Clinical Assessment and Management of Cancer-Related Fatigue
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ABSTRACT

• **Objective:** To review the evidence on interventions for managing cancer-related fatigue (CRF) and provide evidence-based guidance on approaches to its management.

• **Methods:** Nonsystematic review of the literature.

• **Results:** Several theories have been proposed to explain the biology of CRF, but there is no single clear mechanism that can be targeted for therapy. The approach to patients begins with screening for fatigue and assessing its intensity, followed by a thorough history and examination to determine whether any reversible medical conditions are contributing to fatigue. Management of underlying medical comorbidities may help some patients. For patients whose fatigue persists, pharmacologic and nonpharmacologic treatment options are available. Pharmacologic options include psychostimulants, such as methylphenidate and modafinil, and corticosteroids. Nonpharmacologic approaches include exercise, cognitive behavior therapy, yoga, acupuncture, and tai chi.

• **Conclusion:** We recommend an individualized approach, often with a combination of the available options. Patients need to be evaluated periodically to assess their fatigue, and since cancer-related fatigue affects survivors, long-term follow-up is needed.

Key words: fatigue; cancer; pro-inflammatory cytokines; nonpharmacologic; psychostimulants.

Fatigue is a common distressing effect of cancer [1]. It impairs the quality of life of patients undergoing active cancer treatment and of post-treatment survivors. The National Comprehensive Cancer Network (NCCN) defines cancer-related fatigue (CRF) as “a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning [2].” Differences between CRF and fatigue reported by individuals without cancer are that CRF is more severe and is not relieved by rest. The prevalence of CRF in cancer patients and survivors is highly variable, ranging between 25% and 99% [2,3]. This variability may be secondary to methods used for screening fatigue and characteristics of the patient groups. In this article, we discuss recognition of CRF and approaches to its management.

**Pathophysiology**

The specific pathophysiologic mechanism underlying CRF is unknown, making targeted treatment a challenge. The multidimensional and subjective nature of CRF has limited the development of research methodologies to explain this condition. However, research has been done in both human and animal models, and several theories have been proposed to explain the pathophysiology of CRF. While pro-inflammatory cytokines remain the central factor playing a significant role at multiple levels in CRF, there may be a complex interplay of more than 1 mechanism contributing to fatigue in an individual patient.

**Central Nervous System Disturbances**

The basal ganglia are known to influence motivation. Lack of motivation and drive may cause failure to complete physical and mental tasks, even with preserved cognitive ability and motor function. In a study of melanoma patients receiving interferon, increased activity of the basal ganglia and the cerebellum resulted in higher fatigue scores [4]. Higher levels of cytokines may alter blood flow to the cerebellum and lead to the perception of fatigue. In a study of 12 patients and matched controls, when patients were asked to perform sustained elbow flexion until they perceived exhaustion, CRF

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patients perceived physical exhaustion sooner than controls. In CRF patients in this study, muscle fatigue measured by electromyogram was less than that in healthy individuals at the time of exhaustion, suggesting the role of the central nervous system in CRF [5]. However, there is not enough evidence at this time to support central nervous system disturbance as the main contributing factor to fatigue in cancer patients.

**Circadian Rhythm Dysregulation**

Circadian rhythm is regulated by the suprachiasmatic nucleus in the hypothalamus through cortisol and melatonin. Sleep disturbances occur with disruption of the circadian rhythm. Tumor-related peptides such as epidermal growth factor or alterations in serotonin and cortisol can influence the suprachiasmatic nucleus and the complex signaling pathways [2]. Positive feedback loops that are activated by cortisol under the influence of cytokines may lead to continuous cytokine production and altered circadian rhythm. Bower et al showed that changes in the cortisol curve influence fatigue in breast cancer survivors [6]. These patients had a late evening peak in cortisol levels, compared with an early morning peak in individuals without cancer.

**Inhibition of Hypothalamic–Pituitary–Adrenal Axis**

The hypothalamic–pituitary–adrenal (HPA) axis regulates the release of the stress hormone cortisol. One of several hypotheses advanced to explain the effect of serotonin and the HPA axis on CRF suggests that lower serotonin levels cause decreased activation of 5-hydroxytryptophan 1-a (5-HT1-a) receptors in the hypothalamus, leading to decreased activity of the HPA axis [6]. The inhibition of the HPA axis may occur with higher levels of serotonin as well [7]. The 5-HT1-a receptors are also triggered by cytokines. However, the correction of serotonin levels by antidepressants was not shown to improve fatigue [8]. Inhibition of the HPA axis can also lead to lower testosterone, progesterone, or estrogen levels, which may indirectly contribute to fatigue [2].

**Skeletal Muscle Effect**

Chemotherapy- and tumor-related cachexia have a direct effect on the metabolism of skeletal muscles. This effect may lead to impaired adenosine triphosphate (ATP) generation during muscle contraction [9]. ATP infusion improved muscle strength in one trial, but this was not confirmed in another trial [10,11]. Muscle contraction studies showed no differences in the contractile properties of muscles in fatigued patients who failed earlier in motor tasks and healthy controls [12]. This finding suggests that there could be a failure of skeletal muscle activation by the central nervous system or inhibition of skeletal muscle activity. Cytokines and other neurotransmitters activate vagal efferent nerve fibers, which may lead to reflex inhibition in skeletal muscles [13,14].

**Pro-inflammatory Cytokines**

Tumors or treatment of them may cause tissue injury, which triggers immune cells to release cytokines, signaling the brain to manifest the symptom fatigue. Inflammatory pathways are influenced by psychological, behavioral, and biological factors, which play a role as risk factors in CRF. Interleukin 6 (IL-6), interleukin-1 receptor antagonist, interleukin-1, and tumor necrosis factor (TNF) have been shown to be elevated in fatigued patients being treated for leukemia and non-Hodgkin lymphoma [15]. IL-6 was also associated with increased fatigue in breast cancer survivors [16]. Similar findings were reported in patients undergoing stem cell transplantation and high-dose chemotherapy [17]. Elevated levels of IL-6 and C-reactive protein were also linked to fatigue in terminally ill cancer patients [18,19]. Furthermore, TNF-α signaling was associated with post-chemotherapy fatigue in breast cancer patients [20]. Leukocytes in breast cancer survivors with fatigue also have increased gene expression of pro-inflammatory cytokines, emphasizing the role of cytokines and inflammation in the pathogenesis of CRF [21].

**Other Hypotheses**

Several other hypotheses for CRF pathogenesis have been proposed. Activation of latent viruses such as Epstein-Barr virus, lack of social support [22], genetic alterations in immune pathway [23], epigenetic changes [24], accumulation of neurotoxic metabolites and depletion of serotonin by indoleamine 2,3-dioxygenase pathway activation [25], elevated vascular endothelial growth factor levels [26], and hypoxia-related organ dysfunction due to anemia or hemoglobin dysfunction [13] all have been postulated to cause CRF.

**Approach to Evaluation and Treatment**

The evaluation and treatment of CRF involve 4 steps (Figure). First, patients are screened for fatigue, and in the second step those who have fatigue undergo primary
evaluation to assess for potential precipitating causes. The third step is implementation of pharmacologic and non-pharmacologic interventions aimed at alleviating or mitigating fatigue. The fourth step involves re-evaluating patients at periodic intervals to recognize and manage changes in fatigue levels. A multidisciplinary approach involving nursing, physical therapy, social work, and nutrition is critical in managing fatigue in these patients. Education and counselling of patients and involvement of the family are essential for effective management.

**Screening**

Because patients and health care professionals may be unaware of the treatment options available for CRF, patients may not report fatigue levels to their clinicians, and clinicians may not understand the impact of fatigue on their patients’ quality of life. This leads to under-recognition of the problem. The NCCN recommends screening every cancer patient and post-treatment survivor for fatigue [2]. Patients should be screened at their first visit and then at periodic intervals during and after cancer treatment.

Many scales are available to screen patients for CRF in clinical practice and clinical trials [27]. A single item that asks patients to rate their fatigue on a scale from 0 to 10—in which 0 indicates no fatigue, 1 to 3 indicates mild fatigue, 4 to 6 indicates moderate fatigue, 7 to 9 indicates severe fatigue, and 10 indicates the worst fatigue imaginable—is commonly used to screen for CRF [2]. This scale was adapted from the MD Anderson Symptom Inventory scale and is based on a large nationwide study of cancer patients and survivors [28]. The statistically derived cutoff points in this study are consistent with other scales such as the Brief Fatigue Inventory (BFI) and support the cutoff points (4–6 for moderate and ≥7 for severe fatigue) used in various clinical settings.
fatigue management guidelines. Furthermore, studies of fatigue in cancer patients have revealed a marked decrease in physical function at levels of 7 or higher, suggesting 7 as an optimal cutoff to identify severe fatigue [29,30]. The Visual Analog Scale is another simple-to-use tool that helps in understanding variations in fatigue throughout the course of the day [31]. The 9-item BFI is often used in clinical trials [29]. It measures the severity of fatigue over the previous 24 hours and has been validated in non-English speaking patients [32].

CRF affects not only the somatic domain, but also the cognitive, behavioral, and affective domains; therefore, multidimensional scales have been developed for screening. One such tool is the Multidimensional Fatigue Inventory, which measures general, physical, mental, and emotional fatigue domains as well as activity and compares them with those of individuals without cancer [33,34]. The Functional Assessment of Cancer Therapy for Fatigue (FACT-F) is a 13-item questionnaire that has been used to measure CRF in clinical trials as well as in patients receiving various treatments [35]. Although many scales are available, the validity of self-reporting on simple fatigue-rating scales is equal to or better than most complex, lengthy scales [36]. Therefore, unidimensional tools such as the numeric rating scale of 0–10 are commonly used in clinical practice.

Mild fatigue (0–3) requires periodic re-evaluation, and moderate and severe fatigue need further evaluation and management [37].

**Primary Evaluation**
This phase involves a focused history and physical examination and assessment of concurrent symptoms and contributing factors.

**History and Physical Examination**
A detailed history of the patient’s malignancy and type of previous and current treatment may help reveal the cause of fatigue. New-onset fatigue or increase in fatigue may be related to the progression of disease in patients with active malignancy or recurrence of cancer in survivors. These patients may require appropriate testing to assess the underlying disease pattern. A detailed review of systems may help identify some of the contributing factors, which are discussed below. A detailed history regarding medications, including over-the-counter drugs, complementary agents, and past and prior cancer therapies, is helpful as medications can contribute to fatigue.

For example, opioids may cause drowsiness and fatigue, which could be improved by dose adjustments. A focused history of fatigue should be obtained in all patients with moderate to severe CRF, which includes the onset, pattern, duration, associated or alleviating factors, and interference with functioning, including activities of daily living [37]. Physical examination should focus on identifying signs of organ dysfunction and features of substance or alcohol abuse which may cause poor sleep and fatigue.

**Assessment of Contributing Factors**
The management of fatigue should be multifactorial, with a comprehensive assessment and treatment plan to address all modifiable fatigue etiologies. The Table lists potential contributing factors to fatigue that should be considered when evaluating patients for CRF; several common conditions are discussed below.

**Anemia.** Anemia has been correlated with fatigue and quality of life. In a study of 4382 cancer patients receiving chemotherapy, quality-of-life measures using FACT-Anemia scores improved with increased hemoglobin levels [38]. Cancer patients may have anemia due to marrow-suppressing effects of chemotherapy and may also have iron deficiency anemia due to blood loss or autoimmune hemolytic anemia. Therefore, a detailed work-up is required to identify the etiology of anemia. Patients with CRF whose anemia is related to chemotherapy or anemia of chronic disease may benefit from red blood cell transfusion or erythropoiesis-stimulating agents (ESAs). ESAs have been studied extensively; however, their use is controversial because of concerns about thromboembolic side effects leading to adverse outcomes [39]. Also, ESA therapy is not recommended in patients with hematologic malignancies. ESA use should be restricted to patients with chemotherapy-related anemia with hemoglobin below 10 mg/dL and should be discontinued in 6 to 8 weeks if patients do not respond [40]. Other patients may benefit from blood transfusions, which were shown to help in patients with hemoglobin levels between 7.5 and 8.5 g/dL [41].

**Sleep disturbance.** Poor sleep is common in fatigued cancer survivors [42]. Pro-inflammatory cytokines can disrupt the sleep–wake cycle, causing changes in the HPA axis and neuroendocrine system, which in turn may lead to increasing fatigue. Heckler et al showed that improvement in nighttime sleep leads to improvement of fatigue [43]. Cognitive behavioral therapy and sleep
hygiene are important in caring for patients with CRF and poor sleep [44]. Taking a warm bath and/or drinking a glass of milk before bedtime, avoiding caffeinated drinks, and avoiding frequent napping in the day might help. Some patients may require medications such as benzodiazepines or non-benzodiazepine hypnotics (eg, zolpidem) to promote sleep [45]. Melatonin agonists are approved for insomnia in the United states, but not in Europe [46].

**Malnutrition.** Patients with advanced-stage cancer and with cancers affecting the gastrointestinal tract frequently develop mechanical bowel obstructions, especially at the end of their life, which cause malnutrition. Chemotherapy-related nausea and vomiting may also cause poor oral intake and malnutrition, causing fatigue from muscle weakness. Dehydration and electrolyte imbalances frequently occur as a result of poor oral intake, which might worsen fatigue. In our experience, modifying dietary intake with appropriate caloric exchanges with the help of a nutrition expert has lessened fatigue in some patients. However, terminally ill patients are advised to eat based on their comfort.

**Medical comorbidities.** Congestive heart failure from anthracycline chemotherapy, hypothyroidism after radiation therapy for head and neck cancers, renal failure, or hepatic failure from chemotherapy may indirectly lead to fatigue. Chemotherapy, opioids, and steroids may cause hypogonadism, which can contribute to fatigue in men [47].

**Assessment of Concurrent Symptoms**

Depression is common in cancer patients and coexists with pain, insomnia, fatigue, and anxiety as a symptom cluster [48]. A symptom cluster is defined as 2 or more concurrent and interrelated symptoms occurring together; treating of one of these symptoms without addressing other symptoms is not effective [49]. Therefore, screening for and management of depression, anxiety, and insomnia play an important role in the management of CRF.

Physical symptoms due to the tumor or to therapy—such as pain, dyspnea, nausea, and decreased physical activity—may also contribute to fatigue both directly and indirectly. Patients with lung cancer may have hypoxemia, which can contribute to dyspnea with activity and a perception of fatigue. Optimal management of pain and other physical symptoms in patients with cancer may significantly alleviate fatigue [50].

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<th>Medical comorbidities</th>
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<td>Endocrine dysfunction (hypothyroidism, hypogonadism)</td>
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<td>Anemia</td>
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<td>Cancer treatment–related conditions (anthracycline-induced cardiomyopathy)</td>
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<td>Underlying medical conditions (hepatic or renal failure, chronic obstructive pulmonary disease, diabetes)</td>
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<td>Cancer-related causes</td>
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<td>Cancer therapies: radiation therapy, chemotherapy, hormonal therapy, immunotherapy, and surgery</td>
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**Table. Factors Contributing to Fatigue in Cancer Patients**

**Management**

Management of CRF is individualized based on the patient’s clinical status: active cancer treatment, survivor, or end of life. Education and counselling of patients and their caregivers play an important role in CRF. NCCN guidelines recommend focusing on pain control, distress management, energy conservation, physical activity, nutrition, and sleep hygiene.

**Nonpharmacologic Interventions**

**Energy conservation.** Energy conservation strategies, in which patients are advised to set priorities and realistic expectations, are highly recommended. Some energy-conserving strategies are to pace oneself, delegate and
schedule activities at times of peak energy, postpone nonessential activities, attend to 1 activity at a time, structure daily routines, and maintain a diary to identify their peak energy period and structure activities around that time [51,52]. When patients approach the end of life, increasing fatigue may limit their activity level, and they may depend on caregivers for assistance with activities of daily living, monitoring treatment-related adverse effects, and taking medications, especially elderly patients [53].

**Cognitive behavioral therapy.** Cognitive behavioral therapy (CBT) has been shown to improve CRF during active treatment, and the benefits persist for a minimum of 2 years after therapy [54]. CBT interventions that optimize sleep quality may improve fatigue [55]. More studies are needed to understand whether referral to a psychologist for formal CBT is required. Randomized clinical trials (RCTs) showed patient fatigue education, learned self-care, coping techniques, and balancing rest and activity benefit patients with CRF [56].

**Exercise.** Physical activity is highly encouraged in patients with CRF. Exercise increases muscle protein synthesis, improves cytokine response, and decreases the rate of sarcopenia in healthy populations [57]. Studies have shown that exercise helps CRF at all phases of the cancer journey, including radiation therapy, chemotherapy, and survivorship [58]. Some patients may feel less motivated to exercise and may not believe that exercise is possible or could potentially help them. Counselling is needed for such patients.

Older cancer survivors have a decline in their functional capacity and reduced muscle mass. Exercise can improve cardiorespiratory fitness, muscle strength, and body composition [57]. Exercise not only helps at the cellular level but also has psychosocial benefits from improved self-esteem. Therefore, exercise may be recommended not only for younger patients, but also in the older population, who may have comorbidities and less motivation than younger patients.

In a meta-analysis of 56 randomized controlled trials involving 4068 participants, aerobic exercise was found to have beneficial effects on CRF for patients during and after chemotherapy, specifically for patients with solid tumors [59]. In another meta-analysis of breast and prostate cancer survivors, a combination of aerobic exercise with resistance training (3–6 metabolic equivalents, 60%–80% range of motion) was shown to reduce CRF more than aerobic exercise alone [60]. This effect was also shown in an RCT of 160 patients with stage 0 to III breast cancer undergoing radiation therapy [61]. The control group in this study had a group-based non-exercise intervention/relaxation; therefore, the study showed that the effect of resistance training extends beyond the psychosocial benefits of group-based interventions. The intervention comprised 8 progressive machine-based resistance exercises (3 sets, 8–12 repetitions at 60%–80% of 1 repetition maximum) for 60 minutes twice weekly for 12 weeks. However, fatigue assessment questionnaire scores showed benefits in the physical fatigue but not the affective and cognitive components.

The American Society of Clinical Oncology’s guidelines for cancer survivors with fatigue recommends 150 minutes of moderate aerobic exercise (eg, fast walking, cycling, or swimming) per week, with 2 or 3 sessions of strength training per week [62]. An individualized approach to exercise is recommended, as patients’ ability to perform certain types of exercises may be limited by thrombocytopenia, neutropenia, or lytic bone metastasis. Routine use of pre-exercise cardiovascular testing is not recommended but may be considered in high-risk populations, especially patients with risk factors for coronary heart disease and diabetes [63]. Patients with comorbidities, substantial deconditioning, functional and anatomic defects, or recent major surgery may benefit from referral to physical therapy [37]. Patients near end of life may also benefit from an exercise program, as demonstrated in several studies that showed benefit in CRF and quality of life [64,65]. We recommend that physicians use their best clinical judgement in suggesting the type and intensity of exercise program, as it may not be feasible in some patients.

**Mind-body interventions.** Mindfulness-based stress reduction (MBSR) has shown promise in breast cancer survivors, who reported immediate improvements in fatigue severity that continued up to 6 weeks after cessation of the training [66]. Prior studies had similar findings, suggesting that MBSR modestly decreases fatigue and sleep disturbances and has a greater effect on the degree to which symptoms interfere with many facets of life [67].

**Yoga.** A study of a yoga intervention showed a benefit in older cancer survivors [68]. In breast cancer patients undergoing chemotherapy, yoga was shown to benefit not only physical fatigue, but also cognitive fatigue [69]. DVD-based yoga had benefits similar to strengthening exercises in a study of 34 early-stage breast cancer survivors [60].
survivors with CRF [70]. More studies are needed in men and patients and survivors of other cancers, as most studies of yoga were conducted in women with breast cancer.

Tai chi/qigong. Like yoga, tai chi and qigong are practices of meditative movement. These practices use postures or movements with a focus on breath and a meditative state to bring about deep states of relaxation. Qigong is a series of simple, repeated practices including body posture/movement, breath practice, and meditation performed in synchrony. Tai chi easy (TCE) is a simplified set of common, repetitive tai chi movements. In a trial, qigong/TCE was compared with sham qigong, which had physical movements but no breathing or meditative practice. Breast cancer survivors in the qigong/TCE group had improved fatigue scores, and the effect persisted for 3 months [71]. Additional research is needed in this area.

Acupuncture. An RCT in breast cancer patients with CRF showed an improvement in the mean general fatigue score (per the Multidimensional Fatigue Inventory) in patients who received acupuncture versus those who did not (−3.11 [95% confidence interval −3.97 to −2.25]; P < 0.001) at 6 weeks. Improvements were seen in both the mental and physical aspects of fatigue [72]. However, Deng et al noted that true acupuncture was no more effective than sham acupuncture for reducing post-chemotherapy chronic fatigue [73]. Presently, there is not sufficient evidence to evaluate the benefits of acupuncture in CRF.

Other modalities. Massage therapy, music therapy, hypnosis, therapeutic touch, biofield therapies, relaxation, and reiki are other therapies for which few studies have been done, with mixed results, and additional research is needed [74]. Currently, there are not sufficient data to recommend any of these modalities.

Pharmacologic Interventions

Psychostimulants. Methylphenidate and modafinil are psychostimulants or wakefulness-promoting agents. Pilot studies showed benefit from methylphenidate and modafinil in CRF [75–77], but RCTs have yielded mixed results. Therefore, in patients with severe fatigue during cancer therapy, the initial management strategy involves evaluation and treatment of medical conditions such as anemia and a trial of non-pharmacological strategies as discussed above. If symptoms persist, then a therapeutic trial of a psychostimulant may be considered per NCCN guidelines for patients undergoing active cancer treatment [37].

Methylphenidate directly stimulates adrenergic receptors and indirectly releases dopamine and norepinephrine from presynaptic terminals, which may explain why the drug benefits patients receiving opioid-induced sedation. It is a commonly studied psychostimulant, though its mechanism of action in CRF is unclear. RCTs of methylphenidate have resulted in a wide range of findings due to the heterogeneity of study populations and variations in the dosage of methylphenidate. A meta-analysis of 7 studies indicates that methylphenidate benefitted the subgroup of patients with CRF [78]. Likewise, in an analysis of 5 RCTs, Minton et al showed a benefit of psychostimulants in fatigue compared with placebo [79]. However, another study of methylphenidate in patients with CRF showed a benefit only in patients with severe fatigue or advanced disease [80]. Methylphenidate was found to benefit cancer patients receiving opioid-induced sedation, as methylphenidate promotes wakefulness, though fatigue was not studied specifically [81]. In a trial with 30 hospice patients in which the methylphenidate dose was titrated based on response and adverse effects, Kerr at al found that the drug improved fatigue in a dose-dependent manner [82]. However, a study in patients with CRF at the University of Texas MD Anderson Cancer Center found no significant difference in BFI scores between patients receiving methylphenidate and those receiving placebo at the end of 2 weeks of treatment [83]. Also, other RCTs in patients undergoing adjuvant chemotherapy for breast cancer [84] and patients receiving radiation therapy for brain tumors [85] failed to demonstrate the efficacy of methylphenidate in CRF. It should be used cautiously after ruling out other causes of fatigue. The drug is overall well tolerated and side effects include headache and nausea.

Modafinil is a non-amphetamine psychostimulant that has been approved for the treatment of narcolepsy. In a trial studying the effect of modafinil on patients receiving docetaxel-based chemotherapy for metastatic breast or prostate cancer, there was a modest but not statistically significant improvement in fatigue scores on the MD Anderson Symptom Inventory compared with placebo. Nausea and vomiting were higher in the modafinil arm than in the placebo arm [86]. Similarly, modafinil was not superior to placebo for CRF in 208 patients with non-squamous cell lung cancer not undergoing chemotherapy or radiation [87]. A placebo effect
was also noted in patients with multiple myeloma [88] and patients with primary brain tumors [89]. In a phase 3, multicenter, randomized, placebo-controlled, double-blind clinical trial of modafinil for CRF in 867 patients undergoing chemotherapy, there was a reduction in fatigue only for patients with severe baseline fatigue, with no significant effect on mild to moderate fatigue [90]. In another recent study, modafinil was shown to reduce depressive symptoms only in patients with severe fatigue (BFI item 3 score ≥ 7) [91]. This finding is consistent with previous studies showing benefit in patients with high baseline fatigue, but additional RCTs are needed to provide clarity. NCCN guidelines do not recommend the use of modafinil to treat CRF [37].

Other pharmacologic interventions. Corticosteroids are often used for symptom control in cancer patients. These drugs have anti-inflammatory effects through their modulation of pro-inflammatory cytokines [92]. In a RCT evaluating the efficacy of corticosteroids, patients receiving dexamethasone (4 mg twice daily) experienced significant improvement in their FACT-F scores compared with patients receiving placebo [93]. A similar benefit in fatigue was demonstrated in another study of methylprednisolone (32 mg daily) versus placebo [94]. Despite the benefits of steroids, their adverse effects, such as mood swings, gastritis, hyperglycemia, and immune suppression, limit their long-term use. Therefore, the use of steroids should be restricted to terminally ill fatigued patients with other symptoms such as anorexia, brain metastasis, or pain related to bone metastasis [37].

Testosterone replacement has been shown to diminish fatigue in non-cancer patients. Many men with advanced cancer have hypogonadism leading to low serum testosterone, which may cause fatigue. In a small trial in which cancer patients with hypogonadism received intramuscular testosterone every 14 days or placebo, the group receiving testosterone showed improvement in FACT-F scores, but there was no significant difference in FACT-F scores between the 2 groups [95].

Antidepressants have failed to demonstrate benefit in CRF without depression [8]. However, if a patient has both fatigue and depression, antidepressants may help [96]. A selective serotonin receptor inhibitor is recommended as a first-line antidepressant [97]. Patients with cancer are often receiving multiple medications, and medication interactions should be considered to prevent adverse events such as serotonin syndrome.

Complementary and Alternative Supplements
Studies using vitamin supplementation have been inconclusive in patients with CRF [74]. The use of other dietary supplements has yielded mixed results, and coenzyme Q has shown no benefit for patients with CRF [98].

The benefit of ginseng was studied in a RCT involving 364 patients with CRF. There was an improvement in Multidimensional Fatigue Symptom Inventory-short form (MFSI-SF) scores at 8 weeks in patients receiving 2000 mg of Wisconsin ginseng compared with patients receiving placebo [99]. Patients on active treatment had greater improvement as compared to the post-treatment group in this trial. In another study of high-dose panax ginseng (ginseng root) at 800 mg daily for 29 days, patients had improvement of CRF as well as overall quality of life, appetite, and sleep at night. It was also well tolerated with few adverse effects [100]. Interaction with warfarin, calcium channel blockers, antiplatelet agents, thrombolytic agents, imatinib, and other agents may occur; therefore, ginseng must be used with careful monitoring in selected patients. There is not enough evidence at this time to support the routine use of ginseng in CRF.

The seed extract of the guarana plant (Paullinia cupana) traditionally has been used as a stimulant. An improvement in fatigue scores was seen with the use of oral guarana (100 mg daily) at the end of 21 days in breast cancer patients receiving chemotherapy [101]. Further studies are needed for these results to be generalized and to understand the adverse effects and interaction profile of guarana.

Re-evaluation
Patients who have completed cancer treatment must be monitored for fatigue over the long term, as fatigue may exist beyond the period of active treatment. Many studies have shown fatigue in breast cancer survivors, and fatigue has been demonstrated in survivors of colorectal, lung, and prostate cancers as well as myeloproliferative neoplasms [28]. Therefore, it is important to screen patients for fatigue during follow-up visits. There are currently no studies evaluating the long-term treatment of fatigue. In our experience, the timing of follow-up depends on the level of fatigue and interventions prescribed. Once fatigue is stabilized to a level with which the patient is able to cope, the time interval for follow up may be lengthened. Annual visits may suffice in patients with mild fatigue. Follow-up of patients with moderate to severe fatigue
depends on the level of fatigue, the ability to cope, choice of treatment, and presence of contributing factors.

Conclusion

CRF is a complex condition that places a significant burden on patients and caregivers, resulting in emotional distress, poor functioning, and suffering. Fatigue can occur before, during, and long after cancer treatment. The approach to CRF begins with screening for and educating patients and their caregivers about the symptoms. Many screening scales are available that may be used to follow patients’ progress over time. The evaluation and management of contributing conditions may help improve fatigue. If the fatigue persists, an individualized approach with a combination of nonpharmacologic and pharmacologic approaches should be considered. More research is needed to understand brain signaling pathways, cytokine changes, and genomic changes in cancer patients with fatigue. Though many hypotheses have been proposed, to date there is no biological marker to assess this condition. Biomarker research needs to be advanced to help to identify patients at risk for fatigue. As cytokines have a major role in CRF, targeted therapy to block cytokine pathways may also be explored in the future.

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