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Cancer-related fatigue: Mechanisms, risk factors, and treatments

Julienne E. Bower, Ph.D.[1,2,3,4]

[1]UCLA Department of Psychology, Semel institute at UCLA

[2]Cousins Center for Psychoneuroimmunology, Semel institute at UCLA

[3]UCLA Department of Psychiatry and Biobehavioral Sciences, Jonsson Comprehensive Cancer Center at UCLA

[4]Division of Cancer Prevention and Control Research, Jonsson Comprehensive Cancer Center at UCLA

Abstract

Fatigue is one of the most common and distressing side effects of cancer and its treatment, and may persist for years after treatment completion in otherwise healthy survivors. Cancer-related fatigue causes disruption in all aspects of quality of life and may be a risk factor for reduced survival. The prevalence and course of fatigue in cancer patients has been well characterized, and there is growing understanding of underlying biological mechanisms. Inflammation has emerged as a key biological pathway for cancer-related fatigue, with studies documenting links between markers of inflammation and fatigue before, during, and particularly after treatment. There is considerable variability in the experience of cancer-related fatigue that is not explained by disease- or treatment-related characteristics, suggesting that host factors may play an important role in the development and persistence of this symptom. Indeed, longitudinal studies have begun to identify genetic, biological, psychosocial, and behavioral risk factors for cancer-related fatigue. Given the multi-factorial nature of cancer-related fatigue, a variety of intervention approaches have been examined in randomized controlled trials, including physical activity, psychosocial, mind-body, and pharmacological treatments. Although there is currently no gold standard for treating fatigue, several of these approaches have shown beneficial effects and can be recommended to patients. This report provides a state of the science review of mechanisms, risk factors, and interventions for cancer-related fatigue, with a focus on recent longitudinal studies and randomized trials that have targeted fatigued patients.

INTRODUCTION

Fatigue is now recognized as one of the most common and distressing side effects of cancer and its treatment[1]. Fatigue may be elevated before treatment onset and typically increases during cancer treatment, including treatment with radiation[2], chemotherapy[3], hormonal, and/or biological therapies[4]. Prevalence estimates of fatigue during treatment range from 25% to 99% depending on the patient population, type of treatment received, and method of

Address correspondence to: Julienne E. Bower, Ph.D., UCLA Department of Psychology, 1285 Franz Hall, Los Angeles, CA 90095-1563, jbower@ucla.edu, Phone: (310) 825-3004, Fax: (310) 206-5895.

assessment[1, 5]. In the majority of studies, 30% to 60% of patients report moderate to severe fatigue during treatment, which in some cases may lead to treatment discontinuation. Fatigue typically improves in the year after treatment completion, although a significant minority of patients continue to experience fatigue for months or years after successful treatment[6, 7]. Studies of long-term cancer survivors suggest that approximately one-quarter to one-third experience persistent fatigue for up to 10 years after cancer diagnosis[8, 9]. Fatigue has a negative impact on work, social relationships, mood, and daily activities and causes significant impairment in overall quality of life during and after treatment[6, 10–12]. Fatigue may also be a predictor of shorter survival[13, 14].

Patient reports suggest that cancer-related fatigue is more severe, more persistent, and more debilitating than “normal” fatigue caused by lack of sleep or overexertion and is not relieved by adequate sleep or rest[15]. Indeed, studies have confirmed that the intensity and duration of fatigue experienced by cancer patients and survivors is significantly greater than healthy controls and causes greater impairment in quality of life[3, 10, 16, 17]. Cancer-related fatigue is multi-dimensional and may have physical, mental, and emotional manifestations including generalized weakness, diminished concentration or attention, decreased motivation or interest to engage in usual activities, and emotional lability[7] (Box 1). Although cancer-related fatigue shares some characteristics with depression, patients experience fatigue as a distinct and central symptom that impairs mood and functional abilities.

Despite the prevalence and negative impact of cancer-related fatigue, this symptom is underreported by patients and undertreated by clinicians[18]. One of the barriers to the assessment and management of fatigue may be a lack of information about mechanisms underlying this symptom, risk factors, and effective treatments. This review will summarize recent work on the biological mechanisms that underlie cancer-related fatigue, focusing on inflammation as a key pathway. In addition, risk factors for fatigue will be examined, as growing evidence suggests that only certain patients are at risk for severe and persistent fatigue. The identification of potential risk factors has been facilitated by recent longitudinal studies assessing pre-treatment risk factors for on-treatment and post-treatment fatigue. Finally, interventions for cancer-related fatigue will be reviewed, including physical activity, psychosocial, mind-body, and pharmacologic approaches. The focus here is on randomized controlled trials that have specifically targeted fatigue and particularly those that have enrolled fatigued patients.

MECHANISMS FOR CANCER-RELATED FATIGUE

Fatigue in cancer patients is multi-factorial and may be influenced by a variety of demographic, medical, psychosocial, behavioral, and biological factors. In terms of demographic factors, marital status and income have been linked to cancer-related fatigue in some reports, with unmarried patients who have a lower household income reporting higher levels of fatigue[6, 19]. This suggests that contextual factors (e.g., absence of partner who can provide instrumental and emotional support) may influence the experience of this symptom. Other potential contributing factors include medical comorbidities, medications, nutritional issues, physical deconditioning, mood disturbance, and physical symptoms, among others[20]. However, fatigue often occurs in patients who are otherwise healthy and have few if any of

these contributing factors, suggesting that other processes may also be at work. Of note, treatment-related factors (e.g., type of treatment, dose-intensity) are not consistently associated with fatigue, particularly in the post-treatment period.

A variety of biological mechanisms of CRF have been proposed and investigated over the past two decades[21, 22]. These include anemia, cytokine dysregulation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, five hydroxy tryptophan (5-HT) neurotransmitter dysregulation, and alterations in adenosine triphosphate and muscle metabolism, among others. To date, the mechanism that has garnered the most empirical attention and support is cytokine dyregulation, with a focus on pro-inflammatory cytokines.

Inflammation and cancer-related fatigue

The possibility that inflammatory processes may be involved in the etiology of cancer-related fatigue draws from basic research on neural-immune signaling. This body of work has demonstrated that peripheral inflammatory cytokines can signal the central nervous system to generate symptoms of fatigue and other behavioral changes via alterations in neural processes[23, 24] (Box 2). In the cancer context, investigators have proposed that tumors and the treatments used to eradicate them can activate the pro-inflammatory cytokine network, leading to symptoms of fatigue via cytokine signaling in the central nervous system[25–27]. In the pre-treatment period, the tumor itself may be a source for pro-inflammatory cytokines[28, 29] while during treatment, cytokines may be produced in response to tissue damage from radiation or chemotherapy[28, 30]. The inflammatory response may persist well after treatment completion as the host tries to deal with persisting pathogenesis and alterations in homeostatis. Of note, factors other than cancer and its treatment can influence inflammatory activity, including psychological, behavioral, and biological risk factors.

Here, we consider human studies that have examined links between inflammation and fatigue in patients before, during, and after cancer treatment. These studies have examined a range of inflammatory markers, including circulating concentrations of the pro-inflammatory cytokines IL-1β, TNF-α, and IL-6 and markers of their activity, including the IL-1 receptor antagonist (IL-1RA), the soluble TNF receptor (sTNFR), the soluble IL-6 receptor (sIL-6R), and C reactive protein (CRP). Alterations in other biological systems that have been linked to cancer-related fatigue will also be addressed.

Inflammation and fatigue prior to cancer treatment—A handful of studies have examined associations between inflammation and fatigue before treatment. In patients with newly diagnosed acute myelogenous leukemia or myelodysplastic syndrome, levels of several inflammatory markers were correlated with symptoms of fatigue[31]. Similar results have emerged in studies conducted with ovarian cancer patients assessed prior to surgery, which found a positive association between plasma concentrations of IL-6 and fatigue[32, 33]. On the other hand, a recent study of breast cancer patients assessed prior to surgery did not find elevated levels of CRP in those categorized as “fatigued”[34]. It is possible that small, localized breast tumors may not produce elevations in systemic cytokine concentrations that are sufficient to induce symptoms of fatigue. Another recent study conducted with breast

cancer patients assessed prior to chemotherapy found that fatigue was associated with elevations in CRP[35]; however, the majority of patients in this study were assessed after surgery, which is known to elicit an inflammatory response.

Inflammation and fatigue during cancer treatment—Radiation therapy and chemotherapy are two of the most common types of cancer treatment, and both are associated with increases in fatigue[36] and with elevations in certain inflammatory markers[37, 38]. Thus, investigators have hypothesized that activation of pro-inflammatory cytokines may contribute to fatigue during treatment. Early reports conducted with patients undergoing treatment were conflicting, possibly due to constraints of study methods (including use of non-standard measures to detect cytokine levels) and focus on cross-sectional associations between cytokine levels and fatigue[39–42]. However, more recent reports using mixed model analyses to model changes over time have yielded more positive results. In a study of patients undergoing radiation therapy for early-stage breast or prostate cancer, we found that increases in serum levels of inflammatory markers CRP and IL-1 receptor antagonist were associated with increases in fatigue[43]. Similarly, among breast cancer patients undergoing chemotherapy, changes in IL-6 were associated with changes in fatigue over the course of treatment[44]. Wang and colleagues intensively examined sickness symptoms and inflammatory markers in patients undergoing combined radiation and chemotherapy therapy for locally advanced colorectal, esophageal, and non-small cell lung cancer[45, 46]. These investigators documented acute increases in markers of inflammation that were correlated with increases in fatigue and other prominent sickness symptoms. Similar effects were seen in a study of individuals undergoing allogeneic hematopoietic stem cell transplantation (which includes high-dose chemotherapy) for acute myelogenous leukemia and myelodysplastic syndrome[47].

Inflammation and post-treatment fatigue in cancer survivors—Although fatigue typically abates in the year after cancer treatment, approximately 20–30% of cancer survivors report persistent fatigue that may last for 5–10 years post-treatment and beyond[8]. Our group has documented consistent alterations in the pro-inflammatory cytokine network among breast cancer survivors with persistent post-treatment fatigue, including elevations in circulating markers of inflammation[48, 49] and elevated intracellular cytokine production by monocytes after LPS stimulation[49, 50]. We have more recently shown an association between fatigue and elevations in plasma levels of the soluble TNF receptor type II (sTNF-RII), a downstream marker of TNF activity, in breast cancer survivors within one month after treatment; this association was particularly strong among women treated with chemotherapy[51].

These findings have been replicated in larger samples of breast cancer survivors. For example, Alexander et al. found significant elevations in CRP in breast cancer survivors who met stringent criteria for cancer-related fatigue (n = 60) relative to non-fatigued controls (n = 104)[52]. Mean levels of CRP were 3.91 mg/dL among the fatigued survivors (vs. 2.74 in the non-fatigued group), indicating low-grade inflammation. In a sample of 633 breast cancer survivors, higher CRP was associated with increased odds of being classified as fatigued, controlling for age, race, menopausal status, antidepressant/anxiolytic use,

medical comorbidities, and BMI[53]. In a sample of 299 breast cancer survivors, Orre et al. found a positive association between CRP and fatigue that remained significant after controlling for age, BMI, depressive symptoms, sleep disturbance, medication use, and self-rated health[54]. This group has also documented a positive association between inflammatory markers and fatigue in long-term survivors of testicular cancer[55]. In one of the few longitudinal studies to examine associations between inflammation and fatigue following treatment completion, Schrepf et al. found that decreases in IL-6 were correlated with declines in fatigue in ovarian cancer patients in the year after treatment completion[56].

Several recent studies have probed the molecular underpinnings of cancer-related fatigue by conducting genome-wide expression analyses on leukocytes from breast cancer survivors with persistent fatigue compared to non-fatigued survivors. A study conducted by our group focused on transcription of inflammation-related genes, particularly those responsive to the proinflammatory NF-κB transcription control pathway[57]. Results showed that breast cancer survivors with persistent fatigue showed increased expression of genes encoding proinflammatory cytokines and other mediators of immunologic activation. Further, promoter-based bioinformatic analyses indicated increased activity of proinflammatory NF-κB/Rel transcription factors in leukocytes from fatigued breast cancer survivors, which might structure the observed differences in the expression of inflammation-related genes. In contrast, an exploratory study by Landmark-Hoyvik et al. found that fatigued breast cancer survivors showed altered expression of genes involved in plasma or B cell pathways[58]. Gene expression profiling has also been used to identify gene transcripts associated with fatigue in prostate cancer patients, with some preliminary evidence for elevated expression of inflammation-related genes in fatigued patients[59, 60].

Cellular immunity, latent viral reactivation, and fatigue

Cancer treatments can cause pronounced and prolonged alterations in the cellular immune system[61, 62], which may underlie alterations in inflammatory activity and associated symptoms of fatigue. Our group has documented alterations in T cell populations and myeloid dendritic cells in breast cancer survivors with persistent fatigue that are correlated with inflammatory processes[49, 63]. Other groups have shown more global changes in the cellular immune system in relation to fatigue, including elevations in leukocyte numbers among fatigued breast cancer survivors[52, 58], though these effects have not been consistently replicated[64]. One of the few longitudinal studies in this area found that elevated leukocyte counts in the post-treatment period predicted persistent fatigue over a 2–3 year follow-up in breast cancer survivors[65].

Another potential explanation for elevated inflammatory processes and fatigue in cancer patients is reactivation of latent herpesviruses[66, 67]. A recent study conducted with breast cancer patients prior to treatment found that elevated cytomegalovirus (CMV) antibody titers were associated with a greater likelihood of being fatigued, as well as higher levels of CRP[68]. Cancer treatments such as chemotherapy promote viral reactivation and associated increases in inflammatory markers[69] which may have long-term implications for immune regulation and recovery as well as fatigue and other behavioral symptoms.

Neuroendocrine alterations and cancer-related fatigue

Hypothalamic-pituitary-adrenal (HPA) axis dysregulation and fatigue—

Alterations in the HPA axis have been proposed as a mechanism underlying cancer-related fatigue, either directly or through effects on inflammatory processes. The HPA axis is an important regulator of cytokine production and has potent anti-inflammatory effects[70]. These effects can occur via alterations in glucocorticoid production (including dysregulated circadian profiles) and/or decreased sensitivity of the glucocorticoid receptor (GR) to hormone ligation[71]. Preliminary evidence suggests alterations in both pathways among patients with cancer-related fatigue. In terms of cortisol production, breast cancer survivors with persistent fatigue show alterations in diurnal cortisol slope, with elevated levels of evening cortisol relative to non-fatigued controls[72]. Fatigued breast cancer survivors also demonstrate blunted cortisol responses to psychological stress[73] that are correlated with elevations in stimulated cytokine production and may underlie elevated inflammatory activity[50]. However, studies have not shown alterations in total daily cortisol production or 24-hour urinary free cortisol in breast cancer survivors with post-treatment fatigue[52, 72]. In ovarian cancer patients, higher levels of evening cortisol and reduced cortisol variability are associated with fatigue before treatment onset[74], and normalization of cortisol profiles in the following year is associated with reductions in fatigue[56].

In terms of glucocorticoid receptor sensitivity, genome-wide transcriptional profiling of leukocytes from fatigued breast cancer survivors showed a marked down-regulation of genes with response elements for the glucocorticoid receptor, suggesting a state of functional GR resistance[57]. Reduced GR sensitivity may contribute to the tonic upregulation of NF-κB observed in fatigued survivors, consistent with studies linking GR desensitization to increased NF-κB activity in non-cancer populations[75, 76].

Autonomic nervous system dysregulation and fatigue—Preliminary reports suggest that alterations in the autonomic nervous system may also be relevant for cancer-related fatigue. In a study of breast cancer survivors, fatigue was associated with elevated levels of norepinephrine (indicating increased sympathetic activity) and lower heart rate variability (indicating reduced parasympathetic activity), both at rest and in response to a psychological challenge[77]. We recently replicated the association between cancer-related fatigue and lower resting HRV in a sample of pre-menopausal breast cancer survivors, who are at particular risk for elevated fatigue[78].

Like the HPA axis, the autonomic nervous system regulates immune and inflammatory processes[79], which may mediate effects on cancer-related fatigue. In general, sympathetic nervous system activity is associated with increased inflammatory activity, whereas parasympathetic nervous system activity is associated with reduced inflammatory activity. However, inflammation did not mediate the association between low HRV and fatigue in our sample of pre-menopausal breast cancer survivors[78], suggesting that other pathways may also be relevant.

Summary of biological mechanisms

Overall, results from studies conducted with cancer patients and survivors support the hypothesis that inflammatory processes contribute to fatigue during and particularly after treatment. The association between inflammation and fatigue has been documented primarily in breast cancer survivors, though similar effects have been observed in ovarian and testicular cancer survivors. Importantly, most of the studies in this area have controlled for potential biobehavioral confounds, including age and BMI, indicating that links between inflammation and fatigue are not driven by these factors. Findings are not entirely uniform, and associations have not been found in all patient groups[80], for all aspects of fatigue[55, 81], or for all inflammatory markers[51, 54]. Inconsistency across studies may be due to differences in the definition and assessment of cancer-related fatigue, disease- and treatment-related characteristics, and type (and quality) of immunologic assessments. Different components of the pro-inflammatory cytokine network may be associated with different aspects of fatigue, in different patient groups, at difference stages of the cancer trajectory. Thus, it is important to assess key components of the cytokine network, as well as key dimensions of fatigue, using valid and reliable measurement techniques. Of note, one of the most consistent findings in this literature is the link between CRP and post-treatment fatigue, perhaps because CRP is routinely assayed in many clinical laboratories (and thus may be more reliably measured than other markers of inflammation) and because acute effects of treatment have resolved at this time.

Studies have also documented associations between cancer-related fatigue and alterations in the immune and neuroendocrine system, including changes in leukocyte subsets, reactivation of latent herpesviruses, dysregulated cortisol rhythm, reduced glucocorticoid receptor sensitivity, and alterations in the autonomic nervous system. These systems are closely linked to inflammation and may influence fatigue by initiating or maintaining elevated inflammatory activity. In addition, changes in these systems may have direct effects on fatigue. At this point, it is unclear whether these alterations play a causal role in the development and persistence of cancer-related fatigue, as activity in these systems has typically been measured concurrently with fatigue. In addition, because most studies have focused on post-treatment survivors, it is unclear whether the alterations associated with fatigue were driven by cancer treatment (e.g., chemotherapy effects on the cellular immune system) or may have been present prior to cancer diagnosis and treatment. For example, a recent prospective study conducted with military personnel deployed to a war zone found that pre-deployment levels of GR sensitivity predicted the development of post-deployment fatigue[82]. Similarly, it is possible that pre-cancer alterations in GR sensitivity and other biological systems may serve as a risk factor for cancer-related fatigue, comparable to the risk factors discussed below. Prospective, longitudinal studies are required to determine the role of neuroendocrine and immune alterations in the onset and persistence of fatigue and the mechanisms through which this occurs.

RISK FACTORS FOR CANCER-RELATED FATIGUE

As noted previously, fatigue typically increases during cancer treatment and improves in the year after treatment completion. However, there is considerable variability in the experience

of fatigue before, during, and after treatment[19, 83], suggesting that certain individuals may be at particular risk for this disabling symptom. Of note, there is also variability in the inflammatory response to treatment, which is correlated with variability in fatigue (e.g.,[43]). Over the past several years, longitudinal studies have begun to examine risk factors for cancer-related fatigue, and particularly fatigue that persists for months or years after cancer treatment. Studies in this area have focused primarily on demographic, medical, behavioral, and psychosocial predictors, but genetic risk factors are of growing interest. Identification of these factors is important for advancing our understanding of this symptom and for improving identification and treatment of vulnerable patients. In this section, we review this growing literature and suggest pathways through which these factors may influence fatigue.

Genetic risk factors

Given growing evidence that inflammation plays a key role in the onset and persistence of cancer-related fatigue, investigators have begun to examine genetic factors that influence pro-inflammatory cytokine activity as potential risk factors for fatigue in the cancer setting. Most of these studies have used a candidate gene approach, focusing on single nucleotide polymorphisms (SNPs) in inflammation-related genes including *IL1B, IL6,* and *TNF*. There is preliminary evidence that variations in these genes are associated with cancer-related fatigue during and after treatment. In longitudinal studies with patients undergoing radiation therapy, polymorphisms in *TNFA* and *IL6* were associated with elevated fatigue before, during, and for four months after treatment completion[84, 85]. Polymorphisms in *TNFA* and *IL6* were also associated with increases in fatigue in a small longitudinal study of prostate cancer patients undergoing androgen deprivation therapy[86].

Cross-sectional studies conducted with cancer populations have yielded similar results. In two large studies conducted with lung cancer patients, polymorphisms in *IL8* were associated with increased fatigue before treatment onset[87], while polymorphisms in *IL1B* and *IL1RN* were associated with post-treatment fatigue[88]. In studies conducted with breast cancer survivors, polymorphisms in *TNFA, IL6, IL1B* have been associated with elevated fatigue[89, 90], although these findings have not been consistently replicated[91]. Of note, polymorphisms in inflammation-related genes have been linked to fatigue in other patient populations[92, 93] and in cancer caregivers[85], suggesting that inflammation-promoting genes may serve as a general risk factor for fatigue symptomatology.

Overall, research in this area supports the hypothesis that inflammatory processes are important for cancer-related fatigue and suggests that certain cytokine genetic variants may increase risk for this symptom. However, the majority of this work has been conducted in relatively small samples and requires replication. In addition, genome-wide scanning might help to identify other genetic risk factors for fatigue, related to inflammation or other systems[21].

Psychological and biobehavioral risk factors

Pre-treatment fatigue—Across studies, the strongest and most consistent predictor of post-treatment fatigue is pre-treatment fatigue. Patients who report higher levels of fatigue before radiation and/or chemotherapy also report elevated fatigue immediately after

treatment completion[94], over the following year[35, 95, 96], and up to 2.5 years later[97]. In studies that compared multiple predictors, pre-treatment fatigue emerged as one of the strongest, if not the strongest predictor of fatigue in the post-treatment period[35, 95]. Together, these findings suggest that whatever biological, psychological, or behavioral dysregulation contributes to cancer-related fatigue may be present before treatment onset.

Depression—Depression is of particular interest as a risk factor for cancer-related fatigue, as fatigue and depression are strongly correlated in cancer populations[98]. The association between these two constructs is complex; fatigue is a symptom of depression, but may also precipitate depressed mood due to interference with social, occupational, and leisure activities. Rather than trying to disentangle causality, it may be more informative to examine whether mood disturbance predicts the onset and persistence of fatigue and can thus be used to identify vulnerable patients. Indeed, there is evidence from several longitudinal studies that pre-treatment depression and anxiety predict cancer-related fatigue before, during and after treatment[65, 83, 94, 95, 97, 99]. Of note, the majority of these studies did not control for pre-treatment fatigue, and thus the independent contribution of depression over and above pre-existing fatigue is not entirely clear. A history of major depressive disorder (and treatment for mental problems prior to cancer diagnosis) also predicted post-treatment fatigue in several reports[65, 100], with effects observed up to 42 months after treatment completion[101]. Thus, patients with a history of mental illness and those with elevated distress in acute stage of cancer diagnosis and treatment onset appear to be at risk for persistent post-treatment fatigue.

Sleep disturbance—Like depressed mood, sleep disturbance is closely correlated with fatigue in cancer populations, and investigators have hypothesized that sleep problems may contribute to daytime symptoms of fatigue[102]. Indeed, studies conducted with breast and prostate cancer patients undergoing radiation therapy have shown that pre-treatment sleep disturbance is associated with higher levels of fatigue before, during, and for up to 6 months after treatment completion[83, 99]. In patients with gynecologic cancers beginning chemotherapy, higher levels of sleep disturbance (assessed objectively using actigraphy) predicted earlier subsequent peaks in fatigue[103]. Of note, fatigue predicted subsequent elevations in depressed mood in this study, suggesting a cascade effect among these symptoms in the early stages of cancer treatment. Together, these reports suggest that sleep disturbance may be a risk factor for cancer-related fatigue, although additional research in the post-treatment period is needed. Studies of cancer survivors have shown that fatigue can persist even when patients report getting adequate sleep, indicating that other factors contribute to fatigue maintenance over time.

Physical activity, physical deconditioning, and body mass index—Physical inactivity is correlated with cancer-related fatigue; patients who are more fatigued typically report lower levels of physical activity[104, 105]. Lack of physical activity may lead to physical deconditioning, which makes everyday tasks more challenging and potentially contributes to the development and persistence of fatigue. Indeed, cancer survivors with post-treatment fatigue show decreased cardiorespiratory fitness[106]. However, few studies have examined the temporal association between activity, deconditioning, and fatigue, making it difficult to

determine causality. There is evidence from longitudinal studies that lower levels of physical activity *after* treatment completion predict persistent fatigue in breast cancer survivors[19, 107], although elevated fatigue *during* treatment may have preceded (and precipitated) lower physical activity in these reports. In either case, low levels of physical activity and associated decreases in cardiorespiratory fitness may play an important role in the development and/or persistence of cancer-related fatigue. Elevated body mass index (BMI) has also been linked with fatigue, and a longitudinal study of women with early-stage breast cancer found that BMI was one of the key predictors of fatigue at 6[19] and 42 months post-treatment[101]. Body mass index also predicted persistent fatigue in a longitudinal study of post-treatment breast cancer survivors, above and beyond other risk factors[65].

Coping and appraisal—Psychological responses to cancer diagnosis and treatment can also influence fatigue symptoms. In particular, the tendency to "catastrophize", or engage in negative self-statements and thoughts regarding fatigue (e.g., I begin thinking of all the possible bad things that could go wrong in association with the fatigue; I tell myself I don't think I can bear the fatigue any longer) was associated with higher levels of fatigue during[108] and for up to 42 months after treatment[100, 101] in research with breast cancer patients. Indeed, catastrophizing was one of the strongest predictors of persistent elevations in fatigue in these reports. Similarly, patients who expect to experience fatigue are more likely to report elevated fatigue after cancer surgery[109]. Thus, patients' negative expectations and coping strategies early in the cancer trajectory appear to put them at increased risk for post-treatment fatigue.

Other psychosocial risk factors—Emerging evidence has identified other psychological risk factors for cancer-related fatigue. Exposure to childhood stress, including experiences of abuse and neglect, is associated with elevated fatigue in cross-sectional studies of breast cancer survivors[110, 111]. These findings are consistent with research conducted in non-cancer populations showing that early life stress is associated with increased risk for fatigue[112–114]. Loneliness is also associated with elevated fatigue in cancer survivors (and older adults) and predicts increases in fatigue over time[115].

Summary and mechanisms

A growing number of longitudinal studies have identified risk factors for fatigue during and after cancer treatment. These include genetic risk factors (SNPs in inflammation-related genes), psychosocial factors (pre-treatment fatigue, depression, and sleep disturbance, dysfunctional coping and appraisal processes, loneliness, early life stress) and biobehavioral factors (physical inactivity, elevated body mass index). Many of these factors are associated with inflammatory processes, including depression, sleep disturbance, physical inactivity, body mass index, early life stress, and loneliness. Individuals with these risk factors may already have elevated inflammatory activity at the time of diagnosis, increasing risk for pre-treatment fatigue. In addition, these factors may increase the inflammatory response to diagnosis and treatment. Indeed, in experimental studies conducted with non-cancer samples, individuals with a history of depression and early life stress show an exaggerated inflammatory response to psychosocial challenge[116, 117]. The mechanisms through which these and other risk factors influence fatigue are an important topic for future research.

It may also be useful to distinguish between factors that increase risk for fatigue during treatment (precipitating factors) and those that lead to its persistence in the post-treatment period (perpetuating factors)[96]. To date, studies have primarily focused on the period during and immediately after treatment, or in the years after treatment completion. Longitudinal studies that follow patients from pre-treatment into the survivorship period will illuminate which factors are most important for acute and more persistent fatigue. This will help to identify appropriate targets for intervention at different stages of the cancer trajectory.

TREATMENTS FOR CANCER-RELATED FATIGUE

A diverse range of treatment approaches have been used to address cancer-related fatigue during and after cancer treatment. Indeed, a recent review of the literature indicated that more than 170 intervention studies that included fatigue as a primary or secondary outcome have been conducted in patients with cancer[20]. These include physical activity, psychosocial, mind-body, and pharmacological interventions. Perhaps because the etiology of cancer-related fatigue is multi-factorial and still poorly understood, there is currently no "gold standard" for treatment of this symptom. Still, a number of these approaches have been shown to be beneficial in reducing cancer-related fatigue, as reviewed below.

Exercise

There are a large and growing number of randomized controlled trials of exercise as a treatment for cancer-related fatigue. One recent meta-analysis of this literature identified 56 randomized controlled trials that investigated the effects of exercise on cancer-related fatigue[118]. Results from this meta-analysis indicated that exercise was more effective than control in reducing fatigue, with a mean effect size of −0.27. These findings are similar to other recent meta-analyses of exercise interventions for cancer-related fatigue which have yielded effect sizes in the range of −0.30 to −0.38[119–123], suggesting a moderate effect. Beneficial effects of exercise on fatigue have been observed in trials conducted with patients during and after treatment, indicating that exercise can be helpful at different stages of the disease trajectory. During treatment, exercise may buffer treatment-related increases in fatigue, whereas exercise may reduce fatigue in patients after treatment completion[121].

What forms of exercise are particularly beneficial for fatigue? Results from the meta-analyses indicate that aerobic exercise regimens are associated with significant reductions in cancer-related fatigue[118, 121]. More mixed effects are seen for resistance exercise[118, 122, 124]. A number of different aerobic exercise regimens have shown beneficial effects on fatigue, ranging from home-based programs[125] to supervised, laboratory-based programs[126]. Guidelines from the American College of Sports Medicine (ACSM) recommend that cancer patients and survivors engage in at least 150 minutes of moderate intensity aerobic activity each week, consistent with recommendations for the general population[127]. Exercise trials conducted with cancer patients often begin with more modest levels of physical activity that increase in dose and intensity over time[125]. ACSM guidelines further recommend that exercise should be tailored to the individual cancer survivor to account for exercise tolerance and specific diagnosis, and that patients be closely monitored to safely progress exercise intensity and avoid injury.

One important limitation of the literature on exercise for cancer-related fatigue is the lack of studies that have specifically targeted fatigued patients. These trials have typically not enrolled patients who endorse fatigue, but instead have taken all patients who meet other eligibility criteria. Thus, it is unclear whether these interventions will be feasible or effective for patients with more severe fatigue. Indeed, fatigue may be a significant barrier to participation in exercise interventions, particularly among cancer survivors[128]. For these patients, other strategies may be more appropriate.

Psychosocial interventions

There is a large literature on psychosocial interventions for cancer patients and survivors[129], and many of these trials have included measures of fatigue. Meta-analyses of psychosocial intervention trials that included fatigue as a primary or secondary outcome have shown reductions in fatigue relative to control, with effect sizes ranging from −0.10 to −0.30, suggesting a small to moderate effect[130–132]. The more modest effect sizes seen in these trials relative to physical activity interventions may be due to the fact that most were focused on reducing stress and improving general quality of life and did not include fatigue as a primary focus or outcome. Here, we review randomized controlled trials of psychosocial interventions that had a more explicit focus on cancer-related fatigue, including those that enrolled fatigued patients.

Several interventions have targeted fatigue among patients undergoing cancer treatment. In one study, breast cancer patients commencing chemotherapy received a 3-session individualized fatigue education and support program delivered in the clinic and by phone[133]. The intervention buffered the acute increase in fatigue observed in control group participants undergoing treatment, although this effect did not persist. Another trial conducted with a mixed sample of cancer patients undergoing chemotherapy found that a 3-session individualized intervention focusing on fatigue-related thoughts and behavior led to greater reductions in fatigue one month after treatment completion than usual care[134]. A cognitive-behavioral approach combined with hypnosis also showed beneficial effects on fatigue among breast cancer patients undergoing radiation therapy; specifically, the intervention buffered the increase in fatigue observed in controls[135].

Psychoeducational interventions conducted in the post-treatment period have also demonstrated beneficial effects on fatigue. The Moving Beyond Cancer Trial, a multi-center, randomized controlled trial for breast cancer patients who had recently completed treatment, found that a brief psychoeducational video that included information on fatigue (as well as modeling of physical activity) led to significant improvements in fatigue relative to control[136]. Similarly, a brief group-based psychoeducational intervention for breast cancer survivors that also included physical activity led to significant improvements in fatigue[137].

To date, only two psychosocial intervention studies have used fatigue as an entry criteria for trial participation. Both were conducted with cancer survivors who reported moderate to severe fatigue. Gielissen and colleagues randomized 112 fatigued cancer survivors to individual cognitive-behavioral therapy or wait-list control[138]. The therapy focused on perpetuating factors for persistent fatigue, including dysfunctional cognitions concerning

fatigue, poor coping, fear of recurrence, dysregulation of sleep and activity patterns, and low social support. They found a significant decrease in fatigue in the intervention group relative to controls that was maintained over a long-term (1–4 year) follow-up[139]. Yun et al. randomized 273 fatigued cancer survivors to a 12-week, web-based, individually tailored program based on National Comprehensive Cancer Network (NCCN) fatigue guidelines[140]. This program provided information on cancer-related fatigue as well as energy conservation, physical activity, sleep hygiene, distress management, nutrition, and pain control. Results showed a significant decrease in fatigue in the intervention group relative to controls.

Overall, these studies suggest that educating patients about cancer-related fatigue and providing them with cognitive and behavioral strategies to manage fatigue symptoms (including physical activity) can have beneficial effects on fatigue, both during and after treatment. Preliminary evidence also indicates that more intensive interventions targeting post-treatment fatigue, both in-person and web-based, may be effective for fatigued cancer survivors.

Mind-body interventions

There is considerable interest in mind-body approaches among cancer patients, and a growing number of randomized trials have evaluated the efficacy of mind-body interventions for improving health and well-being in this population[141–143]. We focus here on studies that used fatigue as an entry criteria for study participation, including trials of acupuncture, mindfulness meditation, yoga, and biofield therapy. Three acupuncture trials have targeted cancer survivors with moderate to severe post-chemotherapy fatigue. The largest of these trials randomized 302 patients to 6 weeks of acupuncture or usual care, and saw significant improvement in fatigue in the acupuncture group[144]. These findings are consistent with an earlier pilot study conducted by this group that saw beneficial effects of acupuncture relative to real or sham acupressure on post-chemotherapy fatigue[145]. However, in a trial that compared acupuncture to sham acupuncture for cancer survivors with post-chemotherapy fatigue, no group differences were observed[146].

Building on a growing literature on the beneficial effects of mindfulness meditation, Van der Lee and colleagues randomly assigned 100 cancer survivors with severe fatigue to a 9-week program of mindfulness-based cognitive therapy or wait-list control[147]. The intervention was designed to help patients become aware of and inhibit potentially maladaptive automatic responses, including feelings, thoughts, and behaviors, and focused specifically on cancer-related fatigue. Patients randomized to the intervention group showed significant reductions in fatigue at post-treatment that were maintained over a 6-month follow-up. Our group conducted an Iyengar-based yoga intervention for breast cancer survivors with persistent fatigue[148]. The 12-week intervention specifically targeted fatigue and included postures believed to be efficacious for improving this symptom, including restorative poses, passive inversions, and passive backbends. This specialized yoga program led to significant improvements in fatigue relative to the health education control condition and also had beneficial effects on inflammatory activity[149]. Finally, in a study evaluating the efficacy of biofield therapy for cancer-related fatigue, Jain and colleagues randomized breast cancer survivors with fatigue to a 4-week program of biofield healing, mock healing, or wait-list

control[150]. Both biofield healing and mock healing led to significant reductions in fatigue relative to control.

The literature on mind-body interventions for cancer-related fatigue is still quite small, but preliminary findings suggest that certain approaches may be beneficial for survivors with persistent fatigue, including mindfulness, yoga, and acupuncture. Of note, several studies that compared "real" to "sham" approaches did not find differential effects on fatigue (both were helpful)[146, 150], highlighting the importance of including active control conditions in these trials. The same criticism could be applied to psychosocial interventions and physical activity interventions, which typically do not include active control groups. It is also important to note that the interventions showing positive effects were specifically designed to target fatigue, and non-specific approaches may be less effective[151].

Pharmacologic interventions

A number of pharmacologic treatments have been evaluated for the treatment of cancer-related fatigue. A meta-analysis of this literature published in 2008 included 27 randomized controlled trials, including hematopoietic growth factors (14 studies), progestational steroids (4 studies), methylphenidate (a psychostimulant; 2 studies), and paroxetine (an antidepressant; 2 studies), among others[152]. The hematopoietic growth factor trials were all conducted with anemic patients, the majority of whom were undergoing chemotherapy. In general, treatment with hematopoietic agents led to improvements in fatigue caused by chemotherapy-induced anemia (effect size for erythropoietin = −0.30; effect size for darbepoetin = −0.13). Methylphenidate also led to greater reductions in fatigue than placebo (effect size = −0.30), but progestational steroids and paroxetine did not. Another anti-depressant, sertraline, had no beneficial effect on fatigue in patients with advanced cancer who were neither fatigued nor depressed[153]. A recent trial of dexamethasone for patients with advanced stage cancer who reported moderate to severe symptoms of cancer-related fatigue showed significant improvements in fatigue and quality of life[154].

An updated meta-analysis included 5 randomized controlled psychostimulant trials, most of which were conducted among patients with advanced disease and used methylphenidate[155]. Overall, results suggested that psychostimulants were more effective than placebo in improving fatigue (effect size = −0.28), although only one of the five studies yielded a statistically significant treatment effect[156]. Two recent studies conducted with larger samples of patients showed no benefit for methylphenidate vs. placebo for improving fatigue[157, 158], although in sub-group analyses methylphenidate did appear to be effective for patients with severe fatigue and those with advanced disease[158]. There is also interest in a nonamphetamine-based stimulant, the wakefulness agent modafinil, as a potential treatment for cancer-related fatigue. One large multicenter trial of patients undergoing chemotherapy found beneficial effects of modafinil among patients who reported severe fatigue at baseline, but not among those with mild or moderate fatigue[159].

Based on research suggesting an inflammatory basis for cancer-related fatigue, a handful of small Phase II trials have used anti-cytokine agents to treat fatigue in patients with advanced cancer. In a study conducted by Monk and colleagues, patients undergoing dose-intensive chemotherapy who received etanercept (a TNF-decoy receptor) reported significantly less

fatigue than those receiving chemotherapy alone[160]. A small non-randomized study also showed some benefit for infliximab (an anti-TNF antibody) on fatigue in the palliative care setting[161]. Beneficial effects of anti-TNF agents on fatigue have also been observed among patients with inflammatory conditions, including psoriasis[162] and depression[163]. Although there are ongoing trials of other anti-inflammatories for cancer-related fatigue, the effectiveness of other agents (e.g., minocycline) has not been determined.

Despite interest in supplements to treat fatigue, very few controlled trials have examined the efficacy of these agents in cancer patients. One large, multisite trial examined the effect of L-cartinine for patients with fatigue, most of whom were undergoing treatment[164]. There was no evidence that 4 weeks of L-carnitine was more effective than placebo in improving fatigue; instead, fatigue improved in both the treatment and control groups. In contrast, a large multisite trial of American ginseng for patients with cancer-related fatigue did find beneficial effects, particularly among patients undergoing active cancer treatment[165].

Overall, this literature suggests that hematopoietic agents may be effective in improving fatigue that occurs secondary to chemotherapy-induced anemia. However, because most fatigued patients are not anemic, these agents are unlikely to be useful for the majority of patients with cancer-related fatigue, particularly in the post-treatment period. Among the other agents tested to date, methylphenidate appears to be the most promising, although results are quite mixed and two recent trials did not find beneficial effects on fatigue. Because these studies have primarily focused on patients with advanced cancer, there is limited evidence for the use of psychostimulants in the management of fatigue in patients who are disease-free following active treatment. Of note, selective serotonin reuptake inhibitor (SSRI) antidepressants do not appear to have beneficial effects on cancer-related fatigue, supporting the distinction between fatigue and depression in cancer patients and suggesting that fatigue is not solely a side effect of depression. American ginseng and dexamethasone may hold promise for treating cancer-related fatigue but more research on these agents are needed.

Mechanisms for intervention effects

The literature reviewed above suggests that a variety of different intervention approaches may be useful for cancer-related fatigue, including physical activity, psycho-education, cognitive-behavioral, and mind-body approaches. These interventions have different targets and may work through different mechanism, including cognitive, behavioral, and biological mechanisms. For example, cognitive approaches to treating cancer-related fatigue specifically target maladaptive thoughts about fatigue, including catastrophizing[138]. Given that catastrophizing predicts more severe and persistent fatigue symptoms in cancer patients[19], reducing the use of this coping mechanism may be one of the “active ingredients” that promotes reductions in fatigue. Even more physical approaches may work by changing thoughts and beliefs about fatigue; for example, patients felt more confident about their ability to manage fatigue after learning certain yoga postures[148], which might lead to reductions in fatigue symptoms.

Biological mechanisms for intervention effects are also possible, including changes in inflammatory processes. Individuals who are more physically active show lower

inflammatory activity[166]; thus, interventions that increase physical activity (and potentially reduce BMI) may influence fatigue by reducing inflammation. Of note, these interventions may also improve fatigue by improving cardiorespiratory fitness. Mind-body and psychosocial approaches may also work by reducing inflammatory activity. We have shown that a targeted yoga program for fatigued breast cancer survivors was not only effective in reducing fatigue but also led to reductions in NF-kB signaling, a key regulator of inflammatory activity[149]. Similar effects on inflammatory signaling were observed in a recent trial of mindfulness meditation for older adults[167]. Cognitive-behavioral stress management for breast cancer patients also leads to reductions in pro-inflammatory signaling[168], though the effects of cognitive behavioral therapy for cancer-related fatigue on inflammation have not been examined.

CONCLUSIONS

Fatigue is one of the common and distressing side effects of cancer treatment and can persist for months or years after treatment completion. Cancer-related fatigue may be influenced by multiple factors, including demographic, medical, cognitive/emotional, behavioral, and biological factors. In particular, growing evidence suggests an inflammatory basis for cancer-related fatigue, and studies have documented an association between elevated inflammatory processes and fatigue in patients before, during, and after treatment. The evidence linking inflammation and fatigue in cancer survivors is particularly strong, with consistent findings emerging from large, well-controlled studies of breast cancer survivors. Other biological processes that may influence fatigue include alterations in the neuroendocrine and immune systems, which are closely tied to inflammatory activity.

There is considerable variability in the experience of fatigue before, during, and after treatment, indicating that some patients may be particularly vulnerable to this symptom. Longitudinal studies have begun to illuminate risk factors for cancer-related fatigue, including depression, sleep disturbance, physical inactivity, and dysfunctional expectations and beliefs about fatigue. In addition, preliminary evidence indicates that variations in inflammation-related genes may increase risk for fatigue, suggesting a genetic contribution. Of note, the variability in fatigue is not closely tied to cancer treatment; patients who receive similar types of treatment may experience very different levels of fatigue, particularly in the post-treatment period.

A variety of different intervention approaches have been used to treat cancer-related fatigue. Physical activity is among the most promising approaches, and randomized controlled trials have documented beneficial effects of exercise during and after treatment. However, because these trials have not specifically focused on fatigued patients (i.e., presence of fatigue was not used as an inclusion criteria), the feasibility and efficacy of physical activity for patients with moderate to severe fatigue is unclear. Other psychosocial and mind-body interventions have targeted fatigued patients and shown beneficial effects. These include cognitive behavioral approaches, mindfulness, yoga, and acupuncture. Despite interest in psychostimulants such as methylphenidate, the evidence for these agents is quite mixed and recent guidelines do not recommend their use in post-treatment survivors[169].

After two decades of research on cancer-related fatigue, we have a good understanding of the characteristics, prevalence, and course of this symptom and are beginning to elucidate mechanisms, risk factors, and effective treatments. We also have a growing appreciation of the complexity of this symptom, which shows significant inter-individual variability in its severity and expression. To advance our understanding of cancer-related fatigue, and particularly the variability in its experience and expression, the next generation of research must address a few key questions: Who is at risk for fatigue, and why? What are the mechanisms that underlie fatigue during and after treatment? To answer these questions, longitudinal studies are required that track patients before, during, and after treatment and include comprehensive assessment of biobehavioral risk factors. Together with appropriate statistical techniques (e.g., multilevel modeling, latent growth mixture modeling), this longitudinal approach will facilitate the identification of distinct trajectories of fatigue, and associated risk factors. These studies should also include in-depth assessment of underlying mechanisms, which can be used to direct intervention efforts; this is particularly important if the risk factors themselves are not amenable to intervention (e.g., genetic risk factors). Further, determination of factors that influence fatigue onset vs. persistence may be helpful in determining which type of interventions may be most helpful during vs. after treatment. Studies should also examine the co-occurrence of fatigue and related symptoms to elucidate the complex interactions between them, including depression and sleep disturbance. Finally, the degree to which cancer-related fatigue differs from normal age-related fatigue (and fatigue in other contexts) merits focused attention. Cancer and its treatment may accelerate age-related changes in inflammation, aerobic capacity, and other physiological processes, which may contribute to fatigue; thus, the fatigued cancer patient may look biologically “older” and potentially at greater risk for premature conditions of aging. There may also be different contributing factors for fatigue in older vs. younger patients, with implications for treatment.

The identification of underlying mechanisms should guide the development of targeted, individualized interventions for cancer-related fatigue, similar to current individualized approaches to cancer therapy. For example, patients whose fatigue appears to be primarily driven by dysfunctional coping strategies (e.g., catastrophizing) may be more responsive to cognitive-behavioral therapy approaches. In contrast, those whose fatigue is primarily driven by inflammatory activity may be more responsive to anti-inflammatory therapies (either behavioral or pharmacological). The importance of targeting the treatment to the underlying mechanism was illustrated in a recent trial evaluating the effect of the TNF antagonist infliximab for patients with treatment-resistant depression[163]. Results showed that infliximab was only effective for patients with elevated inflammatory markers at baseline. Similarly, anti-inflammatory approaches may be most efficacious for fatigued patients who show evidence of elevated inflammatory activity. Of note, even patients with more biologically driven fatigue (if there is such a group) may have developed dysfunctional cognitions and behaviors about their fatigue that are amenable to cognitive-behavioral intervention. Understanding the complexity of cancer-related fatigue, and using that understanding to identify vulnerable individuals and develop targeted, individualized interventions, is critical for reducing the burden of this symptom and improving quality of life and well-being in cancer patients and survivors.

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Box 1

Defining and assessing cancer-related fatigue

Cancer-related fatigue (CRF) has been defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity and interferes with usual functioning. Fatigue is a subjective experience and patient self-report is the gold-standard method for assessing CRF. A number of measures have been developed to assess fatigue in the cancer context, which vary from single-item assessments of fatigue severity to multi-dimensional scales assessing different components of fatigue (severity, duration, interference; mental, physical, emotional fatigue)[170]. A common approach to assessing fatigue involves asking patients to rate their fatigue on a 0–10 scale, where mild fatigue is indicated as a score of 1 to 2, moderate fatigue as 4 to 6, and severe fatigue as 7 to 10[171]. In 1998, formal diagnostic criteria were proposed to define a clinical syndrome of cancer-related fatigue[172]. One of the advantages of the criteria is that they specifically ask patients whether the fatigue they are experiencing is a consequence of cancer or cancer therapy. In addition, the criteria attempt to distinguish CRF from fatigue that occurs secondary to depression. However, these criteria have not been widely used to identify patients with CRF or to direct intervention efforts[173], and may be overly stringent.

Box 2

Neural immune signaling: Effects on fatigue and other behavioral symptoms

Basic research on neuro-immune interactions has documented behavioral effects of peripheral immune activation that are mediated by pro-inflammatory cytokines[23]. Signals from the peripheral immune system are conveyed to the central nervous system through several routes, including direct neural activation via the afferent vagus nerve, transport of peripheral cytokines across the blood-brain barrier via carrier molecules, and interaction of circulating cytokines with brain cytokine receptors in areas that lack a functional blood-brain barrier (i.e., circumventricular organs) and with brain vascular endothelial cells that release second messages to stimulate cytokine production in the brain[79]. Cytokine signaling leads to changes in neural activity, physiological processes (e.g., fever), and behavior[174]. In animal models, injection or induction of pro-inflammatory cytokines leads to decreased motor activity (presumably a behavioral manifestation of fatigue) as well as reduced food and water intake, social withdrawal, anhedonia, and altered cognition. These behavioral changes have been collectively described as "sickness behavior" and are thought to represent a motivational shift designed to facilitate recovery and prevent the spread of infection[79, 175]. In humans, pharmacologic doses of cytokines given for treatment of cancer or hepatitis C are associated with significant increases in fatigue and other markers of sickness, including depressed mood and sleep disturbance[176–178]. Experimental studies of cytokine induction in healthy individuals have documented similar effects, with subjects reporting increased fatigue following endotoxin administration that are correlated with elevations in circulating concentrations of pro-inflammatory cytokines[179, 180]. In observational studies, sub-clinical levels of inflammatory markers prospectively predict the development of fatigue in otherwise healthy individuals[181, 182]. Further, pharmacologic agents that block the pro-inflammatory cytokine TNF-α lead to reduced fatigue among individuals with inflammatory conditions[162] and in pilot studies with cancer patients[160]. Together, this evidence provides a strong biological rationale for inflammation as a potential mechanism underlying cancer-related fatigue.