
<td>Dextemethylphenidate</td>
<td>Three double-blind, placebo-controlled RCTs in patients who had completed chemotherapy for breast or ovarian cancer (n = 211) (169) or primary or metastatic brain tumor (n = 68) (170). The study by Mar Fan et al (171) was underpowered because of inferior subject accrual.</td>
<td>Improvement in fatigue outcomes in patients with breast and ovarian cancer; no improvement in those with primary or metastatic brain tumors</td>
</tr>
<tr>
<td>Methylphenidate (patient-controlled administration)</td>
<td>RCT, double-blind, placebo-controlled, n = 112 patients with advanced cancer and moderate-to-severe fatigue (172)</td>
<td>No improvement</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Three RCTs, n = 624 patients, most with breast cancer (29,179,180)</td>
<td>No improvement</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Single-arm pilot study, n = 13 patients with localized breast cancer who were post-treatment and experiencing hot flashes (181)</td>
<td>Improvement</td>
</tr>
<tr>
<td>Essiac supplementation</td>
<td>Retrospective cohort study, n = 510 randomly selected women from a primary breast cancer registry with primary breast cancer (182)</td>
<td>No improvement</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Dose-finding, double-blinded RCT (n = 290) in adults with mixed tumors (183)</td>
<td>Trend toward improvement at greater dose levels</td>
</tr>
<tr>
<td>L-carnitine supplementation</td>
<td>Four open-label phase 1-2 trials (n = 172) in patients with mixed advanced solid tumors, and a double-blind, placebo-controlled RCT (n = 39) with advanced cancer and low carnitine levels (186-190)</td>
<td>Improvement</td>
</tr>
<tr>
<td>High-dose vitamin C</td>
<td>Single-arm, open-label trial, n = 39 terminally patients with advanced malignancies (191)</td>
<td>Improvement</td>
</tr>
<tr>
<td>Modafinil</td>
<td>Two single-arm pilot studies (n = 39) in patients with lung cancer or mixed tumor types and a multicenter comparative epidemiological cohort study (n = 741) of women with breast cancer who were in follow-up for 5 years after completing recommended standard therapies (185)</td>
<td>No improvement</td>
</tr>
<tr>
<td>Omega-3 fatty acid</td>
<td>RCT (n = 91) in patients with advanced mixed tumors; open-label phase 2 trial (n = 23) in patients initiating chemotherapy for advanced colorectal cancer (195,196)</td>
<td>No improvement</td>
</tr>
<tr>
<td>Paullinia cupana (Guarana)</td>
<td>RCT (n = 36) in women with breast cancer undergoing adjuvant radiation treatment (197)</td>
<td>No improvement</td>
</tr>
<tr>
<td>Thyrotropin-releasing hormone</td>
<td>Preliminary report of a placebo-controlled randomized crossover pilot study (n = 3) in women with breast cancer meeting the ICD-10 criteria for CRF. (198)</td>
<td>Improvement</td>
</tr>
</tbody>
</table>

(Table 4 continues)
though the mechanisms responsible for the beneficial effects of exercise on fatigue have not been defined [297], exercise improves aerobic capacity, prevents muscle loss and deconditioning, and it may produce favorable effects on sleep, mood, body composition, and the immune system and cytokine milieu, while promoting self-efficacy [298-301].

The exercise modalities that have been evaluated differ in type (walking, cycling, swimming, resistive exercise, or combined exercise), frequency (ranging from 2 times per week to 2 times daily), intensity (with most programs at 50%-90% of the estimated maximal heart rate), degree of supervision (fully supervised group versus self-directed exercise), and duration (from 2 weeks up to 1 year). A lack of empiric knowledge about the type, intensity, and duration of physical exercise that is most beneficial in reducing fatigue at different stages of disease and treatment impedes the development of evidence-based guidelines for exercise prescription [302-304]. More research is necessary to systematically assess the safety of exercise (both aerobic exercise and strength training) in cancer subpopulations, including those who are receiving palliative care. Patients require formal, practical guidance about how to begin, maintain, and advance an exercise program. Referral to a rehabilitation professional, such as a physiatrist or physical therapist, can be helpful in providing specific and detailed recommendations about the type, intensity, and frequency of exercise in which the patient should engage. Ongoing follow-up by rehabilitation professionals can improve motivation and adherence and promote advancement of the exercise program as functional capacity improves.

Psychoeducational and Self-management Interventions. A growing body of evidence that includes several adequately powered randomized controlled trials (RCTs) suggests that educational interventions and psychological support improve fatigue outcomes in patients with fatigue [159,161,305]. Across studies, several common elements were incorporated into the psychoeducational interventions, including anticipatory guidance about patterns of fatigue; tailored recommendations for optimizing exercise activity levels and sleep/rest; coaching to enhance motivation, self-care, and active coping; and praise and encouragement to promote self-efficacy and augment feelings of control. Other elements of effective psychoeducational interventions for fatigue included supportive counseling, and cognitive restructuring to support positive coping and adjust catastrophizing thought patterns (eg, “this fatigue is so terrible; I can’t cope, and there is nothing I can do”) that diminish mood and interfere with goal-setting, self-efficacy, and incremental goal attainment.

Energy conservation and activity management (ECAM) is a self-management intervention that teaches patients to apply the principles to balance energy use and provides coaching to incorporate these principles in daily life. It focuses on helping patients examine their daily routines and find ways to reduce the amount of effort needed to perform certain tasks, eliminate other tasks, and alternate periods of rest and activity throughout the day to limit bursts of activity and to discourage physical inactivity. ECAM has been found to have a modest but significant effect in a large, multisite RCT in patients (predominantly with breast cancer) beginning chemotherapy or radiation

<table>
<thead>
<tr>
<th><strong>Intervention(s)</strong></th>
<th><strong>Design and Sample</strong></th>
<th><strong>Effect on Fatigue</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D supplementation</td>
<td>Single-arm trial of women with breast cancer beginning adjuvant treatment with aromatase inhibitor (n = 60) (199)</td>
<td>No improvement</td>
</tr>
<tr>
<td>Combination: Supplement containing protein together with 1000 mg of eicosapentaenoic acid and 46 mg docosahexaenoic acid given twice daily for 9 weeks</td>
<td></td>
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<tr>
<td>Combination: Diet with high polyphenols content (400 mg), antioxidant supplementation, supplementation with eicosapentaenoic acid, and docosahexaenoic acid, medroxyprogesterone, celecoxib</td>
<td>Open-label, early-phase 2 study, Simon 2-stage design in patients (n = 39) with advanced malignancy of mixed solid tumor types (200)</td>
<td>Improvement</td>
</tr>
<tr>
<td>Combination: Medroxyprogesterone, celecoxib, and enteral supplementation</td>
<td>Single-arm pilot study of 15 patients with adenocarcinoma of the lung (201)</td>
<td>Improvement</td>
</tr>
<tr>
<td>Combination: Soy protein supplementation and nutrition counseling</td>
<td>RCT in patients (n = 32) with colorectal malignancy in the postoperative phase after hospital discharge (202)</td>
<td>No improvement</td>
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</table>

*Effect on fatigue: improvement = statistically significant improvement in fatigue; no improvement = no statistically significant improvement in fatigue. RCT = randomized controlled trial.*
<table>
<thead>
<tr>
<th>Intervention(s)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Acupuncture-like trans-electrical nerve stimulation</td>
<td>Double-blinded, placebo-controlled RCT in patients with mixed tumors at the end of life (n = 15) (203) and a single-arm trial in women with breast cancer experiencing aromatase inhibitor-related arthralgias (n = 12) (204)</td>
<td>Improvement</td>
</tr>
<tr>
<td>Acupuncture (Traditional Chinese)</td>
<td>Double-blinded, placebo-controlled RCT in patients undergoing radiotherapy (n = 23) (205) and 2 single-arm pilot studies in patients with unspecified tumor types (n = 37) (206) and undergoing radiotherapy (n = 16) (207)</td>
<td>Improvement</td>
</tr>
<tr>
<td>Cognitive-behavioral treatment for fatigue, insomnia, depression or other distressing symptoms</td>
<td>Ten RCTs (n = 1045) and 5 uncontrolled trials (n = 74) in patients with mixed tumor types undergoing active treatment, follow-up or at the end of life (119,208-221)</td>
<td>Seven RCTs demonstrated improvement; three uncontrolled trials demonstrated improvement</td>
</tr>
<tr>
<td>Cognitive behavioral therapy and hypnosis</td>
<td>RCT (n = 42) (222) and a case series (n = 2) (223) in women undergoing radiation therapy for breast cancer</td>
<td>Improvement</td>
</tr>
<tr>
<td>Group psychotherapy with or without exercise</td>
<td>Two RCTs (n = 341) in patients with solid tumors undergoing active treatment, long term follow-up and at the end of life (224,225)</td>
<td>No improvement with psychotherapy alone; addition of exercise to psychotherapy produced improvement</td>
</tr>
<tr>
<td>Healing touch</td>
<td>One RCT (226) and a single-arm pre-post test design (n = 12) with leukemia (227)</td>
<td>Improvement</td>
</tr>
<tr>
<td>Hypnosis</td>
<td>RCT (n = 200) women undergoing breast biopsy or lumpectomy (228)</td>
<td>Improvement</td>
</tr>
<tr>
<td>Intensive rehabilitation</td>
<td>Single-arm trials in patients with mixed solid tumors, primarily breast cancer who were post-treatment (n = 72) (229), a single-arm trial in patients with lung cancer (n = 45) (230), and a controlled trial in patients at the end of life (n = 49) (231); 2 RCTs (232,233) and 1 systematic review (234)</td>
<td>Improvement</td>
</tr>
<tr>
<td>Massage therapy</td>
<td>Three RCTs (n = 350), a large single-arm trial (n = 251), a retrospective review (n = 1290) in patients with mixed tumor types and undergoing active treatment, and a mailed survey of patients who had recently been evaluated in a breast clinic for a breast abnormality or a recent diagnosis of breast cancer and had received complimentary massage therapy (n = 35) (235-239)</td>
<td>Improvement</td>
</tr>
<tr>
<td>Mindfulness-based stress reduction intervention</td>
<td>Two RCT and three single-arm studies (240-244)</td>
<td>Single-arm study and one RCT demonstrated improvement; 1 RCT and 2 single-arm studies showed no improvement</td>
</tr>
<tr>
<td>Music therapy</td>
<td>RCT, n = 63 patients undergoing radiation therapy with curative intent (245), and three single-arm pilot studies (246-248)</td>
<td>No improvement</td>
</tr>
<tr>
<td>Polarity therapy</td>
<td>RCT, n = 15 patients with breast cancer undergoing active treatment (249)</td>
<td>Improvement</td>
</tr>
<tr>
<td>Progressive Muscle Relaxation</td>
<td>Three RCTs (n = 208) and a meta-analysis (n = 2 studies in which fatigue outcomes were measured) in patients with mixed tumor types undergoing active treatment (250-253)</td>
<td>Two RCTs demonstrated improvement, one RCT and meta-analysis demonstrated no improvement</td>
</tr>
<tr>
<td>Psychoeducational</td>
<td>Eleven RCTs (n = 1279), 3 single-arm studies (n = 153), a matched pairs design (n = 101), and a meta-analysis in patients with mixed tumor types at all phases across the disease trajectory (159,254-258)</td>
<td>Meta-analysis, 8 RCTs, the matched pairs design, and the 3 single-arm studies demonstrated improvement; 3 RCTs demonstrated no improvement</td>
</tr>
<tr>
<td>Qigong</td>
<td>RCT (n = 162) with mixed tumor types (269)</td>
<td>Improvement</td>
</tr>
<tr>
<td>Reiki</td>
<td>Counterbalanced crossover trial, n = 16 patients with colorectal, breast, lung, or gastric cancer who had recently completed treatment (270)</td>
<td>Improvement</td>
</tr>
</tbody>
</table>

(Table 5 continues)
Table 5. Continued

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Design and Sample</th>
<th>Effect on Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relaxation breathing and yoga-like positioning</td>
<td>RCT, $n = 35$ patients with hematologic malignancies and undergoing stem cell transplantation (271)</td>
<td>Improvement</td>
</tr>
<tr>
<td>Virtual reality distraction</td>
<td>4 RCTs ($n = 189$) and one single-arm pilot study ($n = 22$) in patients with solid tumors undergoing chemotherapy (272-276)</td>
<td>Three RCTs demonstrated no improvement; one RCT and single-arm pilot study demonstrated improvement</td>
</tr>
<tr>
<td>Yoga</td>
<td>6 RCTs ($n = 307$) and 2 single-arm pilot studies ($n = 69$) in patients with breast cancer, lymphoma, or ovarian cancer (277-283)</td>
<td>4 RCTs demonstrated no improvement; 2 single-arm pilot studies and one RCT demonstrated improvement</td>
</tr>
<tr>
<td>Combination: Individualized inpatient rehabilitation incorporating manual lymph drainage, exercise, massage, counseling, relaxation, carbon dioxide baths, and mud packs</td>
<td>Single-arm trial, $n = 149$ women with breast cancer who had undergone either mastectomy or breast conserving surgery in combination with chemotherapy, radiation therapy, and hormonal therapy (284)</td>
<td>Improvement</td>
</tr>
<tr>
<td>Combination: Aromatherapy, footsoak, and reflexology</td>
<td>Single-arm open-label of 20 patients with advanced cancer at the end of life (285)</td>
<td>Improvement</td>
</tr>
</tbody>
</table>

Effect on fatigue: improvement = statistically significant improvement in fatigue; no improvement = no statistically significant improvement in fatigue. RCT = randomized controlled trial.

and in a small pilot study in which the authors used historical controls [307].

The authors of studies [208-213] indicate that cognitive-behavioral interventions designed to improve sleep quality also have a beneficial effect on fatigue. These interventions can be delivered individually or in a group setting and include the following: (1) relaxation training; (2) sleep-consolidation strategies (avoiding long or late afternoon naps, limiting time in bed to actual sleep time); (3) stimulus control therapy (go to bed only when sleepy, use bed/bedroom for sleep and sexual activities only, choose a consistent time to lie down and get up, avoid caffeine and stimulating activity in the evening); and (4) 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).

Cognitive-behavioral therapy (CBT) to treat concurrent symptoms such as pain or depression also may produce beneficial effects on CRF. Although the outcomes of an RCT of CBT for cancer pain in 131 patients demonstrated improvement in the outcomes of pain, the changes in fatigue were not statistically significant [214]. However, 2 RCTs ($n = 200$ cancer patients with major depressive disorder [215] and $n = 45$ women with metastatic breast cancer [220]) and a small case series ($n = 6$ women with metastatic breast cancer [221]) demonstrated that a CBT intervention for depression also resulted in statistically significant improvements in fatigue.

Structured Rehabilitation. The authors of several trials [229,232,284,308] and a systematic review [234] suggest that structured rehabilitation programs result in statistically significant and sustained improvements in fatigue, particularly in patients who have completed treatment and are in the survivorship phase. The rehabilitation interventions studied were multicomponent interventions comprising a structured combination of intensive exercise, physical training, sports, psychoeducation, and physical modalities, such as massage, mudpacks, and manual lymph drainage. In some studies, these therapies were delivered during the course of several weeks of inpatient rehabilitation.

In summary, although a fairly consistent pattern of improved fatigue outcomes has been demonstrated across this broad array of rehabilitative, psychoeducational, and supportive care interventions, many research-tested approaches are not routinely available in general oncology programs. Moreover, the authors of at least one study [254] suggest that programs that are too intensive may actually worsen a patient's CRF. Thus a deliberative selection of management strategies and tailoring of the program on the basis of the patient's current level of energy, attention, motivation, and place on the treatment trajectory are essential.

Pharmacologic Measures. Several pharmacologic agents (including paroxetine, venlafaxine, methylphenidate, donepezil, bupropion, and modafinil) have been evaluated for their effectiveness in reducing fatigue during and after cancer treatment [158]. The investigators of 4 trials examined the effectiveness of paroxetine in treating fatigue during and after cancer treatment with mixed results [29,179-181]. In 3 multicenter, randomized, double-blind, placebo controlled trials, the administration of 20 mg of paroxetine daily did not demonstrate a beneficial effect on fatigue outcomes, although improvements in depression and overall mood were noted in the paroxetine treatment group [29,179,180]. However, the authors of 2 small trials showed a trend towards a possible
benefit for either paroxetine [181] or venlafaxine [309] in treating fatigue in women who are experiencing hot flashes.

The use of methylphenidate or dexmethylphenidate to reduce CRF has been evaluated in 6 open-label, single-arm trials with small samples and in 4 RCTs. In all 6 single-arm trials of methylphenidate [172-177] and an RCT of dexmethylphenidate [169], improvements in fatigue outcomes were observed. However, an RCT of a patient-controlled dosing schedule for methylphenidate [172] and 2 RCTs of dexmethylphenidate [170,171] failed to demonstrate improvements in the outcome of fatigue. In one study [176], more than half of the patients experienced side effects, such as insomnia, agitation, anorexia, nausea and vomiting, or dry mouth; however, the authors of a recent retrospective review [310] suggest that the incidence of adverse effects may be less than 20% and that some side effects improve spontaneously despite continued treatment with methylphenidate.

The results of 4 small trials also suggest that the administration of donepezil, 5 to 10 mg/day [165,166], or bupropion sustained release at a dose of 100 to 150 mg/day [163,164] may be effective in limiting fatigue. However, in a controlled trial of donepezil in a sample with mixed tumor types [167], the authors did not observe improvements in fatigue outcomes. Additional rigorously designed trials are necessary to establish the efficacy of these pharmacologic agents in larger and more homogeneous samples of cancer patients and to determine whether the effects of bupropion are separate from its action as an antidepressant. The authors of several trials [192-194,311] also suggest that modafinil at a dose of 100 mg twice daily may be effective in treating fatigue and improving daytime wakefulness and cognitive function in patients during and after cancer treatment.

The authors of several trials also suggest that levocarnitine supplementation in patients who have low serum carnitine levels [186-190] is safe and potentially efficacious in treating CRF. Although the conclusions that can be drawn from these studies are limited by small sample sizes and by the absence of a double-blinded randomized study design, the results are encouraging and suggest that levocarnitine supplementation should undergo further study.

Treatment of Anemia with Erythropoiesis-stimulating Agents. The authors of meta-analyses and systematic reviews [158,312-318] suggest that patients receiving recombinant erythropoiesis-stimulating agents (ESAs) to correct anemia measured at less than 10 g/dL may experience increased vigor and diminished fatigue. However, there is only limited evidence that ESAs improve fatigue when anemia is less severe, and the use of these agents must be considered in light of emerging safety issues, including an increased risk of thrombotic events, hypertension, and pure red cell aplasia, and concerns that ESAs may decrease locoregional disease control and survival outcomes in particular tumor types [318-323]. Current national clinical practice guidelines [324] concluded that ESAs are not indicated for the treatment of CRF and restrict the use of ESAs for the treatment of anemia specifically related to myelosuppressive chemotherapy without curative intent.

National clinical practice guidelines [324,325] and product labeling from the U.S. Food and Drug Administration should direct the counseling and individualized management of patients with cancer- and chemotherapy-associated anemia, including an analysis of the risks and benefits of ESAs versus packed red blood cell transfusions. Practice guidelines and product labeling should also guide decisions about patient monitoring, treatment thresholds, dose reductions, treatment discontinuation, and the use of supplemental iron in patients receiving ESAs.

Complementary Therapies. There is emerging evidence to support the efficacy of yoga [277], relaxation [250,251,271], medical Qigong [269], biofield therapies such as healing touch and Reiki [227,326] in the management of CRF. Interventions such as massage, mindfulness-based stress reduction, acupuncture, and combined modality interventions that include aromatherapy, lavender footsoak, and reflexology are also supported by preliminary data [327]. These studies tended to be open label and/or uncontrolled, with no random assignment, and with small sample sizes, making it difficult to draw firm conclusions about efficacy. Of note, the studies in which the authors evaluated acupuncture and a combined aromatherapy, footsoak, and reflexology intervention included patients with advanced cancer who were at the end of life. If these approaches are determined to be effective in RCTs, they could represent alternatives for situations in which exercise or medication may not be possible.

Conclusion and Future Directions

Fatigue continues to be the most common symptom experienced by cancer patients receiving therapeutic agents and by cancer survivors. With continued progress in delineating the pathophysiology and etiology of CRF, we have also made gains in identifying interventions that are effective in reducing this symptom. The approach to improving CRF outcomes begins with a consistent, reliable assessment of the symptom by the use of psychometrically valid instruments. Attention to treating comorbidities that may be contributing to fatigue symptoms (eg, deconditioning, impaired sleep quality, concurrent symptoms, mood disturbances, and cardiovascular or endocrine disorders) is also essential. Our understanding of the distinct causative factors of CRF continues to evolve, and treatment approaches are largely empiric. Thus, the intervention approach for each patient is symptom-oriented and must be individualized and regularly reviewed and revised. A multimodal approach that addresses both central and peripheral fatigue and includes exercise, psychoeducational interventions, efforts to manage concurrent symptoms,
and interventions to improve sleep quality, together with the judicious use of medications such as modafinil, methylphenidate, and complementary therapies such as relaxation, massage, healing touch, or acupuncture offers the greatest likelihood of success. Such an approach is also consistent with evidence-based guidelines from the National Comprehensive Cancer Network [20] and the Oncology Nursing Society [156].

Although a wide range of pharmacologic and nonpharmacologic interventions have been studied, several recent systematic reviews [156-159] have noted that many of these interventions were only evaluated in uncontrolled studies with small samples. Moreover, the magnitude of change that can be demonstrated in response to an intervention is significantly eroded if trial designs fail to select for enrollment those patients experiencing at least moderate fatigue [328].

Preliminary evidence suggests that pharmacologic agents, including paroxetine, methylphenidate, donepezil, bupropion sustained-release, modafinil, ginseng, and levocarnitine, may have a role in the management of fatigue. Systematic development studies are needed to define the optimal dosing, gauge the toxicity profile, and determine the effectiveness of these agents in specific populations. Also warranted are rigorously designed and adequately powered randomized trials of therapies for fatigue that have shown initial promise such as structured rehabilitation, CBT for concurrent symptoms and insomnia, and interventions such as yoga, mindfulness-based stress reduction, and acupuncture. Research focused on developing and testing interventions specifically for patients with fatigue in the setting of advanced cancer and at the end of life also would fill a significant gap in our knowledge base. With a substantial body of evidence indicating that selected pharmacologic, rehabilitative, and supportive care interventions are effective for CRF, more research is needed to determine effective strategies to educate and support providers for widespread delivery of these interventions in the community, and to clarify the patient population and phase in the illness trajectory at which specific intervention will be most effective.

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