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Comprehensive Insights into Cancer Related Fatigue

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Abstract

Cancer-related fatigue (CRF) is a distressing, persistent and multidimensional symptom associated with cancer and its treatment. Unlike ordinary tiredness, it is often disproportionate to recent activity and is incompletely relieved by rest. It interferes with physical, emotional, cognitive and social functioning. It occurs during or after treatment and may persist for several years thereafter. Despite its prevalence and substantial effect on quality of life, CRF remains under-recognised and undertreated. Its pathogenesis is incompletely understood and probably involves a complex interplay between inflammatory, neuroendocrine, circadian, metabolic, neuromuscular and psychosocial processes rather than a single mechanism. Assessment therefore requires routine patient-reported screening, evaluation of severity and functional interference and investigation of potentially reversible contributors (such as anaemia, endocrine dysfunction, pain, sleep disorders, infection, malnutrition and depression). Management is individualized and multidisciplinary. Exercise and cognitive behavioural interventions have the most consistent evidence, while yoga, mindfulness-based approaches, acupuncture, massage and other integrative therapies may be useful adjuncts in selected patients. Pharmacological treatment has a more limited and context-dependent role since no drug is established as universal therapy for CRF. Emerging work on the gut microbiome and digital rehabilitation is promising but remains preliminary. This review summarises current understanding of CRF, its clinical evaluation and evidence-based management.

Keywords

Cancer-related fatigue; Cancer survivorship; Inflammation; Exercise; Cognitive behavioural therapy; Supportive care; Quality of life.

Introduction

Clinical significance

Cancer-related fatigue (CRF) is among the most frequent symptoms experienced by people with cancer, from diagnosis through active treatment, survivorship and palliative care. The National Comprehensive Cancer Network (NCCN) describes it as a distressing, persistent and subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or its treatment, which is disproportionate to recent activity and interferes with usual functioning [1,2]. It differs from physiological tiredness since it may occur without substantial exertion and is not reliably relieved by sleep or rest. Patients may experience reduced energy, heaviness, lack of motivation, impaired concentration and slowed thinking. This can compromise daily activities, family and social roles, working hours, treatment adherence and overall health-related quality of life (HRQoL). For some patients, fatigue is more limiting than pain or nausea, even when other toxicities are controlled [2-4]. Observational associations with poorer outcomes have been reported, but do not iterate fatigue itself as a factor influencing mortality [2,4,5]. Still, the CRF domain remains an imperative component of holistic strategies to manage cancer patients.

Epidemiology and Trajectory Across the Cancer Care Continuum

Reported prevalence varies according to cancer type, stage, treatment modality, timing of assessment, fatigue instrument and threshold used to define clinically significant symptoms. In a review of patients receiving active treatment, fatigue was reported in approximately 62%–85%, with moderate-to-severe symptoms in a substantial subset [2]. A systematic review and meta-analysis of 57 studies involving 34,310 participants estimated an overall fatigue prevalence of 43.0%; when mild fatigue was included, the pooled prevalence rose to 70.7% [4-10]. The difference between these estimates illustrates the influence of assessment methods and severity thresholds and cautions against treating prevalence figures as directly interchangeable.

Fatigue may be present before treatment, reflecting tumour-related inflammation, systemic illness, pain, nutritional impairment, sleep disruption or psychological distress. Further, it may also coexist with pain, insomnia, cognitive complaints, menopausal symptoms and emotional distress, producing a cumulative effect on function. Demographic and tumour-related factors may inform risk but cannot reliably predict an individual's experience. It commonly increases during treatment and may peak towards the end of a treatment course. In the meta-analysis by Kang and colleagues, severe fatigue was more frequent during ongoing treatment than before treatment or after treatment. Chemotherapy and targeted therapy such as aromatase inhibitors for breast cancer and androgen-deprivation therapy for prostate cancer were associated with a higher prevalence of severe fatigue than surgery or radiotherapy [2-4]. Combined-modality treatment, advanced disease, comorbidity and poor baseline functional status may increase vulnerability. They also demonstrated that severe fatigue was reported far more commonly reported by patients than recognised by physicians, highlighting the limitations of clinician impression alone [3,11]. Patient-reported assessment should thus remain central to its diagnosis.

Pathophysiology: A multifactorial and evolving model

The pathophysiology of CRF remains incompletely elucidated. Current evidence supports a model involving interactions between peripheral inflammation, central nervous system signaling,

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neuroendocrine dysregulation, circadian disruption, skeletal-muscle dysfunction, altered energy metabolism and psychosocial factors [4,6,12-14]. Mechanisms may differ between patients and change over time; much of the evidence is associative rather than a proof of causation (**Figure 1**).

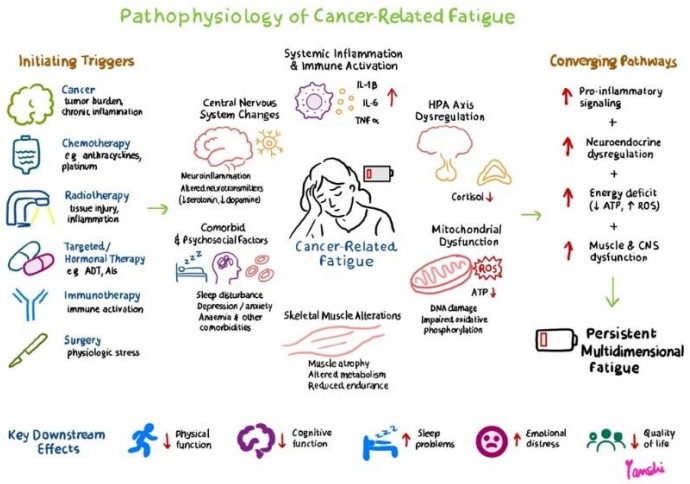


Figure 1: Pathophysiology of Cancer Related Fatigue.

- **Inflammation and immune signaling:** Cancer and anticancer treatment can activate innate and adaptive immune pathways, leading to the release of inflammatory mediators including interleukin (IL)-1, IL-6 and tumour necrosis factor-alpha (TNF-α). These mediators may influence the central nervous system through humoral signaling, neural pathways and interactions with the blood–brain barrier. Neuroimmune signaling may alter circuits involved in motivation, reward, sleep, mood and perceived effort, producing features of CRF [4-6,14-16]. Associations between inflammatory markers and fatigue are inconsistent. Cytokine levels are rather influenced by tumour burden, infection and treatment associated sequalae.
- **Neuroendocrine and hypothalamic–pituitary–adrenal axis changes:** The hypothalamic–pituitary–adrenal (HPA) axis regulates the physiological response to stress and helps coordinate energy mobilization, sleep and circadian rhythms. Cancer-related stress and persistent inflammation may alter cortisol secretion and feedback regulation. Flattening of the normal diurnal cortisol rhythm has been described in some fatigued cancer populations, although it is not a universal finding and is not currently a diagnostic test for CRF [4,5,16-18]. Treatment-related endocrine disorders, including hypothyroidism, adrenal dysfunction and hypogonadism, may independently cause or aggravate fatigue and should be considered during clinical evaluation.
- **Central nervous system and neurotransmitter pathways:** Fatigue is not solely a peripheral muscle phenomenon. Brain networks involved in attention, motivation, reward processing and motor planning contribute to the perception of effort and the ability to sustain activity. Inflammatory signaling may affect neurotransmitter systems, including serotonin, dopamine and glutamate pathways, and may alter functional

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connectivity in brain regions associated with cognitive and affective processing [4,5,19,20]. These pathways may contribute to cognitive and motivational symptoms, but no neuroimaging or neurotransmitter test is used routinely.

- **Skeletal muscle, mitochondria and energy metabolism:** Cancer-associated inflammation, inactivity, malnutrition, cachexia and treatment toxicity can contribute to loss of muscle mass, reduced muscle strength and impaired physical conditioning. Experimental and translational studies suggest that mitochondrial structural or functional abnormalities, oxidative stress, altered mitochondrial DNA and impaired adenosine triphosphate (ATP) production may contribute to reduced muscular energy efficiency [5,20,21]. Chemotherapy and radiotherapy may indirectly worsen these processes through systemic inflammation, tissue injury, reduced activity and nutritional effects. It is more accurate to regard mitochondrial dysfunction as a proposed contributor than to attribute all CRF directly to mitochondrial damage from treatment [22,23].
- **Circadian rhythm, sleep and symptom clusters:** Disruption of sleep–wake rhythms may amplify fatigue. Insomnia, fragmented sleep, nocturnal symptoms, corticosteroid exposure, pain, hot flashes and hospital routines can impair restorative sleep. Fatigue and sleep disturbance are bidirectionally related: poor sleep can worsen daytime fatigue, while severe fatigue and inactivity may disrupt sleep timing and quality [1,2,7,23]. CRF also clusters with pain, depression, anxiety, dyspnea, nausea, cognitive complaints and nutritional problems. These symptoms may share biological pathways and reinforce one another. A symptom-cluster approach is therefore preferable to assessing fatigue in isolation [20-25].

Clinical evaluation and screening

Routine screening is recommended at diagnosis, during treatment, at treatment completion and throughout survivorship or palliative follow-up [1,2]. Screening should be repeated because fatigue is dynamic and may change with treatment cycles, disease progression, comorbidities and psychosocial circumstances. A brief question such as “How would you rate your fatigue over the past week on a scale of 0 to 10?” can identify patients requiring further assessment. Document the score alongside functional interference; it is not a stand-alone diagnosis [1,2,20-25].

Clinical history and examination [1,2,20-25]

Assessment should establish onset, duration, daily pattern, severity, aggravating and relieving factors, relationship to treatment cycles and degree of interference with work, mobility, self-care and social activities. Clinicians should ask about sleep quality, pain, mood, nutrition, physical activity, medication use and substance intake. Examination should be guided by the history and may include performance status, weight change, hydration, muscle wasting, cardiopulmonary findings and evidence of infection or endocrine disease. Potentially treatable contributors should be identified before fatigue is attributed solely to cancer. Relevant investigations depend on the clinical context and may include:

- Complete blood count and assessment of iron status when anemia or iron deficiency is suspected.

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- Thyroid function tests andevaluation for adrenal or gonadal dysfunction.
- Renal and liver function, electrolytes, glucose and calcium where clinically appropriate.
- Assessment for infection, dehydration, malnutrition and drug induced effects (eg. opiod analgesics, immunotherapy)
- Screening for depression, anxiety, cognitive impairment and psychosocial distress.

Assessment instruments [1,2,25-30]

A single-item numerical rating scale or visual analogue scale is practical for routine screening. More detailed instruments can characterize severity, dimensions and functional consequences. The Brief Fatigue Inventory (BFI) is a nine-item instrument that assesses fatigue severity and interference with daily activities [8]. The Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale is a commonly used 13-item measure with established psychometric properties. The Multidimensional Fatigue Inventory (MFI-20) assesses general, physical and mental fatigue, reduced motivation and reduced activity. The revised Piper Fatigue Scale and Multidimensional Fatigue Symptom Inventory provide broader multidimensional assessment. A systematic review identified 15 adult cancer-related fatigue scales and found substantial variation in item number, domains, validation populations and psychometric properties [9]. Short tools may be preferable in busy clinics or in patients with advanced disease, whereas multidimensional measures may be useful in research or specialist supportive-care settings. No single scale is ideal for every clinical context. The same instrument should preferably be used at serial assessments to support meaningful comparison over time. The discrepancy between patient-reported and physician-reported severe fatigue reinforces the need for structured screening and explicit discussion [3]. Normalizing discussion, explaining that fatigue is manageable and establishing referral pathways are essential.

Evidence-Based Management

Management should be individualized according to the likely contributors, severity, treatment phase, comorbidities, patient preferences and available resources. A useful clinical sequence is to identify and treat reversible causes, provide education and self-management support, initiate evidence-based non-pharmacological interventions and reassess response. Pharmacological treatment should be considered selectively rather than routinely.

Exercise and physical activity

Exercise is among the interventions with the most consistent evidence for reducing CRF during and after cancer treatment. Aerobic activity, resistance training and combined programmes can improve fatigue, physical function and quality of life. Exercise may counter deconditioning, preserve muscle strength, improve cardiorespiratory fitness and support sleep and mood. Activity need not be strenuous; it can begin at low intensity and progress according to tolerance [2,7,10]. Programs may include walking or cycling, resistance, flexibility and balance exercises. Frequency, intensity and duration should reflect baseline fitness, symptoms, comorbidities and goals. Patients with bone metastases require modification according to lesion location and fracture risk. Thrombocytopenia, severe anemia, cardiopulmonary disease, neuropathy, fever or acute complications may require modification or specialist assessment. Severe fatigue may require supervised initiation, pacing and graded progression - short bouts may be

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more feasible than prolonged sessions. Negative studies have also been reported in literature regarding the impact of physical activity on CRF.

Psychological and behavioural interventions

Cognitive behavioural therapy (CBT) targets unhelpful beliefs, maladaptive coping, reduced activity, sleep disturbance and the emotional consequences of persistent fatigue. It may help patients establish realistic activity goals, reduce symptom-related distress and improve self-efficacy. CBT may be delivered individually, in groups or digitally. Psychoeducation and energy-conservation strategies can complement it [10-12]. Sleep-focused behavioural treatment is appropriate when insomnia is present. Relaxation training, mindfulness-based cognitive therapy and stress-management programmes may also be useful, especially when fatigue coexists with insomnia.

Yoga, mindfulness and mind–body interventions

Yoga combines physical postures, breathing, relaxation and may improve fatigue, sleep, mood and physical function. Programmes should be adapted to treatment-related limitations, balance impairment, neuropathy, bone disease and postoperative recovery. Mindfulness-based stress reduction and mindfulness-based cognitive therapy aim to reduce distress and improve coping with persistent symptoms. Tai Chi and qigong may provide low-impact movement and mind–body benefits. Evidence supports considering these approaches as adjuncts, although intervention protocols and study populations so investigated are heterogenous [7,13,30-33].

Massage, acupuncture and other integrative approaches

Massage may reduce symptom distress and perceived fatigue in selected patients. The network meta-analysis by Long et al. ranked massage favorably among the non-pharmacological interventions evaluated; however, the authors emphasised the need for larger, better-designed trials and further evaluation of durability [12,13]. Massage requires modification or avoidance with thrombocytopenia, fragile skin, thrombosis, infection, recent surgery or painful bone metastases. Acupuncture and acupressure have been studied in patients with persistent fatigue during and after cancer treatment. Some trials report benefit, but results are heterogeneous and depend on the population, comparator and treatment protocol. Treatment should be delivered by trained practitioners with appropriate infection-control precautions. Patients should understand the limitations of evidence and not substitute these approaches for oncological care [33,34].

Nutrition and microbiome-directed strategies

Nutritional assessment is important because inadequate intake, weight loss, sarcopenia, dehydration and micronutrient deficiencies can aggravate fatigue. Management should correct documented deficiencies, support adequate energy and protein intake and address symptoms that limit eating. There is currently insufficient evidence to recommend a specific diet, supplement or anti-inflammatory dietary pattern as a stand-alone treatment for CRF [7-10]. The gut microbiome has emerged as a possible contributor through immune regulation, inflammation, metabolic signaling and the gut–brain axis. A 2024 systematic review of microbiome modifiers identified only three eligible randomized trials, involving 284 patients with colorectal or breast cancer. The included studies reported variable improvements in fatigue with probiotics or synbiotics [12-13]. These preliminary findings do not support routine probiotic prescription

for CRF. Strain, dose and safety particularly in immunocompromised patients require study in larger trials.

Pharmacological interventions

No pharmacological agent is established as a universal treatment for CRF. Medication should be directed at a defined contributor whenever possible. For example, iron deficiency, hypothyroidism, infection, pain, depression or sleep disorders should be treated according to their respective clinical indications. Psychostimulants such as methylphenidate have been investigated, particularly in advanced cancer and palliative settings, but trial results are inconsistent. Modafinil has also been studied, with no convincing basis for routine use in unselected patients. Potential adverse effects include insomnia, anxiety, appetite changes, tachycardia and drug interactions. These agents may be considered only in selected cases after discussion of uncertain benefit and careful monitoring [1,2,12-14]. Corticosteroids may provide short-term improvement in fatigue or well-being in some patients with advanced cancer, particularly when prognosis is limited and symptom relief is the priority. Their effect is generally transient and prolonged use may cause hyperglycemia, myopathy, infection, mood changes and sleep disturbance. They should therefore be reserved for selected palliative situations and reviewed regularly. Erythropoiesis-stimulating agents are not treatments for CRF itself. They may be considered for selected patients with chemotherapy-associated anemia according to established indications, hemoglobin thresholds and safety guidance. Their use requires discussion of thromboembolic and other risks and should not be justified solely by a fatigue score. Red-cell transfusion may be appropriate for symptomatic anemia in selected clinical circumstances, but decisions should be based on the full clinical context rather than fatigue alone [33-38].

A practical stepped-care approach

A pragmatic stepped-care pathway is:

1. Screen at baseline and at defined treatment and survivorship visits using a 0–10 fatigue scale.
2. For clinically significant fatigue, document functional interference and perform focused history, examination and investigations.
3. Treat reversible causes and optimise symptom control, sleep, nutrition and psychosocial support.
4. Offer an individualised exercise programme and behavioural intervention; consider suitable integrative approaches as adjuncts.
5. Reassess fatigue and function using the same measure, evaluate adherence and barriers, and escalate to rehabilitation, psycho-oncology, palliative care or other specialists as required.

This stepped approach recognizes that fatigue is often multifactorial and that management needs to be adjusted over time.

Future Directions and Research Gaps

Research needs consistent definitions, validated outcomes and clinically meaningful response thresholds since variation between fatigue scales complicates comparisons [9]. Studies should also identify clinical and biological phenotypes that predict response. Inflammatory, neuroendocrine, muscular, sleep and patient-reported measures may contribute, but none is a stand-alone biomarker. Pragmatic trials should test equitable delivery of exercise, CBT and integrative interventions, including in resource-limited

settings. Digital rehabilitation may improve access but must account for literacy, disability, language and connectivity. Microbiome and nutritional interventions require adequately powered trials. Fatigue should be embedded in survivorship plans and quality-improvement programmes [1,2,12,33].

Conclusion

Cancer-related fatigue is a common, multidimensional and clinically important consequence of cancer and its treatment. Its persistence across active treatment and survivorship, together with its effects on function and quality of life, makes systematic recognition essential. The pathophysiology is complex and likely involves interacting inflammatory, neuroendocrine, central nervous system, circadian, muscular, metabolic and psychosocial mechanisms. Assessment should combine routine patient-reported screening with evaluation of functional impact and potentially reversible causes. Exercise and psychological interventions form the foundation of management, while yoga, mindfulness, massage, acupuncture and other integrative approaches may be considered as adjuncts according to patient preference and available evidence. Pharmacological options have a selective role and should not replace correction of underlying causes or non-pharmacological care. Embedding fatigue screening, personalized intervention and repeated reassessment into routine oncology practice offers a practical route to improving patient-centered outcomes.

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