A Practical Approach to Fatigue Management in Colorectal Cancer

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Abstract

Cancer-related fatigue is serious and complex, as well as one of the most common symptoms experienced by patients with colorectal cancer, with the potential to compromise quality of life, activities of daily living, and ultimately survival. There is a lack of consensus about the definition of cancer-related fatigue; however, definitions have been put forward by the European Association for Palliative Care (EAPC) and the National Comprehensive Cancer Network (NCCN). Numerous cancer- and treatment-related factors can contribute to fatigue, including disease progression, comorbidities, medical complications such as anemia, side effects of other medications, and a number of physical and psychologic factors. This underlines the importance of tackling factors that may contribute to fatigue before reducing the dose of treatment. NCCN guidelines and the EAPC have proposed approaches to managing fatigue in cancer patients; however, relatively few therapeutic agents have been demonstrated to reduce fatigue in randomized controlled trials. It is recognized that physical activity produces many beneficial physiologic modifications to markers of physical performance that can help to counteract various causes of fatigue. In appropriately managed and monitored patients with colorectal cancer, emerging evidence indicates that exercise programs may have a favorable influence on cancer-related fatigue, quality of life, and clinical outcomes, and therefore may help patients tolerate chemotherapy. This review assesses fatigue in patients with colorectal cancer and proposes updates to a treatment algorithm that may help clinicians manage this common problem.

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Introduction

Cancer-related fatigue is a serious, debilitating, and complex symptom experienced by many patients[1] that may compromise quality of life (QoL), activities of daily living, and ultimately survival. Yet cancer-related fatigue is underrecognized and undertreated by many physicians and caregivers. For example, clinicians were less likely to report fatigue than their patients, while patients' reports of fatigue were more concordant with their health status score (assessed by the Euro QoL EQ-5D instrument) compared to clinicians' reports.[2] Many oncology professionals report that cancer-related fatigue is inadequately managed; reasons cited include a lack of awareness regarding interventions, limited assessment knowledge, and rating fatigue as a low priority. Barriers to optimal management of fatigue may include a failure to consult guidelines or structured tools.[3] Recent studies offer new insights into the causes and consequences of fatigue as well offering rational approaches to management, in which exercise is central. This review examines fatigue in patients with colorectal cancer (CRC) and suggests an algorithm to help clinicians manage this common problem.

Definition of Fatigue

Currently there is a lack of consensus on how cancer-related fatigue should be defined; however, definitions have been put forward by the European Association for Palliative Care (EAPC) and the National Comprehensive Cancer Network (NCCN) in the United States.

The EAPC offers a working definition of cancer-related fatigue as "a subjective feeling of tiredness, weakness or lack of energy."[4] The NCCN defines cancer-related fatigue 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 function."[5]

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In clinical trials, the Common Terminology Criteria for Adverse Events are used when identifying and grading adverse events associated with treatment.[6] Fatigue (defined as asthenia, lethargy, and malaise) is graded according to the effect on the patient's daily living, with grade 4 identified as disabling.[6] These different definitions may lead to ambiguity when recognizing cancer-related fatigue, and along with potential cultural influences attributing varying importance to this symptom, patients may continue to be undertreated.

It must be noted that discussion is still underway regarding the multidimensional nature of fatigue, including how many dimensions may be involved. The existence of physical and mental aspects of cancer-related fatigue appears to be generally agreed upon. However, it remains to be seen whether fatigue is a single symptom including multiple dimensions (including physical and mental) or whether physical fatigue and mental fatigue are in fact distinct symptoms in a multiple-symptom concept.[7] Indeed, some studies have suggested that physical and mental fatigue behave differently in cancer patients.[7] If physical and mental fatigue represent distinct symptoms, it is plausible that they may have separate pathophysiology and therefore may require different strategies for management and assessment. More information is required regarding the underlying pathophysiology of cancer-related fatigue. For example, physical fatigue may have a peripheral or central origin in neuromuscular disorders but not in cancer-related fatigue.[8]

Epidemiology of Fatigue

In the general population, symptoms of fatigue have been reported by approximately a quarter to a third of those surveyed.[9,10] Cancer-related fatigue can emerge before, during, and after treatment. Up to 40% of patients report fatigue at diagnosis of cancer, although treatment-associated fatigue is experienced by the majority of patients with cancer (90% of patients receiving radiotherapy and 80% of patients receiving chemotherapy).[1] Reported rates of post-treatment fatigue vary (17%-53%) depending on the criteria used for assessment.[1] Fatigue is also a common symptom in patients with CRC, particularly in those undergoing treatment (46% of patients experienced moderate to severe fatigue during treatment, while fatigue persisted in 27% of survivors).[11] Table 1 provides an overview of the grades of fatigue experienced by CRC patients undergoing treatment compared to survivors.

When considering specific treatments in metastatic CRC, grade 3 or 4 fatigue is commonly associated with chemotherapeutic regimens compared to biologic agents provided alone, although caution should be exercised when comparing data across studies (Table 2). In addition, it is well established that symptomatic toxicities, such as fatigue, are underreported in studied cohorts, thus suggesting that these incidences are likely to be higher than documented.[2,22]

Impact of Fatigue

Studies have shown that fatigue can have a marked impact on activities of daily living in patients with cancer, directly affecting their QoL.[11,23] In addition, patients with CRC who experienced continuous fatigue are at a higher risk of death than patients who did not experience fatigue (2.56 increased risk of death).[24] Fatigue in cancer patients who had previously undergone chemotherapy made it harder to take part in social activities and to carry out cognitive tasks.[25] Fatigue also had a substantial impact on patients' working life, with 75% of 177 patients reporting having changed their employment status because of their fatigue,[25] thus suggesting an economic burden of this symptom. A multicenter study including CRC patients in addition to breast, prostate, and lung cancer patients showed that increased fatigue severity was associated

Table 1 Percentage of Colorectal Cancer Patients in Epidemiologic Studies Who Experienced Severe, Moderate, or Mild Fatigue

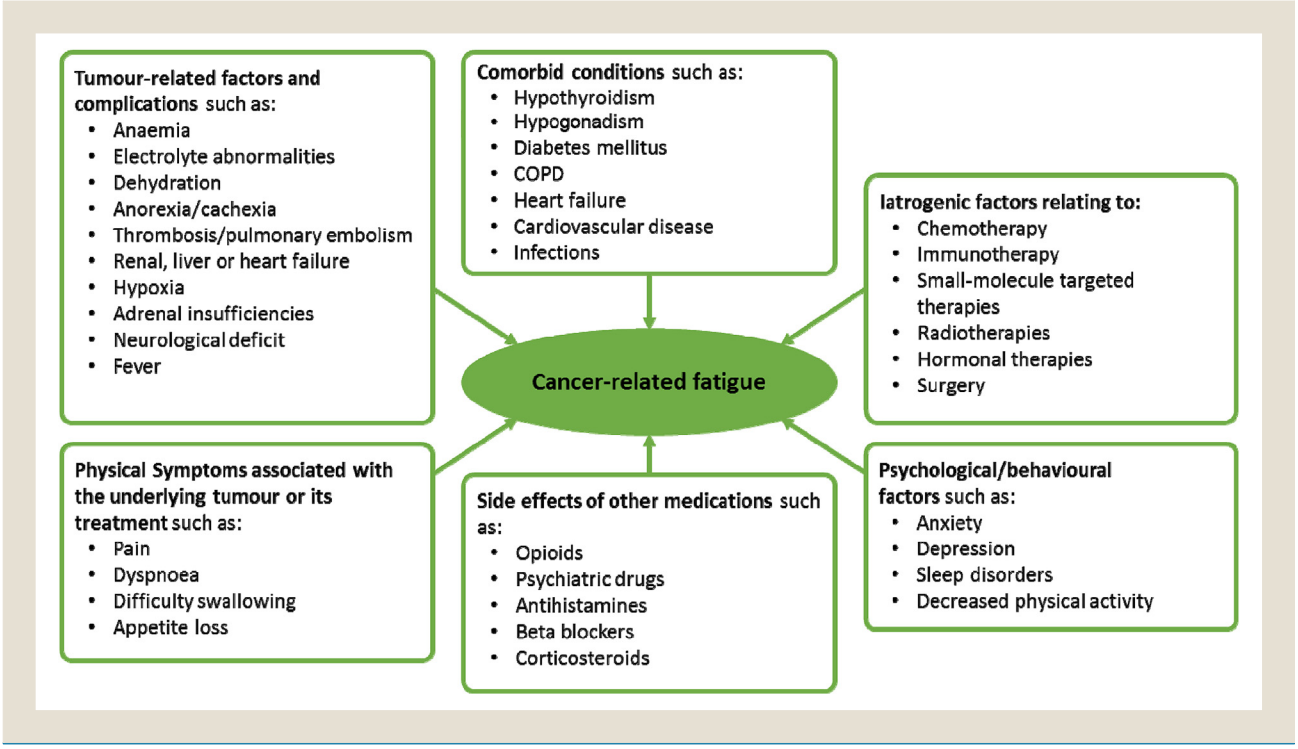
Group	Severe Fatigue (%)	Moderate Fatigue (%)	Mild Fatigue (%)	None (%)
Patients being treated (n = 486)[11]	18	28	36	18
Survivors (n = 142)[11]	11	16	29	44
Survivors <5 years (n = 117)[11]	10	13	32	45
Survivors ≥5 years (n = 23)[11]	13	30	13	44
General cohort (69% stage III/IV; 66% receiving treatment) (n = 157)[12]	4	22	24	50

Table 2 Examples of Rates of Fatigue With Chemotherapy and Targeted Treatments for Metastatic Colorectal Cancer

Regimen	Line	n	Grade 3/4
Chemotherapy			
FOLFIRI[13]	1	209	10%
FOLFOX-4[14]	1	649	7.9%
XELOX[14]	1	655	5.2%
FOLFOX-4[15]	2	308	8.8%
XELOX[15]	2	311	7.1%
Targeted Therapies			
Aflibercept-FOLFIRI[16]	>1[a]	1226	<5% difference compared to FOLFIRI and <20% in combination arm
Bevacizumab-XELOX/FOLFOX-4[17]	1	1401	Not cited in "adverse events of special interest to bevacizumab"
FLOX[18]	1	185	10%
Cetuximab-FLOX[18]	1	194	16%
Cetuximab-FLOX (intermittent)[18]	1	187	11%
Panitumumab-FOLFIRI[19]	2	1186	<5% difference compared to FOLFIRI
Regorafenib[20]	>1	500	9.6% vs. 5.1% in placebo arm (<5% difference)
Regorafenib[21]	>1	136	2.9% vs. 1.5% in placebo arm (<5% difference)

Abbreviations: FLOX = fluorouracil, leucovorin, oxaliplatin; FOLFIRI = fluorouracil, leucovorin, irinotecan; FOLFOX-4 = 5-fluorouracil, leucovorin, oxaliplatin; XELOX = capecitabine, oxaliplatin.
[a]Including adjuvant therapy.

Figure 1 Factors Associated With Cancer-Related Fatigue



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with greater interference with functioning as assessed by the MD Anderson Symptom Inventory (MDASI). This included an impact on relationships, mood, enjoyment of life, walking, general activity, and work.[11] Fatigue and depression frequently occur together in cancer patients and these symptoms may act synergistically, so it is important to address both whenever possible.[26] This is made more complex because fatigue is one criterion for diagnosing depression. Therefore, assessment tools have been developed that omit somatic symptoms, including fatigue, from their criteria.[26] The presence of fatigue is often associated with depression in cancer patients (including in CRC patients); however, the casual relationship between the two is unclear.[11,12] Furthermore, pain, sleep disturbance, and nutritional deficits or imbalance have all been shown to contribute to or be associated with cancer-related fatigue.[27] In addition, because fatigue is a criterion of depression, the Patient Help Questionnaire-2 (PHQ-2) is used to screen fatigued patients for possible depression,[28] which will be treated specifically.

These data highlight the importance of accurate assessment and management of cancer-related fatigue in patients, as under-recognition and undertreatment may ultimately affect clinical outcomes as well as the patient's QoL.

Etiology (or Pathophysiology) of Fatigue

Fatigue can arise from the cancer itself, from treatment, or from a variety of syndromes and concurrent conditions associated with the malignancy.[1] Figure 1 summarizes the numerous factors that can contribute to fatigue in cancer patients.

It is likely that the causes of cancer-related fatigue are multifactorial. The possible causes include comorbidities, medical complications such as anemia, side effects of other medications, and a range of physical and psychologic factors. A recent prospective case–control study investigated the factors associated with fatigue in breast cancer survivors. While chemotherapy was a major contributor to fatigue during patient treatment, lifestyle factors, including physical inactivity and obesity, were associated with persistent physical fatigue. Psychologic conditions relating to depression and pain were also associated with long-term fatigue.[29]

A number of underlying mechanisms have been proposed to drive cancer-related fatigue. For example, a substantial amount of evidence has implicated inflammatory cytokines in cancer-related fatigue, which has been reviewed in detail elsewhere.[30] It has been hypothesized that cancer cells and treatments, as well as other factors, can activate cytokine release, which subsequently mediates changes in the central nervous system that generate symptoms of fatigue. It has been shown that the administration of some cytotoxic chemotherapies can activate the release of pro-inflammatory cytokines.[31] For example, treatment for CRC with raltitrexed or carmofur was associated with serum increases in C-reactive protein (CRP) compared to pretreatment levels.[32]

The tumor can also release cytokines before treatment. Tumors are able to remodel the stroma and create a permissive microenvironment for their progression. They secrete factors that activate stromal cells and/or recruit inflammatory cells. Soluble factors including cytokines that control survival, differentiation, and growth of tumor cells (and therefore assist tumor promotion and

progression) are secreted by cells in the microenvironment.[33] The pro-inflammatory cytokines tumor necrosis factor (TNF) alpha and interleukin (IL)-6 are secreted by adipocytes and adipose tissue, respectively, with increased secretion in obese subjects.[34,35] Subcutaneous and abdominal visceral fat mass increases in volume within months after chemotherapeutic treatment in metastatic but otherwise healthy testicular cancer patients.[36] Cytokine absolute levels also increase in CRC; however, there are additional variations in the relative cytokine levels signifying an alteration in the balance of the immune system.[37] IL-2 treatment-related adverse effects have been reported in patients including fatigue, decreased energy, and anorexia.[38]

Furthermore, the development of fatigue is associated with the production of inflammatory cytokines in cancer patients undergoing treatment. In patients with regional, locally advanced CRC or esophageal cancer undergoing chemoradiation, fatigue was the most severe symptom experienced by patients at the start of therapy according to the MDASI. A significant association was identified between the development of fatigue and an increased blood concentration of the inflammatory marker soluble receptor 1 for tumor necrosis factor (sTNF-R1). Higher concentrations of IL-6 and sTNF-R1 were associated with greater fatigue severity compared to lower concentrations. The link between cytokines and cancer-related fatigue was independent of cancer type, cancer stage, body mass index, age, sex, and previous chemotherapy.[39] A similar study from the same research group also found an association between increased levels of sTNF-R1 and greater cancer-related fatigue in patients with locally advanced non−small-cell lung cancer.[39] More research has been conducted in patients with cancers other than CRC, with the majority of substantiating evidence linking inflammatory cytokines with fatigue coming from breast cancer studies. Increased levels of IL-6 were associated with greater fatigue in breast cancer patients undergoing chemotherapy.[40] Higher levels of the inflammatory markers CRP and IL-1 receptor antagonist were associated with greater fatigue in patients with breast or prostate cancer.[41]

De Sanctis and colleagues[42] investigated the relationship between pro-inflammatory cytokines, fatigue, and erythema of breast skin during radiotherapy in patients with breast cancer. Seven (17.5%) of the 40 patients had cancer-related fatigue. The authors suggested that the relatively low incidence of cancer-related fatigue was because of the strict diagnostic criteria used; patients were not diagnosed with cancer-related fatigue if they presented with concomitant depression or anxiety. Interestingly, levels of IL-1β, IL-2, IL-6, and TNF-α were increased 4 weeks after radiotherapy in breast cancer patients compared to pretreatment levels.[42] There also appeared to be a significant influence (according to Heckman 2-step analysis) of erythema on the production of pro-inflammatory biomarkers, which in turn was positively associated with fatigue.[42] Increased plasma levels of IL-6 have also been associated with greater fatigue severity in patients with multiple myeloma after undergoing autologous stem cell transplantation.[43] Serum levels of soluble IL-6 receptor were inversely related with fatigue in this population.[43]

Some studies have also demonstrated a correlation between the concentration of inflammatory markers and fatigue in patients with ovarian cancer or acute myeloid leukemia before treatment for cancer has started.[44,45] In patients with peritoneal carcinomatosis, fatigue assessed before surgery was associated with increased levels of IL-6 and CRP.[46] Drugs, including chemotherapy, steroids, and immunosuppressants, are routinely withheld for approximately 4 weeks before surgery for peritoneal carcinomatosis, suggesting that cytokine production and fatigue were independent of cancer treatment.[46] However, the treatment histories of patients included in the study were unclear. In a study of patients that had metastatic CRC and "dampened" rest/activity patterns, fatigue and cytokines were higher before treatment with chemotherapy compared to those that had normal rest/activity patterns.[47] Patients who had fatigue scores of over 33% (measured by European Organization for Research and Treatment of Cancer [EORTC] QLQ-C30) had higher transforming growth factor-α (TGF-α) levels compared to patients who were not fatigued. There was a positive correlation between TGF-α serum concentration and fatigue score.[47] In contrast, a 2014 study of 291 early-stage CRC patients, 72 metastatic CRC patients, and 72 healthy controls failed to demonstrate an association after diagnosis between pretreatment cancer-related fatigue and inflammatory cytokines.[48] Fatigue, assessed by the Functional Assessment of Cancer Therapies−Fatigue (FACT-F) subscale, was reported by 52% of early-stage patients and 26% of healthy controls ($P < .001$), with 68% of patients with metastatic disease feeling fatigued. While median levels of most of the cytokines tested for was higher in cancer patients overall, no association was found between cytokine and fatigue levels. Median hemoglobin levels were lower in early-stage CRC patients compared to healthy controls (131 g/L vs. 142 g/L; $P < .001$), and lower hemoglobin was also weakly associated with greater fatigue levels.[48]

In cancer patients, cytokines and systemic inflammatory response have been implicated in the development of both sarcopenia, which is characterized by a loss of muscle and function and cachexia, which is a multifactorial and complex syndrome affecting energy metabolism, skeletal muscle, adipose tissue, and the metabolism of protein lipid and glucose in cancer patients.[49] Both sarcopenia and cachexia are interwoven with the development of fatigue in cancer patients. For example, there is a correlation between cancer-related fatigue and midarm circumference.[50,51] In a study of 84 patients with inoperable gastrointestinal cancer (n = 68) or non−small-cell lung cancer (n = 16), higher cancer-related fatigue was correlated with a loss of muscle mass and strength. Fatigue, as measured by the Brief Fatigue Inventory (BFI), was associated with poor hand grip and quadriceps strength, and low skeletal muscle mass index.[52] In addition, sarcopenia is a negative prognostic factor for survival in CRC patients who have undergone resection[53] and predicts postoperative infections and longer hospital stays.[54] In esophagogastric cancer, sarcopenia was predictive of dose-limiting toxicity (odds ratio [OR], 2.95; 95% confidence interval [CI], 1.23 to 7.09; $P = .0015$).[55]

Male hypogonadism is an important contributor to the pathophysiology of both sarcopenia and cachexia in advanced cancer patients.[49] In a recent study, 100 men with advanced lung and gastrointestinal cancer showed that 76% of patients presented with male hypogonadism due to low free testosterone levels (< 31.2 pmol/L).[56] In this cohort, male hypogonadism was independently associated with lower albumin (−3.8 g/L; 95% CI, −6.8 to −0.8), muscle strength (−11.7 lb; 95% CI, −20.4 to −3.0), and mass in

upper limbs (−0.8 kg; 95% CI, −1.4 to −0.1), overall performance status (Eastern Cooperative Oncology Group Performance Scale, 0.6; 95% CI, 0.1 to 1.1), cancer-related fatigue (BFI, 16.7; 95% CI, 2.0 to 31.3), and overall QoL (McGill Quality of Life Questionnaire [MQoL] total score −1.42; 95% CI, −2.5 to −0.3).

These data highlight the importance of accurate screening and assessment of cancer-related fatigue and its pathophysiologic mechanisms. Either the reversal of these mechanisms or the palliation of fatigue may ultimately affect clinical outcomes as well as CRC patients' QoL.

Diagnosis of Fatigue

The EAPC has developed an algorithm for the diagnosis of fatigue in cancer patients,[4] which involves initial screening of patients for fatigue in the clinic, where a single question inquiring how the patient feels is asked (eg, "Do you feel unusually tired or weak?," "How weak are you?," or "How tired are you?"). The NCCN recommends screening every patient for fatigue at regular intervals using a single-item scale before a more in-depth assessment of fatigue.[5] Once it has been established that patients are experiencing fatigue, a more thorough assessment by questionnaire or interview can be performed along with physical and laboratory evaluations, compiled together with a complete overview of their medical history.[57]

The interview should focus on determining 3 different major symptoms that can characterize fatigue in cancer patients: (1) easy tiring and reduced capacity to maintain performance (often associated with anemia or muscular demise); (2) generalized weakness often reported as lack of stamina or anticipatory sensation of difficulties in initiating activities; and (3) mental fatigue (often defined as "total fatigue"), characterized by presence of impaired mental concentration, loss of memory, and emotional lability.[58]

A number of different assessment tools may be used. General cancer QoL questionnaires (such as the European Organisation for Research and Treatment of Cancer QoL questionnaire [EORTC QLQ-C30]) assess the overall well-being of the patient, with specific questions that relate to cancer- or treatment-related symptoms. There are also tools that are specific to fatigue assessment in patients (BFI, Multidimensional Fatigue Symptom Inventory [MFSI], Multidimensional Fatigue Inventory [MFI-20], the Piper fatigue scale, and Visual Analogue Scale to Evaluate Fatigue Severity [VAS-F]), as well as those that specifically look at cancer-related fatigue (Functional Assessment of Cancer Therapy Fatigue Instrument [FACIT-F] and Schwartz cancer fatigue scale). In terms of simplicity and ease of use, the VAS-F and BFI are valuable tools, and the FACIT-F and MFSI have been validated in a number of languages. Other tools exist that do not provide as much detail; these are rarely used in clinical trials.[57]

Some tools are unidimensional (BFI) and others multidimensional (MFSI; EORTC QLQ-FA13) explorations of the physical, cognitive, and emotional aspects of cancer-related fatigue. It is important to select a tool that provides enough detail to obtain useful information on the scope and severity of fatigue while being simple and easy for patients to complete. These questionnaires can take a long time to complete and evaluate, so patients are often asked to rate their fatigue on a single-item scale as a screening procedure. Typically, on a numerical rating from 0 to 10, scores of 4 or above instigate the use of more complex questionnaires exploring different dimensions of fatigue (either separately in a series of questionnaires or in a single multidimensional inventory).[5,59]

As outlined, a detailed laboratory assessment should also be performed for differential diagnosis of fatigue, including indicators of anemia (hemoglobin, transferrin, ferritin, iron, erythropoietin, transferrin saturation), electrolyte dysregulation (sodium, potassium, calcium, magnesium, phosphate), organ dysfunction (creatinine, bilirubin), hypothyroidism (thyroid-stimulating hormone, free T3 and T4), infection (white blood cell count, C-reactive protein), hormone imbalance (adrenocorticotropic hormone, cortisol, free testosterone, melatonin), vitamin deficiency (B1, B6, B12), and disrupted cytokine load (markers for increased cytokine load might be better suited than cytokines themselves).[4] Nutritional markers should also be considered, such as albumin and prealbumin.[60]

Management of Fatigue

Approaches to managing fatigue in people with cancer have been proposed in the NCCN guidelines[5] and by the EAPC. A practical guide to managing cancer-related fatigue has recently been published by Koornstra and colleagues,[1] in which a treatment algorithm was proposed that includes preventative measures as well as psychosocial support and pharmacologic and nonpharmacologic interventions.

Across the different recommendations, it is agreed that health care professionals should educate their patients on fatigue, including causes and potential self-management strategies. Proactive discussion and appraisal of fatigue should be part of clinical evaluations, and patients should be encouraged to monitor fatigue between appointments, particularly those who did not report it at screening.[1,61] In these discussions, patients should be made aware of the likelihood of fatigue with their disease and treatment, and how this may affect their daily life. It is also important to emphasize the benefits of early reporting of fatigue to allow for rapid and effective management.[61] Patients should be encouraged to remain positive and resourceful and to find a daily routine that conserves energy by balancing activity and rest.

Although not specifically recommended by the guidelines, nonpharmacologic interventions include psychosocial support (eg, counseling, psychotherapy, cognitive behavioral therapy), sleep therapy, and complementary therapies (eg, relaxation techniques, massage, herbal remedies [eg, American ginseng], yoga, acupuncture).[1] Additional support from dieticians, physiotherapists, and occupational therapists may also be beneficial so patients maintain a healthy diet and lifestyle that helps them to cope with their fatigue.[1] Exercise is also an important factor in fatigue management.

Most patients with fatigue will require symptomatic treatment using a combination of pharmacologic and nonpharmacologic approaches. For example, correcting anemia and electrolyte disturbances; managing comorbidities; alleviating pain, emotional distress, and sleep disturbances; and addressing dehydration can help improve fatigue. If the fatigue seems to arise as a side effect of therapy, then a change to the treatment regimen might be appropriate; however, care must be taken not to compromise clinical outcomes, so this approach should only be used if the fatigue is severe and unresponsive to other management approaches.[1] The causes of fatigue differ markedly between patients and can vary over

the course of the disease; as such, treatment needs to be individualized and reviewed regularly.[1]

Pharmacologic Interventions for Cancer-Related Fatigue

Relatively few therapeutic agents have been shown to alleviate fatigue in randomized controlled trials.[62] The NCCN recommendations to use psychostimulants as active treatment is not widely followed outside of the United States, with recent publications recommending that their use be reevaluated and perhaps reserved for fatigue in advanced disease only.[63,64] Data from a placebo-controlled trial of modafinil in lung cancer patients found no effect on cancer-related fatigue and was associated with a clinically significant placebo effect, questioning its use at all in this setting.[65] A previous multicenter, double-blind, randomized trial found that modafinil only improved symptoms in severely fatigued cancer patients undergoing chemotherapy and showed no benefit for those with mild or moderate fatigue.[66] The heterogeneity of patients with cancer-related fatigue and the complexity of designing rigorous studies in this setting may explain the disparity in results.[62] A meta-analysis of 27 randomized controlled trials investigating drug interventions for cancer-related fatigue found that there may be evidence for methylphenidate, a psychostimulant, being superior to placebo.[67] The meta-analysis included 2 studies of methylphenidate (n = 264), which demonstrated a greater change in FACT-F score versus placebo (−0.30; 95% CI, −0.54 to −0.05; $P = .02$).[67] Authors of the meta-analysis noted that the effect was not large and that 1 of the 2 studies included had not demonstrated a benefit on fatigue over placebo. In an updated review in 2010, including 2 further trials of methylphenidate and another of dexamphetamine, psychostimulants again demonstrated a small but significant improvement in fatigue scores versus placebo (n = 426). It was concluded that large-scale trials of methylphenidate are required to validate these preliminary results.[68] A recent study by Del Fabbro et al[69] investigating the effect of testosterone replacement on fatigue in hypogonadal men with advanced cancer by the FACIT-F scale showed significant improvement of fatigue only after 10 weeks of treatment. However, the same authors concluded that larger studies of longer duration were warranted before routine testosterone replacement could be recommended. Table 3 summarizes some of the studies to date assessing pharmacologic interventions for cancer-related fatigue. For the purposes of this review, we have not included treatment for anemia in Table 3, which can be argued to be a reversible contributing factor.

Although some of the pharmacologic interventions in Table 3 have demonstrated efficacy in clinical trials of cancer-related fatigue, only a few are currently recommended by the NCCN.[5] Considering methylphenidate after ruling out other causes of fatigue is recommended by the NCCN. However, it is stated that its use remains investigational and that optimal dosing has yet to be established.[5] In addition, several studies have shown the effectiveness of corticosteroids (eg, dexamethasone) in providing short-term relief for fatigue and improving QoL. However, long-term toxicity restricts their use to specific patient groups, especially given their catabolic effects on muscle, with the NCCN recommending considering corticosteroids as an intervention for cancer-related fatigue in the palliative setting.[5]

Several interventions in Table 3 have shown promising preliminary results that require further assessment before they can be considered for inclusion in clinical guidelines. Currently etanercept, testosterone, guarana, and sertraline are not mentioned in the NCCN guidelines for cancer-related fatigue. However, the positive results from small trials of these interventions warrant further investigation. There may also be some preliminary data to support the use of ginseng. In a double-blind study of 364 cancer survivors with fatigue, 2000 mg of ginseng per day resulted in greater changes in MFSI score at 8 weeks versus placebo (change in MFSI = 20, SD = 27, vs. 10.3, SD = 26.1).[77] A greater benefit was derived in those undergoing active treatment. Other dietary supplements were excluded from the current NCCN guidelines because of mixed results.[5] While coenzyme Q10 and L-carnitine have shown no benefit when assessed alone,[76,78] one small study found an improvement when they were combined with other supplements.[79]

In patients where fatigue arises as a side effect of treatment, experience from clinical trials indicates that it can be effectively managed with treatment breaks, dose adjustments, and appropriate intervention.[81] Therefore, early assessment and frequent monitoring of fatigue should be part of the treatment evaluation.[82]

Effect of Exercise on Fatigue

It is known that physical activity produces numerous beneficial physiologic changes on markers of physical performance that may help to counteract some of the causes of fatigue, such as increasing hemoglobin levels, cardiorespiratory fitness and capacity, muscle mass, and strength.[83]

In addition, vigorous physical activity limits the loss of sarcopenia and skeletal muscle oxidative capacity in early-stage disease.[84] The typical response to high levels of physical activity involves the secretion of a regular sequence of anti-inflammatory and pro-inflammatory cytokines, with IL-6 playing a major role.[85] IL-6 induces modifications including insulin resistance in adipose tissue,[86] and it profoundly decreases muscle protein turnover in healthy individuals.[87] Adipose tissue is able to produce various cytokines, including IL-6, that may modulate glucose homeostasis,[88] and baseline levels of IL-6 are required to modulate lipid homeostasis.[89] In studies of healthy and obese participants, it appears that exercise programs reduce TNF-α levels and may increase muscle-derived IL-6.[90]

A meta-analysis of 7 observational studies assessed the effect of physical activity—initiated before or after diagnosis of CRC—on overall survival and cancer-specific survival. Increased levels of physical activity after diagnosis of CRC were associated with a greater-specific survival compared to low levels of physical activity (hazard ratio, 0.61; 95% CI, 0.44 to 0.86; $P < .001$). Higher levels of activity after diagnosis were also associated with significantly improved overall survival compared to lower levels of activity (hazard ratio, 0.62; 95% CI, 0.54 to 0.71; $P < .001$).[91] The authors of the study suggested that the impact of physical activity on overall survival was likely an expected product of the benefits of exercise on cardiovascular health.[91]

The results of the studies provide initial support for incorporating a program of exercise into the treatment of CRC patients based on improved outcomes.[91] However, exactly what can be inferred from the studies as to necessary intensity or the design of an exercise

Table 3 Pharmacologic Interventions Assessed for Efficacy in Cancer-Related Fatigue[a]

Treatment	Study	Study Design	Sample Size	Dose	Outcome Measure	Summary of Results
Dexamethasone	Yennurajalingam 2013[70]	Double-blind, randomized, placebo-controlled trial	84	Dexamethasone (n = 43) 4 mg or placebo (n = 41) orally twice daily	FACIT-F	Significantly higher mean ± SD improvement in FACIT-F at day 15 in the dexamethasone group vs. placebo (9 ± 10.3 vs. 3.1 ± 9.59; $P = .008$)
Dexmethylphenidate	Lower 2009[71]	Double-blind, randomized, placebo-controlled, parallel-group study	154	Dexmethylphenidate 5 mg (n = 76) placebo or (n = 78) twice daily	FACIT-F	Significant improvement in FACIT-F at week 8 for dexmethylphenidate group vs. placebo ($P = .02$)
Methylphenidate	Bruera 2013[72]	Randomized, placebo-controlled, phase 2 trial	141	Methylphenidate dose 5 mg every 2 hours as needed up to 20 mg daily or placebo	FACIT-F	No significant difference in the median improvement in FACIT-F fatigue for methylphenidate vs. placebo (5.5 vs. 6.0, $P = .69$)
Methylphenidate	Moraska 2010[73]	Randomized, placebo-controlled, phase 2 trial	148	Methylphenidate (n = 74) target dose, 54 mg daily or placebo (n = 74)	BFI	No significant effect
Modafinil	Jean-Pierre 2010[66]	Double-blind, randomized, placebo-controlled, phase 3 trial	867	Oral modafinil 200 mg daily (n = 315) or a placebo (n = 316)	BFI	Significant interaction between modafinil and baseline fatigue (ANCOVA; $P = .017$); only patients with severe baseline fatigue benefited
Etanercept	Monk 2006[74]	Randomized, controlled pilot	12	Etanercept 25 mg (n = 6) subcutaneously twice weekly or placebo	FSI	Etanercept group reported less fatigue vs. no etanercept ($P < .001$)
Sertraline	Stockler 2007[75]	Double-blind, randomized, placebo-controlled trial	189	Sertraline 50 mg (n = 95), or placebo (n = 94), once daily	FACT-F	No significant effect
L-Carnitine	Cruciani 2012[76]	Double-blind, randomized, placebo-controlled trial	376	Oral L-carnitine 2 g/d (n = 189) or placebo (n = 187)	BFI	No significant difference between groups ($P = .57$)
Ginseng	Barton 2013[77]	Double-blind, randomized, placebo-controlled trial	364	Ginseng 2000 mg (n = 183) or placebo (n = 181)	MFSI-SF	Significant difference at 8 weeks for ginseng with change in MFSI-SF of 20 (SD = 27) group vs. 10.3 (SD = 26.1) for placebo ($P = .003$)
Coenzyme Q10	Lesser 2013[78]	Randomized, placebo-controlled trial	236	300 mg oral coenzyme Q10 + 300 IU vitamin E (n = 122) or placebo 300 IU vitamin E (n = 114)	POMS-F; FACIT-F	No improvement over 24 weeks
Inner Power (branched-chain amino acids (2500 mg), coenzyme Q10 (30 mg), and L-carnitine (50 mg))	Iwase 2015[79]	Randomized controlled trial	57	Oral Inner Power once daily for 21 days + regular care (n = 28) or regular care (n = 29)	BFI item 3; global fatigue score	Changes in worst level of fatigue and global fatigue score improved in intervention group
Guarana	de Oliveira Campos 2011[80]	Randomized placebo-controlled trial	75	50 mg oral guarana twice daily (n = 32) or placebo (n = 43)	FACIT-F; FACT-ES; BFI	Improved FACIT-F; FACT-ES; BFI on days 21 and 49 ($P < .01$)
Testosterone	Del Fabbro 2013[69]	Double-blind, randomized, placebo-controlled trial	29	150-200 mg intramuscular testosterone (n = 13) or placebo (n = 16) every 2 weeks	FACIT-F	Improved FACIT-F not at day 29 but only at day 79 ($P = .03$)

Abbreviations: ANCOVA = analysis of covariance; BFI = Brief Fatigue Inventory; FACIT-F = Functional Assessment of Chronic Illness—Fatigue subscale; FACT-ES = Functional Assessment of Chronic Illness Therapy—Endocrine Symptoms; FSI = Fatigue Symptom Inventory; FSS = Fatigue Severity Scale; MFSI-SF = Multidimensional Fatigue Symptom Inventory—Short Form; POMS-F = Profile of Moods States Fatigue subscale.

[a]This list is not exhaustive for treatments that have been assessed in cancer-related fatigue or number of clinical studies for each treatment.

program is unclear. Three of the studies included in the meta-analysis had a high-activity cutoff of ≥ 18 MET (metabolic equivalent) hours per week.[91] Prospective randomized controlled trials investigating the impact of exercise in CRC are limited. A long-term prospective study, the Colon Health and Life-Long Exercise Change (CHALLENGE) study, is currently underway to assess the effects of exercise on disease-free survival in patients with (predominately stage III) CRC who have completed adjuvant chemotherapy over the last 2 to 6 months.[92] This study will, we hope, provide a clearer picture of the impact of exercise on outcomes in CRC. Furthermore, cancer-related fatigue as measured by the FACT-F subscale is a secondary end point for the study.

Clinical studies that have assessed the effect of physical exercise on levels of fatigue and evidence show that aerobic or resistance

exercise reduces fatigue and demonstrates beneficial effects in cancer survivors and those receiving cancer treatment.[83,93-97] In addition to a reduction in fatigue itself, other benefits of exercise reported in cancer patients include increased strength, reduced risk of relapse, less discomfort during therapy, and improved mood, QoL, and physical performance.[98-100] In CRC patients, improved QoL, improved anxiety, and disease-free survival have been reported in patients who engaged in regular exercise compared to those who were less physically active.[99,101]

In a meta-analysis of 44 randomized clinical trials, it was found that exercise reduced fatigue in cancer survivors to a greater extent than those receiving standard care (no exercise program—patients maintained current activity). The trials investigated the impact of various exercise interventions in survivors with various cancer types (25 studies included breast cancer patients, while only 1 study included CRC patients).[94] A 2012 meta-analysis of 56 randomized clinical trials (the majority in breast cancer) showed that improvements in fatigue were greater in cancer patients undergoing an exercise program compared to a control intervention, with improvements in fatigue observed after exercise either during cancer treatment or after therapy.[93]

There have been few studies investigating the impact of exercise in patients with CRC undergoing chemotherapy. One randomized clinical trial of 66 adults assessed the impact of a home-based exercise program; improvements in fatigue, mobility, and sleep quality in people with stage IV lung cancer or CRC compared to those receiving usual care (not instructed to exercise) were observed.[102]

In a small study of 45 patients with CRC, a significant improvement in fatigue was reported in those taking part in a supervised exercise program when assessed as a subscale of the EORTC QLC-C30 compared to usual care, although when assessed by the Fatigue Symptom Inventory (FSI), the exercise program did not have a significant impact on fatigue.[103] In addition to the small sample size, this discordance may be due to the severity of fatigue in patients included in the study, as the authors noted that mean scores of fatigue using FSI were on the borderline of being clinically meaningful. Furthermore, after 3 months, patients with CRC who followed the exercise program showed improvements in physical and social functioning as well as pain.[103]

While regular physical activity is beneficial for patients with cancer who experience fatigue, an exercise program may not be appropriate for all patients, including those with thrombocytopenia, fever, or active infection; pain; bony metastases or spinal instability; malnourishment; or orthopedic or rheumatic disease.[82,83] However, in appropriately managed and monitored patients with CRC, there appears to be provisional evidence that exercise programs can have a positive impact on cancer-related fatigue, QoL, and clinical outcomes. Physicians will need to consider relative and absolute contraindications for an exercise program, which have recently been reviewed in detail elsewhere and are summarized in Table 4. More studies are needed to fully establish the effects of exercise in the CRC patient population specifically.

We suggest modifications to the current NCCN approaches to managing fatigue in CRC patients, including an increased focus on the recognized benefits of exercise and psychosocial interventions (Figure 2).[5]

Table 4 Relative and Absolute Contraindications to Exercise Programs

Relative Contraindications
- Recent weight gain (>2 kg during the 3 days preceding exercise).
- Decrease in systolic BP during exercise.
- NYHA class IV cardiac status.
- Ventricular arrhythmia at rest or during exercise.
- Supine cardiac frequency ≥100 beats/minute.
- Neurologic toxicity greater than grade 2.
- Asymptomatic central neurologic lesions.
- Asymptomatic bone metastases.

Absolute Contraindications
- Progressive increase in dyspnea at rest or during exercise for 3-5 days preceding exercise.
- Low-flow ischemia.
- Uncontrolled diabetes mellitus.
- Acute disease or fever.
- Recent embolism.
- Thrombophlebitis.
- Myocarditis or active pericarditis.
- Moderate to severe aortic stenosis.
- Valvulopathy requiring surgery.
- Myocardial infarction during 3 preceding weeks.
- Relapsing atrial fibrillation.
- Symptomatic central neurologic lesions.
- Hematologic toxicity: platelets <50,000/mm^3, leucocytes <1500/mm^3, hemoglobin <8 g/dL.
- Symptomatic central neurologic lesions.
- Osteolytic or painful bone metastases.

Reasons to Stop or Modify Program
- Dyspnea or fatigue (≤14 on Borg scale).
- Exercise asthma crisis.
- Respiratory frequency >40/minute during exercise.
- Increase in crackles at auscultation.
- Hypotension (difference between systolic BP and diastolic BP <10 mm Hg).
- Supraventricular or ventricular tachycardia during exercise.
- Paleness or confusion.
- Paraesthesias (platinum salts, taxanes, etc) may cause proprioceptive alterations with increased risk of falls during PAS.
- Dermatoses, especially exudative dermatoses (postradiation, tyrosine kinase inhibitors, 5-fluorouracil) with pain related to rubbing and risks of wound or skin infection. Skin toxicity higher than grade 2.

Abbreviations: BP = blood pressure; NYHA = New York Heart Association.
Reproduced with permission from Bouillet et al (2015).[104]

Conclusion

The literature suggests that fatigue may be common, with the potential to compromise outcomes and well-being in people with CRC. Fatigue associated with CRC has a complex etiology, underscoring the importance of addressing factors that may contribute to fatigue before reducing the dose of therapy. Emerging evidence suggests that exercise may improve QoL and survival, and therefore may help patients tolerate chemotherapy. This review proposes a treatment algorithm that may help clinicians tackle fatigue related to CRC.

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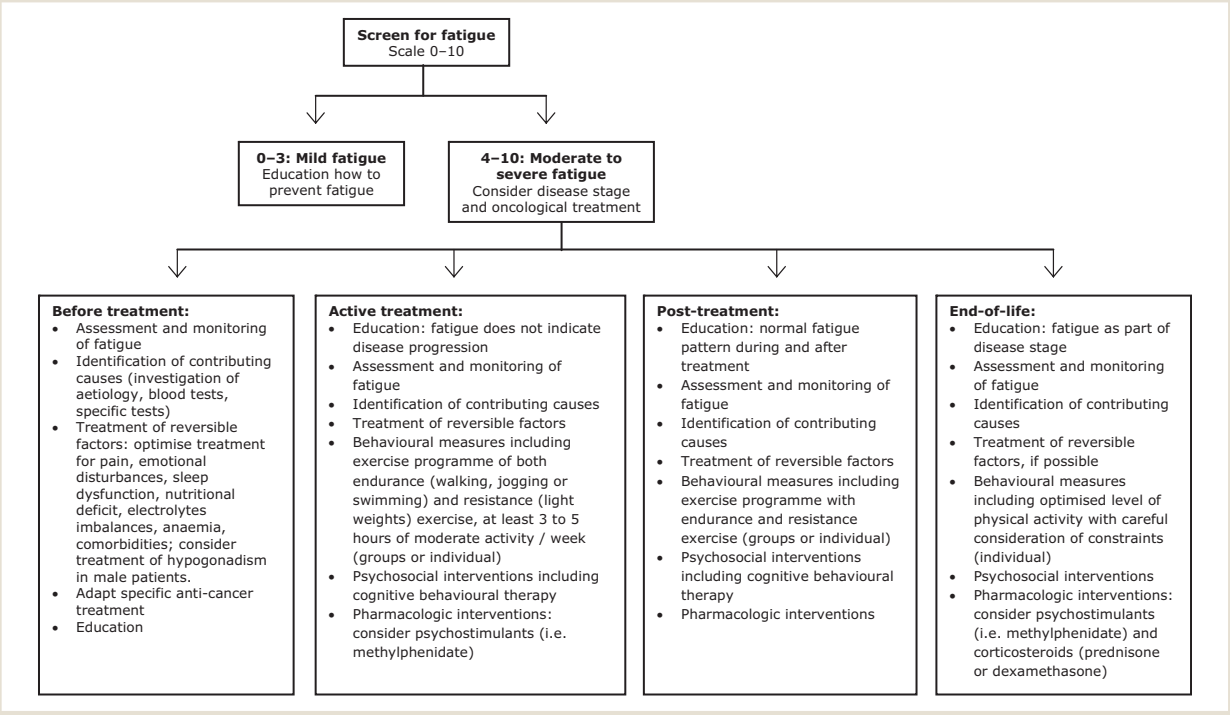
Disclosure

The authors have stated that they have no conflict of interest.

Figure 2 Proposed Treatment Algorithm for Fatigue in Cancer Patients



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