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Cancer-Related Fatigue—Is There a Role for Complementary and Integrative Medicine?

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Abstract

Purpose of Review This review aims to assess recent data on possible effective and safe complementary and integrative medicine (CIM) modalities that can be of help to patients affected by cancer that suffer from cancer-related fatigue (CRF).

Recent Findings Cancer-related fatigue (CRF) is one of the most common, persistent, and challenging symptoms among cancer patients and survivors. Many world-leading cancer centers incorporate CIM into routine cancer care including integrating multiple approaches to address CRF. Approaches that are supported by clinical evidence on the use of CIM during and following conventional oncology treatments are being discussed in this review.

Summary The review suggests that some CIM modalities might have a potential role in alleviating cancer-related fatigue. These modalities include acupuncture, touch therapies, nutrition, nutritional supplements, stress reduction, homeopathy, and circadian rhythm management. Additional research is still needed to better support the process of integrating CIM into a routine approach to cancer-related fatigue.

Keywords Cancer-related fatigue · Unmet needs · Cancer care · Complementary medicine · Integrative medicine · Touch therapies · Nutrition · Nutritional supplements · Physical activity · Acupuncture · Mind–body medicine · Dietary supplements · Herbal medicines

Introduction

Cancer-related fatigue (CRF) is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatments that is not proportional to recent activity and interferes with usual functioning (NCCN Guidelines 2021) [1•]. Despite its prevalence, CRF is often underdiagnosed and poorly treated by conventional medical treatment.

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CRF is experienced by up to 90% of individuals under chemotherapy and/or radiotherapy treatment [2–4] and up to 82% of cancer survivors of breast, prostate, colorectal, or lung cancer [5, 6].

The effect of CRF on a patient's quality of life (QoL) is both profound and pervasive. It interferes with all aspects of life including simple daily activities, work, social interaction, leisure activities, and relations with family and friends. CRF may also affect compliance and adherence to cancer treatments.

The etiology is multifactorial and consists of physiological, biochemical, and psychological contributing factors that usually coexist and have additive effects. It can be attributed directly to the cancer illness and its complications, to treatments' side effects, and to patients' comorbidities and psychosocial factors [3].

Furthermore, fatigue is rarely an isolated symptom. It usually occurs in a cluster with other symptoms such as pain, sleep disorders, nausea, and muscle weakness [1•].

Although the specific pathophysiology of CRF is unknown, mechanisms related to its development include changes in serotonin levels, hypothalamic–pituitary–adrenocortical axis

dysregulation, skeletal muscle wasting, circadian rhythm desynchronization, and rise in certain cytokine levels, primarily pro-inflammatory cytokines due to the activation of the immune system by infection, inflammation, injury, or trauma. There is also evidence of dysfunction within the central nervous system, including elevations in specific neurotransmitters and metabolites [7–9].

The complexity of the etiological factors makes CRF difficult to treat. The conventional medical approach can provide treatments for some of the abovementioned conditions, but oftentimes solutions are limited [10,11]. The lack of proven effective methods of treatment for CRF in conventional medical care leaves this common and distressful symptom underreported and undertreated.

The NCCN guidelines on CRF (Version 1.2021) recommend a multidisciplinary approach for the assessment, treatment, and monitoring of CRF including integrative oncology.

In their systematic literature review, covering data from 1990 through 2019, Arring et al. concluded that there is no consensus as to the best CIM therapy that patients should utilize, due to a limited evidence supporting these therapies. Nevertheless, five interventions were found to be likely effective: CBT, hypnosis during cancer treatments, acupressure, mindfulness-based cognitive therapy, Qigong, and Tai-chi in the post-treatment phase [4].

This paper is a narrative literature review on the value of adding CIM modalities that have some scientific support for alleviating CRF. The purpose of this review is to encompass the thoughts of several authors from different institutions and form a unified approach to the integration of CIM in CRF. A review might lead clinicians and researchers to additional directions of care in approaching this complicated clinical entity. The data in this review were all obtained from published studies and/or publicly available study information. Scientific articles with relevance for the discussion of the topic were searched using PubMed with emphasis on articles published over the last 15 years and cross-referenced with international guideline statements. Only articles published in the English language were included.

Physical Activity

The 2009 Society of Integrative Oncology (SIO) guidelines recommend physical activity for the alleviation of CRF, mainly for post-treatment patients [12•].

The NCCN 2020 guidelines and a meta-analysis of 113 studies reveal that pharmacological treatment does not improve CRF significantly, while exercise and psychological interventions have a positive effect [1•, 11].

Physical activity improves cardiorespiratory fitness, reduces inflammatory processes [13], relieves emotional and mental distress, improves mood, and reduces anxiety and fear [14, 15]. All the abovementioned factors are strongly related to CRF [3].

A 2012 Cochrane database systematic review, consisting of twenty-eight studies, found physical activity statistically more effective than regular care received by control groups (SMD, − 0.27, 95% CI, − 0.37 to − 0.17). In addition, exercise significantly reduced cancer-related fatigue both, during and following cancer treatments [16, 17].

The American College of Sports Medicine (ACSM) 2018 guidelines state that physical activity is safe for cancer survivors and that every survivor should "avoid inactivity" [18]. This statement is reinforced by the ACS recommendations for cancer survivors, which recommends at least 150 min per week of moderate aerobic exercise with an additional two to three sessions of strength training, such as weightlifting unless contraindicated. People who were not active before diagnosis are advised to implement a combination of light movement and stretching [19]. ACSM guidelines also offer a specific routine for CRF alleviation among patients, both during and following treatment, which consists of 90 min per week of moderate aerobic exercise along with twice-weekly resistance exercise [20]. Following research on the beneficial effect of exposure to morning light, it is recommended to involve physical activity in the early hours of the day [21, 22].

Research emphasizes the need to consider the in-treatment energy conservation needs and the benefits derived from exercise regarding CRF. Therefore, the exercise program should be monitored by a specialist taking into account the patient's age, gender, type of cancer, complications, comorbidities, and physical fitness level [20, 23, 24].

Nevertheless, the exercise parameters (frequency, duration of each exercise session, and intensity) on fatigue management still need further clinical research.

Touch Therapies

Touch therapies such as massage, Shiatsu, reflexology, and others are used by cancer care centers primarily for stress management and improving quality of life. These treatments are provided during and following cancer treatments and are recommended by the NCCN and the SIO for CRF alleviation [1•, 12•].

The advantage of touch therapies over regular clinical care for both CRF reduction and other physiological or psychological symptoms was presented in a 2013 meta-analysis of five RCT's covering 665 patients [25].

A regimen consisting of up to nine 20-min massage sessions for hospitalized patients scheduled to undergo bone

marrow transplantation demonstrated a reduction of fatigue, distress, and anxiety as soon as day seven of the treatment [26]. In a study by Tarrasch et al., conducted on 58 breast cancer patients during radiation treatment, the reflexology-treated group demonstrated statistically significant lower levels of fatigue ($p < 0.001$), compared to the control group, after 5 and 10 weeks of weekly treatments [27].

Touch therapies were shown to induce muscle and fascia tension relief, reduce stress hormones secretion, and improve deep sleep. Increased vagal activity following massage has been associated with decreased cortisol levels [28, 29]. A growing body of evidence suggests that cancer patients' social environment plays a role in their symptom experience, including fatigue. Touch therapies can reduce a feeling of loneliness and isolation often described by cancer patients, thus having the potential to improve health outcomes and quality of life indicators [30–33].

It is difficult to recommend an optimal regimen as trials vary in the number and length of sessions, from 20–45 min, with a frequency ranging between 1 and 3 times per week. The total number of sessions also varied, from 4 to 24 sessions [10].

The SIO finds massage therapies safe when provided by a qualified massage therapist and finds no limitations to treatment but recommends refraining from deep body massage in metastases or radiation areas [12•].

Acupuncture/Acupressure

Acupuncture and Acupressure have gained significant attention as modalities for CRF management and quality of life improvement. Most oncology units in the USA, Europe, and Australia utilize acupuncture as a leading CIM treatment. A 2020 meta-analysis found a reduction of 2.12 points in brief fatigue scores (BFI) with acupuncture treatment versus control groups. The data derived from nine studies included patients with various types of cancers, both in treatment and post-treatment [34].

Garcia et al. found a significant fatigue improvement in hospitalized cancer patients after one acupuncture treatment. The improvement was assessed through the modified Edmonton Symptom Assessment Scale (ESAS) scale, comparing pre- and post-acupuncture treatment [35]. Among outpatients, an assessment using the same scale and method ($n = 375$) found that acupuncture treatments reduced fatigue by 1.72 points ($p < 0.001$) [36].

Several small-scaled trials support CRF in the post-treatment phase. A Memorial Sloan Kettering cancer center phase two trial found a 31% improvement in fatigue. The improvement was measured 2 weeks after the final treatment [26]. Another study revealed a significant beneficial effect on fatigue over control or sham acupuncture arms [10]. The SIO also finds acupuncture to be safe when provided by a qualified therapist and concluded that acupuncture may have a role in cancer care [12•].

Acupressure and self-acupressure also seem to be useful interventions for post-treatment fatigue. In a study that evaluated the effect of a daily self-administered acupressure on persistent fatigue among breast cancer survivors, 66% of participants achieved normal fatigue levels after 6 weeks, compared with 31.3% in the usual care arm ($P < 0.001$) [37].

Mind–Body Therapies

Mind–body therapies include stress reduction techniques such as mindfulness and hypnosis as well as physical activity-based modalities such as yoga, Tai-chi, and Qigong.

Hypnosis and guided imagery have been shown to improve fatigue under various cancer treatments including chemotherapy, surgery, and radiation treatments. It has been found in multiple studies that these therapies reduce pre-surgical emotional distress when applied in the right circumstance [38, 39].

In the radiotherapy setting, a study of breast cancer patients ($n = 200$) found that combined hypnosis and CBT (CBTH) significantly reduced fatigue. The improvement was demonstrated immediately after the radiation session, 4 weeks and 6 months later, showing increasing effect over time [4].

The SIO guidelines recommend hypnosis for CRF reduction in breast cancer patients. It has also been found helpful for control of pain, anxiety, phobias, nausea, and vomiting: symptoms related to fatigue in cancer patients in general [12•, 40].

The duration of each hypnotic session and session number may vary according to the chronicity of the complaint, its etiology, hypnotizability (ability to achieve a hypnotic state) of the patient, and the experience of the hypnotherapist.

Mindfulness-based stress reduction (MBSR) has been found to reduce fatigue significantly in a meta-analysis of multiple studies consisting of 3008 patients (MBSR, 1502; control, 1506). The researchers found that 8 weeks of MBSR had a substantial effect on CRF [41]. The NCCN guidelines recommend mindfulness-based therapies for CRF treatment among breast cancer patients [1•].

Moreover, it has been found that self-administered mind–body modalities, such as meditation, mindfulness, self-hypnosis, and guided imagery, are easily used by cancer patients [4, 12•, 39, 42, 43].

Yoga, Tai-chi, and Qigong also have a relaxation effect, combined with fitness improvement. The evaluation of these techniques' effect on CRF alleviation showed mixed results in several studies [4, 10, 26]; among those, yoga is

recommended by the NCCN for CRF alleviation during and post-treatment [1•].

Diet and Nutrition

Cancer and cancer treatments may increase catabolism over anabolism, altering body nutritional demands. Symptoms of the disease or treatment side effects may include nausea and vomiting, altered or loss of taste and appetite, xerostomia, stomatitis, stomach aches, constipation or diarrhea, and reflux esophagitis. These situations may lower nutritional intake and increase nutritional deficits. Reduced lean body mass is tied to fatigue, whereas maintaining or even building muscle mass appears to prevent or mitigate CRF symptoms [44•]. Additionally, sarcopenic adiposity in cancer patients is shown to promote inflammation and fatigue [45].

Both the NCCN and the SIO recommend cancer patients to review their diet and meet increased nutritional goals in order to manage the disease and treatment-related symptoms [1•, 12•, 46].

In the "Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective Expert Report," recommendations include (1) consuming a greater variety of vegetables, fruits, whole grains, and legumes; (2) planning plant-based meals (two-thirds vegetables, fruits, whole grains, or beans and one-third (or less) animal protein; (3) avoiding sugary drinks; and (4) limiting consumption of processed foods high in added sugar, low in fiber, or high in fat [47].

Those are generally accepted recommendations for cancer prevention, but it is not clear if nutrition has a direct effect on cancer-related fatigue. One study tried to answer this question. The study was conducted on 30 post-breast cancer treatment patients. Their 3-month diet, named "The Fatigue Reduction Diet," was rich in fruit, vegetables, whole grains, and omega-3 fatty acid-rich foods. By the end of the study, fatigue improved by $44 \pm 39\%$ in patients on the diet program compared to $8 \pm 34\%$ in the control group ($p = 0.01$) [48].

In another observational study ($n = 42$, post-treatment breast cancer patients), a positive association was found between increased fatigue and percentage of kcal/day fat intake ($r = 0.31$, $P < 0.05$) and inversely related to fiber g/day ($r = 0.38$, $P < 0.05$) and carbohydrate gram per day intake ($r = 0.31$, $P < 0.05$) [44•].

An additional observational study ($n = 285$) was conducted on advanced cancer patients during chemotherapy treatment. In this study, researchers found a positive correlation between fatigue and a low protein intake (< 1 g/kg body weight) [49].

In a qualitative review looking at nutritional interventions for treating cancer-related fatigue, researchers found that plant-based protein sources such as soy isoflavones have probable beneficial effects against CRF by various mechanisms [44•], while animal protein was found to be linked to higher systemic inflammation, and might increase CRF.

A recent innovative pilot study was designed to evaluate an intervention to improve the nutritional status of 90 cancer patients and improve CRF. The study utilized a group-based two-session culinary intervention aimed at increasing understanding of how food choices can impact energy levels and establishing basic food preparation as well as the application of culinary techniques that minimize the effort required to prepare meals. The researchers describe a high adhesion to the program, along with a significant improvement in fatigue scores [50].

Nutritional Supplements

Nutritional supplements are one of the easiest and most accessible modes of complementary modalities that patients use. Unfortunately, the current knowledge on the effectiveness of these nutritional supplements in cancer care is limited, and only a few benefits have been proven in clinical trials.

In the recent 2018 WCRF/AICR report, the conclusion is that the evidence from both observational studies and clinical trials suggests that nutritional supplements are unlikely to improve prognosis or overall survival after the diagnosis of cancer [47].

On the other hand, frequent micronutrient deficiencies related to cancer are vitamin D, calcium, B12, folate, iron, selenium, and magnesium. Common pathologies induced by those deficiencies are oxidative stress, inflammation, muscle weakness, anorexia, anemia, and immune system deficiency. All of the above increase the risk for CRF [44•, 51, 52]. In addition, some herbal supplements such as ginseng, astragalus, and *Withania somniferra* might have some clinical clues that they might be helpful in cancer-related fatigue (Table 1).

But, one has to be cautious with this use, be clear with the patient and their family about the benefit and possible harms that can be related to this use in addition to the complexity related to reliability of the source of these herbal supplements as well as the need to monitor this use [53]. Therefore, the educated use of nutritional supplements is essential when addressing CRF among cancer patients. Treatment should be adjusted according to the patient's needs, condition, digestive and absorption capacity, and deficiency level, while communicating openly the benefits and harms of this use.

Melatonin and Circadian Rhythm

Circadian rhythm disruption is well documented among patients with cancer, including lower evening melatonin levels, resulting in interrupted sleep and rest [53–56].

Table 1 Complementary and integrative interventions for cancer-related fatigue

Modality	Main mechanisms of CRF reduction	References
Physical activity -Avoid inactivity -Consider needs for energy conservation -Combine aerobic and strength training -Utilize early morning exercise to balance melatonin levels -The exercise program should be monitored by a specialist	↑ cardiorespiratory fitness ↑ muscle mass & strength ↓ inflammation ↓ distress, anxiety, fear	[13–18, 21, 22]
Touch therapies -Length of sessions: 20–45 min -Frequency: 1–3 times per week	↑ muscle and fascia tension relief ↑ deep sleep ↓ physio-psychological symptoms: ↓ stress hormones ↓ pain reduction ↓ cortisol levels ↓ feeling of loneliness	[10, 25,26, 28–31]
Acupuncture/acupressure -Length of sessions: 20–45 min -Frequency: 1–3 times per week	↓ CRF	[10, 26, 34–37,34]
Mind–body therapies -Yoga, Tai-chi, Qigong -Hypnosis, guided imagery -Length of sessions & frequency: according to therapist discretion -Mindfulness	↑ relaxation ↑fitness ↓ pre/post-surgery stress ↓ pain ↓ nausea & vomiting ↓ anxiety ↓ phobias	[4, 10, 26] [4, 10, 12•, 38–40] [41]
Nutrition: -Maintain an optimal nutritional status to avoid deficiencies -Base meals on a variety of vegetables, fruits, whole grains, and legumes -Consume omega-3-rich foods -Reduce consumption of animal-based products -Avoid sugary drinks -Limit consumption of processed foods	↓ CRF	[12•, 46] [44•, 47–50]
Nutritional supplementation -**Micronutrients** -Monitor potential micronutrient deficiencies, especially vitamin D, calcium, B12, folate, iron, selenium, and magnesium	↓ CRF	[44•, 51, 52]
-Melatonin -Maintain sleep hygiene: sleeping in complete darkness along with early morning sun exposure	↑ sleep quality	[53–59] [21, 26]
-Homeopathy	↓ CRF	[61] [62–64]
Astragalus membranaceus (AM), Huan Qi	↓ oxidative stress ↓ inflammation ↑ cardiovascular protection	[53, 65–69] [69, 70]
-Ginseng (Panax ginseng, American ginseng, Siberian ginseng)	Enhance immune system ↑ GABA and dopamine ↑ immune System ↓ inflammation	[4, 71–74]
Withania somniferra—Ashwagandha (WS)	↓ inflammation ↓ oxidative stress ↓ anxiety & stress ↑ GABA ↑ sleep quality	[75, 76]

Recent data reinforce previous outcomes regarding the beneficial effects of sleep hygiene in preventing circadian rhythm disruption. A twenty-eight-day morning exposure to bright light for 30 min significantly reduced fatigue and improved mood among cancer survivors [21, 26]. A trial among breast cancer patients during chemotherapy,

conducted with a similar regimen, suggested a protection from experiencing circadian rhythm disruption during chemotherapy [22].

Melatonin levels can be improved by supplementation [57, 58]. Five milligrams of melatonin at bedtime demonstrated improved sleep and lower fatigue parameters in patients suffering from nocturnal hot flashes caused by androgen-suppressing drugs [59]

Daily dosages of melatonin range from 0.5 to 20 mg have been reported. Wang et al. [58] found that a daily dosage of 20 mg of melatonin during chemotherapy and radiation showed a statistically significant fatigue reduction compared to patients without melatonin addition (data drawn from 8 RCT's, $n = 761$, 49.1 vs. 17.2%; $RR = 0.37$; 95% CI, 0.28–0.48; $P < 0.00001$). The effects were consistent across various types of cancer.

Melatonin can be effectively and safely administered in the abovementioned dosages, as no adverse impact on conventional therapy outcomes was reported. Caution should be practiced in the face of a possible CYP1A2 and CYP2C9 metabolized drug interactions. Melatonin may also affect glucose tolerance and anticoagulant pharmacology.

Homeopathy

Homeopathy is a treatment modality that utilizes highly diluted natural substances [60] and is one of the most debated modalities in integrative oncology. Nevertheless, a growing body of research suggests that homeopathy might be effective for cancer side effects alleviation, including CRF [61–64].

One of these studies was a prospective observational study done in Germany. The researchers observed two groups of cancer patients. One group of patients utilized homeopathic treatment in addition to conventional care ($n = 259$), and the other group utilized only conventional cancer care ($n = 380$). An improvement in quality of life was observed in patients taking the addition of homeopathic treatment, as well as a tendency of fatigue to decrease significantly in the homeopathy group [62].

Another recent descriptive study was conducted in France in three oncology centers in one city. Researchers observed that homeopathy was used in 30% of cancer patients ($n = 633$). Homeopathy was used as an additional supportive measure. Fatigue was one of the leading symptoms that improved in 80% of the patients that homeopathy was added to their care [61].

An Israeli study evaluated the adherence to homeopathic treatment among cancer patients who received a CIM consultation ($n = 124$). The authors found that homeopathy treatment was feasible, with two-thirds of patients acquiring and self-administering the remedies as prescribed. Fatigue was one of the main symptoms that patients felt that improved with the addition of homeopathy [64].

Homeopathy is considered safe and without adverse effects, neither direct (i.e., toxic effects) nor indirect (i.e., interactions with conventional anticancer agents) [60–64].

Conclusions

Cancer-related fatigue is a complex and highly distressing symptom among patients affected by cancer and requires a comprehensive patient-centered approach.

There is an increase in scientific support that CIM modalities, such as acupuncture, touch therapies, homeopathy, nutrition and nutritional supplements, stress management, and physical activity can have a role in alleviating cancer-related fatigue. Additional research is still needed to bring better support in utilizing these modalities in routine cancer care.

Declarations

Conflict of Interest The authors declare no competing interests.

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