

Non pharmacological interventions to manage Cancer-related fatigue (CRF) - An overview

ABSTRACT

Fatigue is almost common problem often reported by the cancer patients that severely affects all aspects of quality of life. Prevalence of cancer related fatigue ranges from 50% to 90% of cancer patients overall. After addressing treatable contributing factors, such as hypothyroidism, anemia, insomnia, pain, emotional distress, medication adverse effects, metabolic disturbances, or organ dysfunction such as heart failure, myopathy, and pulmonary fibrosis, patients may be screened with a short fatigue assessment tool. There is a pressure for pharmacologic therapy to shift away from reliance on opioids and ineffective procedures toward comprehensive cancer related fatigue (CRF) management that includes evidence-based nonpharmacologic options. This white paper details the magnitude of the current CRF problem including its impact on quality of life as well as the challenges of CRF management for patients and a healthcare workforce engaging prevalent strategies not entirely based in current evidence. Transforming the current system of CRF care to a responsive comprehensive model necessitates those options for treatment and collaborative care must be evidence-based and include effective nonpharmacologic strategies that have the advantage of reduced risks of adverse events and addiction liability. Patients with cancer related fatigue may benefit from self-administrable nonpharmacological interventions without any side effects.

Health care personnel often have insufficient knowledge about fatigue and its treatments or underestimate the impact of fatigue on quality of life. A practical review may be useful to health care professionals in order to identify the cancer related fatigue during the early period of cancer process and treat it effectively to improve the quality of life which contribute to the positive outcomes in cancer clients. Therefore, the main purpose of this review is to analyze the possible nonpharmacological approach to manage cancer related fatigue and recommend future research that will clarify these approaches and facilitate the formulation of new treatment options.

Keywords: [Cancer-related fatigue, Non pharmacological, intervention]

INTRODUCTION

Fatigue is one of the most common problems often reported by the cancer patients that severely affect all aspects of quality of life.^[1] CRF is the highly prevalent and devastating symptom experienced by many of the cancer patients at diagnosis, which elevate during treatment and often continue for months to years after treatment. It is subjective in nature; fatigue is common in people with cancer, but it's different for each person.^[2] National Comprehensive Cancer Network defines cancer-related fatigue (CRF) as 'a distressing persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not related to recent activity and interferes with usual functioning'.^[3]

A lot of evidence and research findings on CRF have been provided within the last two decades; still CRF is continued as underreported, underdiagnosed, and undertreated problem. The pathogenesis of cancer-related fatigue is not well explained, and a variety of mechanisms may contribute to the fatigue in cancer patients.^[4] These includes effects of cancer and its treatment on neuropsychological impairment, muscle metabolism dysregulation, circadian rhythms disruption, inflammatory mediators and stress, immune activation, and hormonal imbalance related to effects on the hypothalamic-pituitary axis, early menopause in women, or androgen deficiency in men.^[5, 6, 7, 8, 9]

MAGNITUDE OF THE CRF

Radiation therapy forms a fundamental part of management of a cancer patient. Largely, about 80% of cancer patients require radiation at some point of time either in the form of radical, adjuvant or palliative intent. The radiation treatment is delivered over a period of several weeks in which invariably normal tissues are also exposed. These result in side effects impairing the nutrition, general condition of the patient and enhance the fatigue already present.^[10] Fatigue prevalence surges over the course of radiotherapy.^[11] Unlike simple tiredness or situational fatigue, it is more devastating and severe; less likely to be relieved by simple rest; and may lead to withdrawal from meaningful and enjoyable events and may even lead to discontinuation of treatment.^[12] During the course of radiotherapy, fatigue usually increases, but typically wanes within weeks after the end of radiation treatment.^[13] However, in up to 40% of patients, it can persist long after the completion of therapy.^[14] Similar to radiotherapy a very high percentage of patients who are receiving chemotherapy also experience fatigue.^[15, 16]

POSSIBLE CAUSES OR CONTRIBUTORS TO CANCER-RELATED FATIGUE

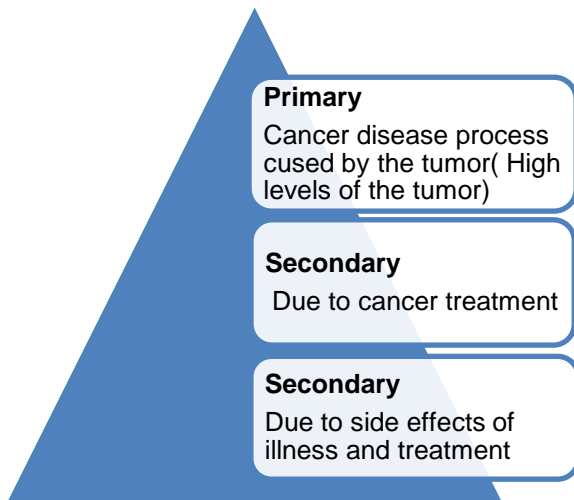


Fig 1- Possible causes or contributors to cancer-related fatigue

Underlying etiology and risk factors for CRF are not fully known.^[17] Studies have identified risk factors which are associated with cancer related fatigue. It may be the cancer and/or the cancer treatment. Fatigue is often caused by more than one factor. Commonest causes of cancer-related fatigue are: anemia, pain, emotional distress, sleep problems and drugs.^[18]

IMPACT OF CRF ON QUALITY OF LIFE

Cancer therapy-related side effects include: chest pain, nausea or vomiting, oral infections, diarrhea, constipation, fever, exhaustion, loss of appetite, difficulty to breathe, dermatitis, sensory or motor problems, hemorrhage, palmar-plantar syndrome, pain, bruising and other rare side effects.^[19] The presence of any one or a combination of these side effects can have a detrimental effect on one's overall well-being, body image, and self-perception.^[20] The impact of CRF on physical, psychosocial, and economic and occupational domains was evaluated in the year 2000 in Fatigue Coalition follow-up survey. In this survey eighty percent of the respondents were reported decreased energy levels and a feeling of tiredness. The survey also sought to clarify the psychosocial effects of cancer therapy. Decreased overall motivation, needing to push oneself, and feeling sad, frustrated, and irritability are most commonly reported symptoms by the cancer patients, cognitive function was also affected; manifested as decreased concentration, decreased memory, and difficulty keeping dates straight. Patients who still employed were absent from work 4.2 days per month during and after treatment had ended. The potential economic impact of fatigue is considerably high; 75% of patients and 40% of caregivers are forced to change their employment status due to cancer-related fatigue.^[21] Another study about employment participation

in early-breast cancer patients further highlighted the enormous socioeconomic impact of fatigue by showing that fatigue patients were more likely to experience diminished employment after 2 years of follow-up.^[22] Patients identified the certain activities as the most difficult; walking distances, doing household tasks, cleaning the house, socializing, and cooking food.²¹ A research study also revealed that CRF is an independent causative factor for dissatisfaction of patient with life. Those individuals reporting fatigue levels in the severe range (7–10/10) were least likely to feel satisfied with life (odds ratio 0.28, 95% confidence interval: 0.09–0.91, $P=0.03$).^[23]

Table1-The impact of fatigue: outcomes of a survey by the Fatigue Coalition ^[21]

Physical impact	Financial impact	Social and emotional impact
Difficulty in carrying out tasks -56%	71% of patients lost one or more days of work	59% reported difficulty in mingling with friends and family
Difficulty in climbing stairs -56%	31% lost a complete week of work	37% had difficulty in preserving relationships
Difficulty in walking long distances- 69%	28% had to stop working	30% found difficult to have intercourse with spouse
Difficulty in continuing exercise- 67%		

NON-PHARMACOLOGICAL APPROACHES (COMPLEMENTARY THERAPIES) FOR MANAGEMENT OF CANCER-RELATED FATIGUE

Most of the nonpharmacological approaches are considered for some extent as they improve overall wellbeing of the patients. Small sample studies involving yoga, acupuncture and acupressure, massage, healing touch and aromatherapy, foot soak with reflexology has demonstrated promising results in relieving fatigue. Further intervention studies with higher statistical power are required to develop a larger body of evidence with more applicable conclusions.^[24]

Few common non-pharmacological approaches either as a single therapy or in combination used in the management of cancer-related fatigue, which can be self-administered after a brief training or education, accepted and affordable by the clients are;

- Exercise
- Nutrition and hydration
- Acupressure and
- Yoga and
- psychosocial interventions

EXERCISE

There is growing evidence which provides a strong indication that exercise is advantageous to cancer patients. Exercise during and after cancer treatment has been shown to be safe and sound to reduce fatigue, increase physical fitness and enhance the health-related quality of life. Aerobic exercise significantly reduces fatigue; however, the role of resistance training and alternative forms of exercise are less clear.^[25] Exercise is likely to play an effective role in managing the side effects of CRF such as cognitive impairment, sleep disturbances, depression, pain, anxiety and physical impairment including defective muscular function, cardio-pulmonary function and bone mass. It can be tailor-made to the precise needs of each cancer client or survivor.^[26, 27, 28]

Exercise helps to produce endorphins, a chemical secreted in the brain that act as natural analgesic and also helps to induce sleep which in turn helps to reduce stress. Conventional wisdom holds that a workout of low to moderate intensity makes one to feel energized and healthy. Researchers found that patients those who have participated regularly in

aerobic exercise had reduction in level of stress, stabilized mood, improved sleep, and improvement in self-esteem. Five minutes of aerobic exercise also can contribute to anti-anxiety effects.^[29]

All forms of exercise are recommended to help decrease fatigue, but the more aerobic the activity the better, e.g., walking, swimming, cycling, running, rowing. Interval training is best for physical and psychological benefit which means that the exercise should be rhythmic, involve repetitive movements of large muscle groups, include a series of short, intensive periods, be at a moderate intensity (60-85% of estimated maximum heart rate), ideally done several times a week and sustained. The exercise should be progressive. A daily record or exercise diary can be very helpful to set realistic goals, record progress and help motivate the individual toward helping themselves to reduce their fatigue.^[30]

Precautions to be taken by anyone taking up this approach would be:

- No lifting of heavy weights following lymph node surgery
- Recent vomiting
- Chemotherapy within previous 24 hours
- Confusion, pallor, blurred vision, fever, chest pain, dizziness, sudden shortness of breath, irregular pulse
- Current viral infections
- Pain.^[31,32]

ACUPRESSURE

Acupressure is a component of traditional Chinese medicine that uses pressure via finger, thumb or a device to stimulate specific acupoints for therapeutic purposes and stimulating these points can correct imbalance between *Qi* (*Qi* is a vital energy of life) via channels and subsequently treat the diseases. Balancing of *Qi* helps to attain therapeutic supports by improving the physiological functions.^[33, 34, 35] Biochemical mechanism of acupressure describes the stimulation of specific acupoints along the meridian leads to complex neuro-hormonal responses. It involves the counteraction among hypothalamic-pituitary-adrenocortical (HPA) axis that leads to overrun of cortisol and cause a relaxation response. Also, it modulates the physiological response by increasing endorphin and serotonin transmittance to the brain and specific organs through nerves and meridians.^[36]

As per the Meridian theory, on stimulation of acupoints, the area along the meridian will be affected whereas activating proximate acupoints would affect the functioning of local tissues. Acupressure mediates nitric oxide (NO) signal, known to improve local microcirculation via cyclic guanosine monophosphate (cGMP). It helps in enhancing the physical performance by suppressing fatigue-inducing molecules in the blood.^[37] Several randomized controlled trials of acupressure to reduce fatigue in patients with cancer have been conducted. In these studies, acupressure has been administered by a traditional Chinese medicine provider; self-administered; delivered as auricular acupressure; or combined with other therapies such as aerobic exercise, essential oils, and education.^[38, 39, 40, 41] Acupressure has been shown to be safe and acceptable by patients with cancer.^[33, 34, 35] Also, acupressure appears to affect significant improvements, on the order of 30% to 40%, in fatigue severity.^[42]

Acupoints LI-4 (middle of bisector between the first and second metacarpus) or Heguacupoint, ST36 (width of one finger lateral to lower edge of tibia tuberosity and 4 fingers lower than knee joint) or Zusanliacupoint, and SP-6 (4 fingers above the medial ankle and posterior of tibia) or Sanyingjiaocupoint, which have been related to energy in the human body and were shown to alleviate fatigue in patients with cancer.^[43]

NUTRITIONAL THERAPY

There are various reasons for developing nutritional complications in cancer patients which contributes to the cancer related fatigue.^[44] The systemic nature of cancer promotes metabolic dysregulation and increased catabolism or even cachexia.^[45,46,47] Adverse effects of drugs including altered taste, anorexia, unintentional weight loss, xerostomia, nausea and vomiting and eventual malnutrition in some cases, increased adiposity or obesity. Sarcopenic obesity may lead to greater loss of functionality, lower quality of life and greater mortality risk compared to cachexia or obesity alone.^[48]

Breast cancer patients experience unintentional weight gain due to the effects of chemotherapy, endocrine treatment and/or postmenopausal status.^[49] Chronic low-grade inflammation, as seen in obesity, is considered a factor in the development of CRF.^[48]

Nutrition Strategies to manage fatigue are:

- Select balanced meals and snacks
- Eating every three hours to keep energy levels up. Each meal and snack must contain a source of complex carbohydrates, protein and healthy fats to give sustained energy. Whole grains, sweet potatoes and other fiber-rich foods must be chosen for complex carbohydrates. They provide a continuous supply of energy.

- Sources of protein consist of fish, chicken, meat, dairy products, nuts, seeds, beans and lentils. Protein-rich food must be added at all meals and snacks to keep energy levels up and to preserve muscle.
- Healthy fat such as avocado, olive oil, nuts and seeds must be comprised with each meal and snack. This will give a constant supply of energy.
- Whole grains, fruits and vegetables, beans, peas, lentils, nuts and seeds contain adequate fiber.
- Vegetables and fruit are excellent sources of phytochemicals, antioxidants and vitamins that protect healthy cells help fight cancer cells, lower inflammation and boost immune system.
- Fish such as salmon, mackerel, sardines and Arctic char are rich in omega-3 fatty acids which lower inflammation
- Need at least 2 liters of fluid each day. ^[50]

YOGA

The traditional Indian form of yoga encompasses several domains including ethical disciplines, physical postures, and spiritual practices, with the goal of uniting the mind, body, and spirit for health and self-awareness. ^[51] There are a variety of types of yoga but the most common form adopted to improve various aspects of physiological and psychological well-being consists of three basic components; asanas (physical poses), pranayama (breath control), and dhyana (meditation). Specific postures are performed to help improve flexibility and strength, controlled breathing intends to increase focus and relaxation, and meditation aims to relax the mind. The practice of yoga induces parasympathetic nervous system activation (PNS): neurotransmitters responsible for relaxation response, decreasing blood pressure and heart rate; and activation of limbic regions of the brain and suppresses sympathetic nervous system activation (SNS), which is responsible for the stress response including the release of cortisol and epinephrine. Clinical trials suggested that yoga reduces symptoms of anxiety and depression and reduces inflammation, maintains a balance of autonomic nervous system tone, and increases in vagal activity ^[52, 53] Yoga tailored for cancer patients aims to be a gentle practice that appropriately accommodates the needs of the clients. For patients, approval from an oncologist is needed before beginning the practice, and instructions are modified as needed to accommodate each individual patient's needs. Research directs that yoga can produce invigorating effects on physical and mental energy, which are similar to some of the effects of aerobic exercise, and thereby may contribute to reduce level of fatigue. ^[54]

PSYCHOSOCIAL INTERVENTIONS

Psychologically based interventions include methods that focus on cognition, coping skills, and behavior. Psychological interventions such as cognitive-behavioral therapy (CBT) aim to influence or change cognitions, emotions, behaviors or a combination of these. ^[55] Interventions which target these processes may improve symptom management in CRF. ^[56] These therapies may increase knowledge, improve emotional adjustment and enhance quality of life, and have also been associated with improved coping skills, physical health and functional adjustment. ^[57, 58] Patients and healthcare professionals have been reported to have high expectations of, and relatively positive attitudes towards psychological therapies. ^[58] Studies also report that psychosocial therapies are effective in managing the fatigue of patients undergoing treatment for cancer. ^[55] Psychosocial therapies include cognitive behavioral therapy [CBT], counseling, or psychoeducation. ^[59]

Model of Nonpharmacological management of Cancer Related Fatigue (Fig-2)

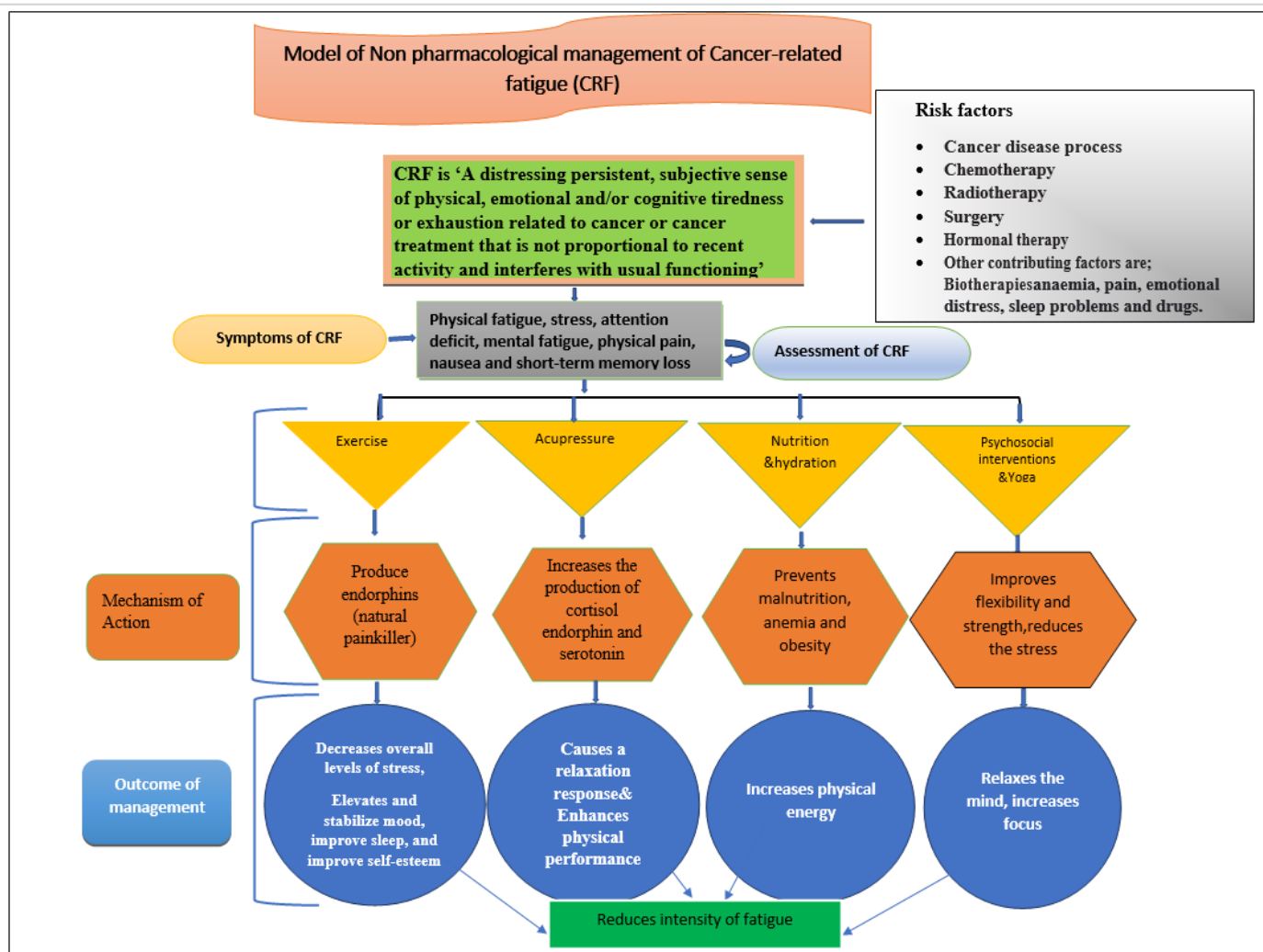


Fig 2: Model of nonpharmacological management of cancer related fatigue

Conclusion:

Cancer-related fatigue is the most prevalent symptom of cancer, severely impacting quality of life and functional capacity. The condition remains under-recognized. It's necessary to identify the cancer related fatigue during the early period of cancer process and treat it effectively to contribute to the positive outcomes in cancer clients. A review (Dr. Berger, Dr. Mitchell, Dr. Jacobsen, and Dr. Pirl. 2015) concluded that when patients report moderate to severe fatigue, clinicians can assist them to select an intervention likely to be beneficial and to receive adequate instruction to execute the intervention in a safe and effective manner. Ongoing reassessment will assist in documenting both short-term and long-term outcomes of the intervention on fatigue and various functional outcomes⁶⁰. Nonpharmacologic measures that have shown promising results to reduce CRF include exercise, acupressure, nutritional counseling, yoga, psychological interventions and perhaps sleep therapy. A systematic review (Meneses-Echávez J F, González-Jiménez E, Ramírez-Vélez R. 2015) concluded that supervised exercise reduces CRF and must be implemented in breast cancer rehabilitation settings. High-volume exercises are safe and effective in improving CRF.^[61] In addition to this an interventional study concluded that acupressure can be used as a nontoxic and harmless nonpharmacological therapy to reduce adverse events in patients with cancer. Many other modalities may be beneficial and can be used on an individual basis, but insufficient evidence exists to promote any one treatment.⁴³ Nonpharmacological therapies prove to be very effective for cancer related fatigue. A number of treatments discussed above should be tested on RCTs on a number of patients to find the best treatment for cancer-related fatigue.

ETHICAL APPROVAL

Not applicable

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