

Cancer-related fatigue: impact on patient quality of life and management approaches

Theresa Pluth Yeo^{1,2}
Shawna Cannaday¹

¹Thomas Jefferson University Hospital, Department of Surgery Thomas Jefferson University, ²Jefferson College of Nursing, Philadelphia, PA, USA

Abstract: Cancer-related fatigue is a common and distressing symptom that is present in the majority of cancer patients at some point during the disease course. Cancer-related fatigue has a profound influence on patients, affecting functional performance, mood, and one's overall quality of life. The etiology of cancer-related fatigue is multifactorial, involving a complex interplay of biological and body system factors. All cancer patients should be screened for fatigue, as it often coexists with other symptoms and its side effects may be underdiagnosed. Treatment modalities for cancer-related fatigue are still evolving. Current recommendations for management from national and international cancer experts and societies focus on patient and family education regarding cancer-related fatigue, exercise and physical activity, and psychosocial interventions. Pharmacologic interventions are less effective but may be helpful in a selected subset of affected individuals.

Keywords: evidence based practice, CRF, disease management, quality of life, exercise

Introduction and background

The American Cancer Society estimates that there will be 18 million cancer survivors in the United States alone by 2022.¹ The traditional definition of a cancer survivor is any living person who has ever received a diagnosis of cancer, beginning at the time of diagnosis until the end of life is reached.² Recognizing that survivorship is a multistage process with acute, extended, and permanent phases, patients in the cancer journey experience a plethora of symptoms and therapy-related side effects. One of the most prevalent symptoms is cancer-related fatigue (CRF). The National Comprehensive Cancer Network (NCCN) defines CRF as “a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.”³ CRF was accepted by the International Classification of Diseases, Tenth Revision, Clinical Modification in 1999; this acceptance has improved the ability to characterize the incidence and prevalence of the condition.⁴ CRF is typically not relieved simply by rest and this distinguishes it from many non-cancer-related forms of fatigue.⁵ CRF is caused by the cancer itself and is present in the majority of patients at the time of the cancer diagnosis. CRF often persists following cancer surgery and may intensify during chemotherapy and radiation therapy, morphing into cancer therapy-related fatigue. A number of studies have documented that fatigue occurs in 30%–70% of all patients at some point during the cancer journey⁶ and that it may continue after cancer treatment has been completed. This wide variation may represent differences in how fatigue is defined and the measurement tool used. The incidence of CRF in

Correspondence: Theresa Pluth Yeo
Jefferson Department of Surgery, 1025 Walnut Street, Suite 605B, College Building, Philadelphia, PA 19107, USA
Tel +1 215 955 5542
Fax +1 215 923 6609
Email theresa.yeo@jefferson.edu

survivorship cohorts is reported to be between 10% and 30%.⁷ In patients with metastatic disease, the prevalence of CRF exceeds 75%.³ The etiology of CRF is multifactorial, with varying degrees of contribution from biological cancer factors, cancer treatment, immune system dysregulation, hypothalamic–pituitary–adrenal axis dysfunction, secondary anemia, opioid medications, anorexia/cachexia, poor sleep quality, and cognitive dysfunction.^{8–10} CRF affects one's perceived overall quality of life by impacting physical, functional, and cognitive domains.

The current recommendations for management of CRF include: patient and family education, self-care, nonpharmacologic interventions, and pharmacologic treatment.^{3,11–14} Several systematic reviews have indicated that the effectiveness of pharmacologic regimens is limited and that nonpharmacologic interventions are moderately effective.^{15,16} The purpose of this article is to review the current knowledge about CRF and cancer therapy-related fatigue and to discuss the evidence regarding best practices for their management.

Impact on quality of life

Cancer therapy-related side effects are well documented and include: chest pain, nausea/vomiting, stomatitis, diarrhea, constipation, fever, fatigue, anorexia, dyspnea, dermatitis, neurosensory or motor problems, bleeding, palmar-plantar syndrome, pain, bruising and extravasation, as well as other less common side effects.¹⁷ The presence of any or a combination of these side effects can have a detrimental effect on one's well-being, body image, and self-perception. CRF is often reported as the most distressing symptom¹⁸ while pain is the most feared side effect of cancer therapy. Although fatigue and a lack of energy are frequently reported by cancer patients and cancer survivors, the impact on one's quality of life had not been well described in a large patient sample until the 1996 Fatigue Coalition⁶ reported on the functional impact of CRF. The impact of CRF on physical, psychosocial, and economic and occupational domains was further evaluated in the 2000 Fatigue Coalition follow-up survey.⁶ Diminished energy levels, needing to slow down, and a subjective sense of tiredness were reported by 80% of the respondents.⁶ The survey also sought to elucidate the psychosocial effects of cancer therapy. Patients commonly reported decreased overall motivation, needing to push oneself, and feeling sad, frustrated, and irritable. Cognitive function was also affected, manifested as decreased concentration, trouble with memory, and difficulty keeping dates straight. Patients who were still employed were absent from work 4.2 days per month, during and after treatment had ended.⁶ Patients identified the following activities as the

most difficult: walking distances, doing household chores, cleaning the house, socializing, and preparing food. In a separate investigation, Lis et al found that increasing CRF was an independent predictor of overall dissatisfaction with life.¹⁹ Those individuals reporting fatigue levels in the severe range (7–10/10) were least likely to feel satisfied with life (odds ratio 0.28, 95% confidence interval: 0.09–0.91, $P=0.03$).

Therapy-related fatigue

Estimates of the occurrence of cancer therapy-related fatigue vary from 30% to 91% in patients receiving chemotherapy, 25% to 83% in patients receiving radiation therapy, and 59% to 83% in patients undergoing combined chemo- and radiation therapy.⁶ The use of different chemotherapeutic agents and regimes may account for some of this variance. When patients were queried about the most bothersome side effects of chemotherapy, nausea was first (34%), followed by fatigue (18%), with hair loss third (11%).⁶ However, when asked which side effect had the greatest impact on their life after completion of therapy, fatigue was number one, with 54% reporting fatigue that lasted more than 2 weeks after the completion of chemotherapy.⁶ CRF may linger after cancer treatments have been completed, being reported for up to a year in many cancer survivors.

Management principles in CRF

CRF has been underappreciated as a common and persistent symptom of cancer and cancer treatment. Health care providers often underestimate the frequency and intensity of CRF and feel challenged in treating it.²⁰ James et al conducted two surveys of cancer patients undergoing either radiation therapy or chemotherapy. In Survey 1, 29 patients reported experiencing fatigue during treatment, but only two received any advice on managing CRF. In Survey 2, which included 148 patients, 86% stated that they were advised about the risk of CRF; however, only 67% were assessed at their visit or were given recommendations for CRF.²⁰

In the Fatigue Coalition survey, physicians were given recommendations for treating CRF.⁶ The standard of care in CRF has been set forth by the NCCN and includes recognition that fatigue is a complex entity, typically occurring in conjunction with pain, insomnia, anxiety, distress, and, often, anemia, as part of defined symptoms clusters (Table 1).^{3,21} The NCCN, the Oncology Nursing Society (ONS), the American Society of Clinical Oncology (ASCO), and the Pan-Canadian Practice Guideline¹⁰ provide evidence-based guidelines for the management of CRF and cancer therapy-related side effects. These four guidelines are generally congruent in their recommendations, though some variations

Table I NCCN CRF Standard of Care overview

- Assess fatigue at initial encounter and evaluate for systemic causes.
- Reassess fatigue at regular intervals during cancer treatment and after treatment has ended.
- Manage fatigue according to established clinical guidelines.
- Patients and their families should be aware that CRF management is an integral part of cancer care.

Notes: Adapted from Berger AM, Abernethy AP, Atkinson A, et al. Cancer-related fatigue. *J Natl Compr Canc Netw*. 2010;8(8):904–931.³ To view the NCCN complete Standard of Care for CRF, see Berger et al.³

Abbreviations: CRF, cancer-related fatigue; NCCN, National Comprehensive Cancer Network.

do exist. Managing CRF requires a coordinated effort by all members of the health team including physicians, nurses, advanced practice nurses, social workers, physical therapists, cancer rehabilitation specialists, nutrition support teams,

and mental health providers. The basic recommendations for CRF intervention include ongoing assessment; non-pharmacologic interventions, including patient and family education on CRF and self-care strategies; and pharmacologic treatment^{3–14} and will be discussed in the following sections (Figure 1).

Ongoing patient assessment

All cancer patients should be screened for CRF at their initial health care encounter in order to establish a baseline and at subsequent visits to monitor trends. Many cancer care practitioners consider fatigue as the sixth vital sign, following temperature, pulse, blood pressure, respirations, and pain level. A numeric rating scale (0= none to 10= worst)

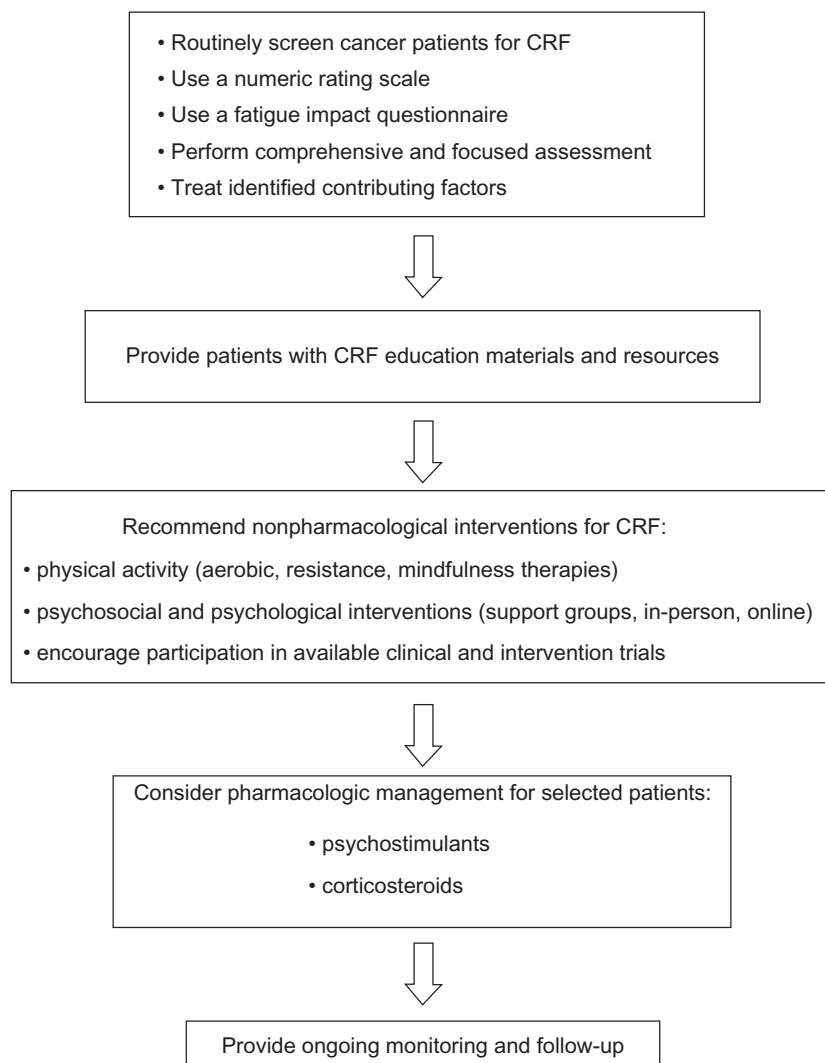


Figure 1 Guidelines for management of CRF.

Notes: Adapted from NCCN Clinical Practice Guidelines. *Cancer-Related Fatigue*. Version 1.2014. Available from: http://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf. Accessed January 25, 2015.¹² And from Mitchell SA, Clark JC, DeGennaro RM, et al. Fatigue [webpage on the Internet]. Pittsburgh: Oncology Nursing Society; 2011–2014. Available from: <http://www.ons.org/practice-resources/pep/fatigue>. Accessed January 26, 2015.¹⁴

Abbreviation: CRF, cancer-related fatigue.

is considered a valid screening and monitoring tool and is recommended by the NCCN (Table 2).^{3,12} Research has shown that the fatigue score of 7/10 or higher is a significant break point in that it correlates with a marked decrease in physical functioning.²² The initial encounter should include a clinical assessment and physical examination of the patient to determine other possible underlying causes for CRF or conditions that will aggravate CRF. Clinically evident expressions of CRF may include: weakness, diminished mental capacity, insomnia or hypersomnia, and emotional lability.²³ The evaluation should include consideration of the disease stage, evidence of disease spread or recurrence, current and past treatment received (both for cancer and psychiatric disorders), current medications, over-the-counter preparations, herbal remedies used, and a review of associated symptoms such as pain, depression, anxiety, sleep disturbance, shortness of breath, change in appetite, and assessment of alcohol or substance misuse.^{3,11,13} The provider should also assess for the presence of comorbidities that could contribute to CRF, including: cardiac dysfunction, pulmonary disease, anemia or pancytopenia, renal or liver failure, psychological conditions, neurological problems, and endocrine disease (diabetes, thyroid disorders, or adrenal insufficiency).^{3,13} A fatigue-specific assessment tool which is reliable and well validated such as the FACIT-Fatigue Scale,²² the Brief Fatigue Inventory,²³ the Piper Fatigue Scale,²⁴ or the European Organization of Research and Treatment-Related Quality of Life Core Questionnaire (EORTC-QLC30),²⁵ among others, should be used to document fatigue frequency and intensity in a standardized fashion (Table 3).^{26,27} The Medical Outcomes Short-Form 36 or 12,^{28,29} or the Eastern Cooperative Oncology Group (ECOG) Performance Status rating scale,³⁰ are acceptable to use in combination with a fatigue-intensity tool (ie, numeric rating scale)³¹ to document the effect of CRF on health-related quality of life. The Medical Outcomes Short-Form 36 assesses eight domains: cognitive functioning, sleep, health distress, social support, family and marital functioning, sexual functioning, physical symptoms, and psychological symptoms,²⁸ while the ECOG scale is a more general measure of functional capacity.³⁰

Table 2 Fatigue numeric rating scale (0–10)

- 0= no fatigue
- 1, 2, 3= mild fatigue
- 4, 5, 6= moderate fatigue
- 7, 8, 9, 10= severe fatigue

Note: Reproduced from Berger AM, Abernethy AP, Atkinson A, et al. Cancer-related fatigue. *J Natl Compr Canc Netw*. 2010;8(8):904–931.³

Nonpharmacological interventions

A number of systematic reviews have concluded that non-pharmacological interventions are effective in reducing CRF both alone and in combination with selected pharmacologic therapies.³² Nonpharmacologic interventions for the management of CRF are varied and include home-based and supervised exercise, patient and family education and psychological and psychosocial therapy, distracting activities, complementary therapies, and nutritional counseling.

Exercise/physical activity

Replacing the word “exercise” with, simply, the word “movement” may be less intimidating to cancer patients, many of whom (like 75% of adult Americans) are not regular exercisers.³³ Movement is defined as any bodily activity produced by skeletal muscle contraction that increases energy use above the baseline level and requires tissue oxygenation.⁷ Planned, structured, and repetitive body movement has been found in a number of patient populations to decrease CRF, improve mood, and increase one’s functional capability. The ONS’s Putting Evidence into Practice (PEP) guidelines were updated in 2014.³⁴ Physical activity/exercise/movement are termed “effective” in reducing CRF in more than 40 meta-analyses and randomized controlled trials (RCTs). The populations included in the studies included patients with varied cancer types and patients undergoing treatment utilizing radiation, chemotherapy, or hematopoietic stem cell transplantation.³⁴ A 2012 Cochrane Review of exercise for the management of CRF considered 56 published RCTs on the topic.³⁵ The study samples included patients with breast, prostate, colorectal, head, and neck cancers and hematologic malignancies, although the majority of the studies were performed in breast cancer patients. A significant improvement in CRF was found with aerobic exercise programs but not for resistance training or mind–body techniques. Lack of long-term follow-up regarding exercise maintenance and insensitive outcome measures may have limited the ability to detect individual benefits from the programs.³⁶ None of the studies included biomarkers (proinflammatory cytokines) of the interrelated pathways of fatigue, such as the inflammatory, nervous system, metabolic and hypothalamic–pituitary–adrenal axis. Correlating this data will allow the development of strategies and pharmacologic treatments that more specifically target the offending pathway. No study in the Cochrane Review reported complications, such as falls or dizziness that were related to the exercise regimen.³⁵ It is possible that the occurrence of adverse events contributed to patients dropping out of the studies or failing to complete the program. Patients with comorbid conditions that would limit physical

Table 3 Summary of selected fatigue and quality-of-life assessment tools

Name of tool and description	Reliability and validity	Typical completion time	Advantages of tool
<p>Fatigue Visual Numeric rating scale.²³ Single item asks severity of fatigue at the present time rated on a 0–10 rating scale where 0= no fatigue and 10= worst possible fatigue.</p>	<ul style="list-style-type: none"> • Useful for obtaining ordinal preferences. • Prone to bias when used as the only measure of fatigue. 	<1 minute	<ul style="list-style-type: none"> • One-dimensional measure of fatigue. • Use only as a screening tool. • Provides serial monitoring of fatigue severity. • Best used in conjunction with an in-depth fatigue or symptom questionnaire.
<p>FACIT-Fatigue Scale.²² Thirteen-item fatigue subscale of the FACT-F tool. Developed in 1997 from 32 items submitted by five medical experts and 221 items from 14 cancer patients.</p>	<p>Reliability: high test–retest reliability, $r=0.87$.</p> <p>Internal consistency: $\alpha=0.93–0.95$.</p>	<5 minutes	<ul style="list-style-type: none"> • Independent, one-dimensional measure of fatigue. • Asks patients to consider fatigue in context of last 7 days.
<p>Revised Piper Fatigue Scale.²⁴ Twenty-two-item questionnaire that assesses four subscales (behavioral/severity, affective meaning, sensory, and cognitive/mood).</p>	<p>Reliability: $r=0.30–0.70$.</p> <p>Internal consistency: $\alpha=0.97$.</p>	~10–15 minutes	<ul style="list-style-type: none"> • Multidimensional measure of fatigue. • Allows accurate measurement and can be followed to evaluate efficacy of cancer-related fatigue interventions.
<p>Medical Outcomes Study SF-36.²⁸ Thirty-six-item questionnaire that address eight domains (cognitive functioning, sleep, health distress, social support, family and marital functioning, sexual functioning, physical symptoms, and psychological symptoms).</p>	<p>Reliability: $r=0.8–0.93$.</p> <p>Internal consistency: $\alpha\geq 0.70$.</p>	~10–15 minutes	<ul style="list-style-type: none"> • Valid and reliable multipurpose general health survey. • In addition to the eight domains assessed, two psychometrically based composite scores, PCS and MCS, are generated when using the Quality Metric™ Scoring Software. These scores are considered a valid representation of health-related quality of life.
<p>Medical Outcomes Study SF-12.²⁹ Twelve-item multidimensional assessment of general health. Derived from the SF-36.</p>	<p>Reliability: $R^2=0.91–0.92$.</p> <p>Internal consistency: $\alpha=0.93–0.98$.</p>	~2 minutes	<ul style="list-style-type: none"> • Shorter than the SF-36. • Retains accuracy of the PCS and MCS composite scores. • Precision increases with large sample sizes. • Correlations between SF-12 and SF-36 versions of PCS and MCS were 0.95 and 0.97.
<p>ECOG Performance Status rating scale.^{30,70,71} The ECOG scale is a six-level assessment tool that provides a measure of physical functioning by determining the degree to which cancer patients are able to participate in activities of daily living, and their need for rest during the day.</p>	<ul style="list-style-type: none"> • Considered to have moderate reliability and validity. • When compared head-to-head with the Karnofsky Performance Status scale, in a sample of patients with lung cancer, the ECOG scale had better prognostic ability.⁷⁰ <p>Reliability: $r=0.75$, $P<0.00–1$.</p> <p>Internal consistency: $\alpha=0.6$.</p>	<2 minutes	<ul style="list-style-type: none"> • Widely used global measure to assess functional capability. • Used both in clinical oncology and clinical trials.
<p>Brief Fatigue Inventory.²³ Nine-item single-dimension report of subjective fatigue.</p>	<p>Reliability: $r=0.88$, $P\leq 0.001$.</p> <p>Internal consistency: $\alpha=0.96$.</p>	<2 minutes	<ul style="list-style-type: none"> • Correlates well with measures of performance status, physiologic markers of anemia, and nutritional status. • Provides a global fatigue score.
<p>EORTC-QLC30.²⁵ Thirty-item health-related quality-of-life questionnaire that measures five functions (physical, role, cognitive, emotional, and social) and nine symptoms (fatigue, pain, nausea and vomiting, dyspnea, loss of appetite, insomnia, constipation, diarrhea, and financial difficulties).</p>	<p>Validity: three approaches used:</p> <ol style="list-style-type: none"> 1. interscale correlations statistically significant; 2. performance status items statistically significant in the expected direction; and 3. functional and symptom measures were discriminatory. <p>Internal consistency: $\alpha=0.70$.</p>	~10–15 minutes	<ul style="list-style-type: none"> • A comprehensive measure of quality of life. • Strong prognostic value.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EORTC-QLC30, European Organization of Research and Treatment-Related Quality of Life Core Questionnaire; MCS, Mental Component Score; PCS, Physical Component Score; SF-12, Short-Form 12; SF-36, Short-Form 36.

activity should consult their physician or oncology provider before participating in an exercise program.

The ONS PEP guidelines and the NCCN both recommend including physical activity in the treatment plan for CRF.^{12,14} Low-intensity aerobic exercise has been studied extensively, mainly in breast, prostate, and hematological malignancy patients,^{37,38} and significant improvements in fatigue and pain levels were demonstrated. A progressive home walking program, which emphasized starting at low intensity and gradually increasing distance and/or walking time, was well tolerated and significantly reduced fatigue and pain levels in both postoperative resected breast cancer and pancreas cancer patients.^{21,36} Patients in the walking intervention group had higher self-reported quality-of-life scores than those in the control group.²¹ However, neither the most effective type of exercise nor the frequency and intensity needed to optimally reduce CRF have been determined. Before initiating any exercise program, home-based, gym-based, or part of a cancer rehabilitation program, the level of deconditioning present must be assessed.³⁹ Areas to consider are: pre-diagnosis level of activity, current ability to accomplish activities of daily living, and physical impediments that would warrant exercise modifications. The recent ASCO CRF guidelines state that low-intensity exercise can be initiated without physician approval, but very deconditioned individuals will benefit from referral to a physical rehabilitation program.¹³ Cancer rehabilitation is a growing field that recognizes cancer as an acute and chronic condition and seeks to minimize the impact of cancer treatment and disease-related side effects.³⁴ The American College of Sports Medicine established a certification program for fitness experts working with cancer survivors.³⁹ These types of programs, when administered to cancer survivors, can help reduce CRF and the decline in functional capacity that often accompanies CRF. Longitudinal studies documenting improvement in CRF and other cancer side effects in cancer rehabilitation programs are needed. Based on the multitude of available evidence, health care providers should feel comfortable encouraging patient participation in physical activity during the cancer journey.

Patient and family education and self-care strategies

All cancer patients and their families should receive education and counseling about the association between cancer, cancer therapy, and CRF.¹³ Many patients are reluctant to mention their fatigue or lack of energy issues to their providers because they believe that this is to be expected or that it is not important or related to their cancer. Patients

may worry that their treatment will be halted or delayed if they report fatigue.³ Of note, 78% of cancer patients queried reported an increased need for sleep, typically requiring an additional 3 hours of sleep per day.⁶ Patients should be given information about self-care strategies that may help them manage their CRF. These strategies include: keeping a daily log of symptoms and feelings, recording fatigue level (0–10 scale), and tracking activities of daily living, sleep/nap schedule, and movement (exercise). Energy conservation is important and can be enhanced by setting daily priorities for what needs to be accomplished and postponing nonessential duties, maintaining a realistic pace, delegating activities if possible, scheduling activities for times of peak energy, and limiting daytime naps so as not to interfere with nighttime sleep. Intentionally promoting distracting activities such as listening to music, playing card or board games, watching educational television, and reading can divert attention from CRF and energize patients.^{3,32}

Fatigue and depression are often reported as concurrent symptoms,⁴⁰ but patients and their families should be aware that they are independent conditions; one does not predict the other. Patients should be informed that needing more sleep is usual and not a cause in itself for worry. However, ongoing sleep disturbances may be a sign of depression. Cancer patients have been observed to have prevalence rates of major depression that are higher than in the general population.⁴¹ Depression rates are highest for those with pancreatic cancer and oropharyngeal cancers.⁴¹ Persistent depression should be evaluated and treated by a mental health professional. Medical oncologists, palliative care specialists, and psychiatric social workers, as well as oncology clinical nurse specialists, nurse practitioners, and physician assistants, are positioned to assist patients with uncomplicated emotional issues, anxiety, and depression. Depending on the American state and the country in which one practices, physicians, psychiatric clinical nurse specialists, and nurse practitioners will be able to prescribe antidepressant medications when indicated.

Psychologically based interventions

Psychologically based interventions (also called psychosocial interventions) include methods that focus on cognition, coping skills, and behavior. Jacobsen et al and Goedendorp et al reviewed psychologically based interventional studies and concluded that interventions that alter cognition, improve coping skills, and change behaviors are more effective in decreasing CRF than physical activity and medications.^{27,42} Moreover, the ONS PEP guidelines state that psychoeducational interventions are “likely to be effective”

based on more than 12 RCTs and quasi-experimental studies that have demonstrated positive effects on fatigue outcomes.³⁴ In some studies, CRF was not improved but other symptoms, such as psychological issues, activity levels, and sleep quality, did improve. Psychological strategies that were found to be beneficial were: cognitive behavioral therapy, group psychotherapy, and psychoeducational and supportive-expressive techniques. They determined that the most important elements to incorporate in the treatment plan were patient education about the nature of CRF and self-care techniques to conserve energy and boost energy, as well as activity management that focuses on balancing activity and rest intervals. Coping strategies to lessen one's focus on CRF were also beneficial.

One example of an effective psychologically based intervention for cancer therapy-related fatigue was recently reported by Ream et al.⁴³ They determined that CRF worsened the week following chemotherapy and that it became cumulative over the course of chemotherapy, often resulting in being bedridden by the end of treatment. A telephone version of Beating Fatigue, a psychologically based intervention for CRF that used a trained cancer nurse, was implemented. The intervention consisted of providing patients with a publication that addressed coping with fatigue, facilitating self-evaluation, and establishing personal goals and included structured telephone interviews. The researchers found a statistically significant reduction in fatigue intensity and fatigue-associated distress in those who participated in the intervention compared to those who did not participate. One's sense of self-efficacy in managing their fatigue and anxiety was also improved. Of note, however, depression did not improve with the intervention. A subset of patients in the study felt that reflecting on their CRF and keeping a daily log of fatigue and associated feelings increased their awareness of CRF, which in turn allowed them to take control. The telephone call itself from a trained cancer nurse had a therapeutic benefit. The technique of motivational interviewing which emphasizes the benefits of managing CRF through maintaining and enhancing one's physical activity was utilized in the study and provides a framework for assisting patients with CRF during chemotherapy.

An example of supportive-expressive therapy is professional or self-help support groups. Group-based interventions can significantly impact fatigue. Many self-help groups are available via the Internet. In 2008, there were more than 600 online breast cancer support groups with more than 1 million followers. Millions of people rely on the Internet for information about cancer and to identify

resources for treatment and symptom management and for social networking with other cancer survivors,⁴⁴ despite ongoing concerns about monitoring the content of websites. In 2013, it was estimated that 85% of American adults use the Internet,⁴⁴ and in 2008, 60% of patients relied on the Internet as their first source of information.⁴⁵ The American Cancer Society piloted an online cancer fatigue class in 2010⁴⁶ which was positively perceived, and significant improvements in fatigue knowledge were demonstrated post hoc. Yun et al demonstrated the efficacy of an RCT of a web-based CRF education program for 273 long-term cancer survivors (off therapy for 24 months), who were still experiencing fatigue.⁴⁷ The 12-week course, Health Navigation, covered six strategic areas: energy conservation, physical activity, nutrition, sleep hygiene, pain control, and distress management. Patients in the intervention group experienced clinically meaningful improvement in anxiety, severe fatigue, and global quality of life. Those with the most severe symptoms experienced the greatest improvement. This study, the first to use a web-based program for CRF, indicates that the Internet is an important route for successful self-management of CRF.

The following four complementary interventions are now recommended in the 2014 ONS PEP guidelines due to accumulation of study evidence demonstrating their effectiveness in reducing CRF: 1) progressive muscle relaxation and relaxation breathing with or without guided imagery or distraction; 2) yoga practices; 3) meditation; and 4) mindfulness stress reduction.³⁴ Many patients are eager to try these techniques, which are increasingly available even in rural areas and can be accessed by the Internet as well. Although there is evidence that acupuncture, acupressure, and self-acupuncture are effective in reducing CRF and improving quality of life,⁴⁸ caution is recommended when advising patients regarding these therapies as many of the study sample sizes were small, with short follow-up times, and with notable variations in techniques used by the acupuncturists. Preliminary data indicate that expressive writing, biofeedback, viewing art, listening to music, animal therapy, cranial stimulation, exposure to nature, distraction, tai chi, qigong, aromatherapy, lavender foot soaks, and reflexology are promising in reducing CRF.³⁴ Morning exposure to bright light also appears promising as an adjunct therapy for CRF.⁴⁹ Four studies have demonstrated lessened CRF and improved quality of life in study populations that include cancer patients with mixed diagnoses.^{49–52} More rigorous study design and methodology are needed before these strategies are recommended as part of the ONS PEP guidelines.

Nutrition and supplements

Maintaining adequate nutrition can be a difficult for patients undergoing active adjuvant cancer therapy. Anorexia, nausea and vomiting, bowel dysregulation, stomatitis, and alterations in one's sense of taste or smell all lessen the appeal of food and decrease the pleasure of eating. Maintaining energy balance and preventing excessive weight loss are the goals for those in active cancer treatment and may lessen therapy-related adverse effects. The American Cancer Society recommends smaller, more frequent meals to increase food intake.⁵³ Commercially prepared or homemade nutritious snacks and drinks may be helpful and are soundly recommended.

Patients frequently ask their health care providers about the use of vitamins and nutritional supplements. There is controversy regarding the role of antioxidant supplements. Antioxidants repair cellular oxidative damage to cells, including cancer cells. Melatonin may enhance the effect of chemotherapy. There is not a clear answer regarding the use of antioxidants, therefore patients are cautioned not to exceed the daily recommended intake of vitamins C and E.⁵³ A number of nutritional supplements and herbal remedies have been evaluated to assess their efficacy in reducing CRF. These include levocarnitine, vitamin supplements, high-dose vitamin C, lechtin-standardized mistletoe, megestrol with omega-3 fatty acids, protein supplements, guaran, valerian, and Chinese herbal medicines. The data indicate that improvement in CRF was inconsistent and many of the trials described in this review article may have been biased from nonrandomized study designs, open-label drug use, small samples, and testing multiple secondary endpoints.¹⁴ Therefore, these supplements are not recommended at this time to be used for reduction of CRF. An 8-week course of Wisconsin ginseng (2,000 mg daily) was well tolerated in a double-blind placebo-controlled trial and improved CRF.⁵⁴ The ONS PEP guidelines have termed ginseng as "likely to be effective" in reducing CRF.¹⁴

Pharmacologic management

The effectiveness of pharmacologic (prescription medications) treatment for CRF has been limited to specific patient populations and has been generally disappointing. Patients experiencing the most severe fatigue and greater constellation of symptoms (pain, nausea, anorexia, depression, anxiety, or sleep disturbances) have derived the most benefit from stimulant, nonstimulant, and erythropoiesis-stimulating agents, though study results are mixed. The ONS PEP guidelines term pharmacological interventions "effectiveness not established".¹⁴

Psychostimulants

The use of methylphenidate, a psychostimulant used in the treatment of attention-deficit disorder, has been the subject of controversy for a number of years. It is the most studied pharmacological agent for treatment of CRF. Both methylphenidate and dexamphetamine derive their benefit from decreasing drowsiness and increasing activity. Bruera et al in 2003 compared methylphenidate (5 mg every 2 hours) to placebo and used the FACIT-Fatigue Scale to measure CRF levels.⁵⁵ Fatigue intensity improved in both groups over a 7-day study period but there were no differences in fatigue scores, suggesting a positive placebo effect. A 2010 RTC using long-acting methylphenidate also did not find a benefit for CRF patients.⁵⁶ Kerr et al found a decrease in fatigue with the use of methylphenidate, but five larger RCTs did not find a benefit.⁵⁷ Minton et al conducted a systematic review and meta-analysis of four psychostimulant trials using methylphenidate and one with dexamphetamine for CRF in 2011 and concluded that there may a slight reduction in CRF with methylphenidate but that the potential side effects, adrenal suppression and alterations in bone metabolism, outweighed the benefits.¹⁶

Modafinil is another psychostimulant that has been used to treat CRF. Several RCTs have reported conflicting results. Spathis et al found no difference between the modafinil and the placebo groups in terms of CRF improvement.⁵⁸ A 2010 RCT of 877 cancer patients with hematologic malignancies, lung cancer, colorectal cancer, and gynecologic cancers found that 95% of the patients, when queried, expected to have fatigue while undergoing chemotherapy or radiation therapy.⁵⁹ Patients were randomized to either the non-amphetamine stimulant (modafinil) group (n=431) or the placebo group (n=436). They found that modafinil was most effective in patients with the most severe fatigue levels (>7/10). Further, their results confirmed other findings in studies of brain cancer and breast cancer patients, in that modafinil reduced fatigue intensity and lessened daytime sleepiness, but did not improve depression. These results suggest that while fatigue and depression often co-occur in cancer patients, the underlying bio mechanisms are not identical.

Selective serotonin reuptake inhibitors

The selective serotonin reuptake inhibitors (SSRIs), particularly paroxetine (PaxilTM), are often used in cancer patients experiencing CRF and depression.⁶⁰ Paroxetine was previously found to be effective in treating depression and reducing hot flashes in women with breast cancer, but it had no significant effect on CRF.⁶¹ More recently, paroxetine has been shown

to have weak estrogenic effects and behaves as an endocrine disrupter.⁶² About 70% of female breast cancers are sensitive to estrogen, and the use of paroxetine and other similar SSRIs could contribute to the development of breast cancer.⁶¹

In women already diagnosed and treated for estrogen-positive breast cancers, tamoxifen is used to reduce the risk of breast cancer recurrence.⁶³ Some of these women are also treated with SSRIs for depression. Another SSRI risk is related to drug metabolism effects that arise when using the combination of an SSRI and tamoxifen. Both the SSRIs and tamoxifen are metabolized by cytochrome P450 2D6 (*CYP2D6*). SSRIs have the potential to inhibit *CYP2D6* activity thereby reducing the effectiveness of tamoxifen.⁶² Lash et al evaluated the effect of the SSRI citalopram on tamoxifen.^{60,63} They concluded that citalopram has the least anti-*CYP2D6* activity of the SSRIs and, in registry studies, it did not increase the risk of breast cancer recurrence.^{60,63} Providers considering use of SSRIs in women with estrogen-positive breast cancers should be familiar with these data and should avoid the use of known *CYP2D6* inhibitors in hormone receptor-positive breast cancers.

Corticosteroids

Corticosteroids are the most used drug for relief of adverse symptoms in cancer patients, particularly those patients receiving palliative care, where the frequency of use is 32%–80%.⁶⁴ The benefit from corticosteroids is derived from its anti-inflammatory properties and its modulatory effects on the proinflammatory cytokines (interleukins 6 and 1b, tumor necrosis factor- α), prostaglandins, and dopamine.⁶⁵

A few RCTS conducted in the 1980s and 1990s indicated that low-dose methylprednisolone (32 mg per day) produced modest reduction in fatigue.⁶⁵ Unfortunately, many of these studies did not assess CRF as the primary outcome metric or did not use validated measurement tools to assess CRF. A 2013 RCT compared dexamethasone (4 mg twice a day) to placebo in 83 advanced-stage cancer patients⁶⁶ and found that both groups had significant improvement in fatigue scores, but only the dexamethasone group experienced improvement in physical distress scores. These results should be interpreted with cautious optimism favoring the use of steroids in palliative care cancer patients.

Progestational steroids have been used to treat anorexia, cachexia, nausea, and fatigue based on older work. Minton et al reviewed four studies on progestational steroids used for anorexia and cachexia; fatigue was a secondary outcome. A significant difference was found between pregestational steroids and placebo in improving CRF.¹⁵

Erythropoiesis-stimulating agents

Erythropoiesis-stimulating agents (ESAs) are effective for treating anemias in cancer patients and may reduce fatigue and improve other symptoms, such as shortness of breath, when the hemoglobin is less than 10 g/dL.⁶⁷ The use of ESAs has been documented to significantly improve CRF and, in some studies, quality of life, when a hemoglobin of 11–12 g/dL is achieved.^{15,67} Concerns have been raised over the safety of ESAs as an increased risk of thromboembolic complications and death has been observed in some cancer patients.⁶⁷ ASCO and the American Society of Hematology recommend that ESAs should not be used unless cancer patients are receiving concurrent chemotherapy, except in certain circumstances, such as decreased cardiopulmonary reserve in a patient with a hemoglobin less than 10 g/dL.⁶⁸ Therefore, while the use of ESAs is appropriate when the hemoglobin is below the recommended level, its use is discouraged for milder forms of anemia and in patients with known thromboembolic issues.

Summary: implications for practice

CRF, a multidimensional condition characterized by subjective findings such as tiredness, lack of energy, and weakness, is generally under-recognized in clinical practice and therefore undertreated. The best therapy for CRF is neither obvious nor intuitive. A wide range of strategies have been employed from pharmacologically based to nonpharmacological interventions. A 2012 review of the literature evaluated over 170 studies of cancer patients with fatigue.⁶⁹ Exercise had the strongest empirical evidence, with physical activity providing moderate benefit in CRF patients. Psychological interventions, particularly those that provided patient education about CRF, coaching on self-care measures and activity management, showed moderate patient benefit. Enthusiasm for pharmacologic measures is limited, with much conflicting evidence about currently available medications. It is challenging to recruit fatigued cancer patients for clinical and intervention trials and difficult to conduct the studies. Many studies have only included patients with moderate fatigue and not those with severe fatigue, thereby excluding those in most need. There is a critical need for basic research that elucidates the underlying mechanisms of CRF.

Providers should gain familiarity with the NCCN and ONS PEP guidelines for management of CRF, as well monitor the medical and nursing literature for published studies of advances in the treatment of CRF. Whenever clinical trials or drug trials are available at an accessible institution, cancer patients with CRF should be referred and encouraged to

participate in those investigations. Management of patients with CRF, whether they have active disease or are in disease-free remission, should be individualized using the available national and oncologic societal guidelines, based on the individual's overall health status, type and stage of cancer, therapy received, and their personal preferences. Survivorship care plans should address CRF and related issues of concern. As more cancer survivors transition from specialized oncologic care to community physicians and nurse practitioners for their care, it is imperative to translate knowledge of the late and long-term effects of cancer and cancer therapy into useful information for providers. Perhaps more important is to provide patients and their families with lifestyle education and guidance programs on the benefits of diet, exercise, and psychosocial interventions to effectively manage CRF and other symptoms to enhance survival and quality of life.

Disclosure

The authors report no conflicts of interest in this work.

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