

Nonpharmacologic Approach to Fatigue in Patients With Cancer

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Abstract: Cancer-related fatigue is a common yet underappreciated problem with a significant impact on functional ability and quality of life. Practice guidelines mandate that all cancer patients and survivors be screened for cancer-related fatigue (CRF) at regular intervals. Comorbidities that could contribute to fatigue should be treated, and patients with moderate to severe fatigue should undergo a comprehensive evaluation. Nonpharmacologic interventions are important tools to combat CRF and should be incorporated into routine practice. Physical activity, educational interventions, and cognitive-behavioral therapy have the most supportive data and can be recommended to patients with confidence. From a practical standpoint, general education on CRF is something that most care providers can readily offer patients as part of routine care. Other interventions that appear promising but are as yet lacking convincing evidence include mindfulness-based stress reduction, yoga, and acupuncture. Reiki, Qigong, hypnosis, and music therapy may be worthy of further investigation.

Key Words: Cancer-related fatigue, cancer, fatigue, symptom management, palliative, nonpharmacologic, cancer survivorship

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Cancer-related fatigue (CRF) is recognized as one of the most common and debilitating symptoms associated with cancer and its treatment, and yet it remains underreported and undertreated.^{1,2} The National Comprehensive Cancer Network (NCCN) defines CRF as “a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.”³ Cancer-related fatigue tends to be more severe and distressing than fatigue experienced by noncancer patients, and rest does not relieve CRF.^{3,4} It has been estimated that approximately 80% of patients undergoing treatment for cancer will experience some degree of fatigue.⁵ These symptoms often improve after treatment completion; however, about 30% of patients will be left with persistent CRF.⁶ In patients with metastatic disease, the prevalence of CRF exceeds 75%.³ Despite its prevalence, the specific pathophysiology of CRF is not well understood.

Chronic CRF has a negative impact on overall quality of life and is associated with impaired mood, distress, and increased disability and health care utilization.⁷ Indeed, cancer patients perceive fatigue to be among the most distressing symptoms associated with cancer and its treatments.^{3,8} Other distressing symptoms, such as pain or nausea and vomiting can generally be effectively managed with medications. Between cancer survivors and the many patients currently receiving cancer-directed therapies, there are more patients than ever suffering from CRF. The lack of consistent benefit of pharmacological treatments for CRF underscores

the importance of developing nonpharmacologic interventions. The goal of this review was to describe a practical approach to the evaluation and management of CRF, with a particular focus on examining the evidence for the various nonpharmacologic interventions used to treat CRF.

EVALUATING PATIENTS FOR CRF

Given its prevalence and impact on quality of life, guidelines published by the NCCN and the American Society of Clinical Oncology recommend regular screening and assessment of CRF, as well as appropriate management according to their published guidelines.^{3,9} The NCCN recommends that all patients be screened for the presence and severity of CRF at their initial clinic visit, at regular intervals during and following cancer-directed therapies, and as clinically indicated. Importantly, CRF most commonly occurs in conjunction with other symptoms and comorbidities, such as pain, sleep disturbance, depression, and anemia, any one of which can exacerbate the CRF. As such, patients must be regularly screened both for CRF and for treatable contributing symptoms and conditions.

Cancer-related fatigue is a subjective experience that must be systematically assessed either by patient self-report or by talking with family and caregivers about CRF’s impact on the patient’s life and function. The basic screening question recommended by the NCCN guidelines is straightforward and efficient: “How would you rate your fatigue on a scale of 0 to 10 over the past 7 days?” On the fatigue scale, a score of 0 to 3 indicated mild fatigue; 4 to 6, moderate fatigue; and 7 to 10, severe fatigue. If the patient indicates moderate-severe fatigue (a score between 4 and 10), then a more thorough evaluation is indicated.

Further evaluation of CRF requires taking a focused history and assessing whether the patient has any treatable contributing factors. The clinician must determine the patient’s current disease status, consider the potential contribution of cancer-directed therapies to CRF, and determine if the patient is taking any medications that may be exacerbating CRF. In addition, the provider must assess whether the patient has concurrent symptoms or comorbid conditions that might be contributing to the fatigue and whether any of those can be improved with treatment.

MANAGING PATIENTS WITH CRF

After treating concurrent symptoms and contributing factors aggressively, the clinician must assess the patient’s clinical status and treatment goals in order to make recommendations consistent with the patient’s wishes and appropriate for the patient’s clinical status. In all cases, the management of CRF starts with patient and family counseling and education, including what the patient should expect based on the patient’s treatment status and level of illness as well as general strategies for managing fatigue. Multiple studies have demonstrated the benefit of educational interventions for patients with CRF.^{10–12} Moreover, educational interventions can be readily integrated into clinical encounters as part of routine office visits. Patient and family education is

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TABLE 1. Office Tips for Providers—Essential Points of Education and Counseling for Patients and Families Regarding Cancer Related Fatigue³

(1) Advise patient and family to monitor fatigue levels	Monitoring can be achieved by any combination of: <ul style="list-style-type: none"> • Patient self-monitoring and report • Family/caregiver monitoring 	Monitoring can clarify severity, pattern, contributors, etc
(2) Describe strategies for energy conservation	Encourage patient to...	Examples
	Set priorities/realistic expectations	<ul style="list-style-type: none"> • Help patient accept that fatigue means that energy is truly limited • Encourage patient to make choices that acknowledge that limitation, effectively creating an “energy budget” for themselves
	Pace self	<ul style="list-style-type: none"> • Schedule important but tiring family events on different days • Monitor fatigue to avoid wearing out and to sustain enjoyment and engagement in each task
	Delegate	<ul style="list-style-type: none"> • Rely on others to do tasks that take energy away from more enjoyable tasks or tasks only the patient can do
	Schedule desired activities at times of peak energy	<ul style="list-style-type: none"> • Advise the patient to listen to their body and follow its rhythms
	Structure daily routine	<ul style="list-style-type: none"> • Consider times of peak and low energy in building this structure
	Prioritize and conserve energy for valued activities	For many patients, this includes <ul style="list-style-type: none"> • Time with family • Task that bring joy
	Postpone or cancel nonessential activities	<ul style="list-style-type: none"> • Prioritize tasks that bring peace and joy • Limit tasks patient does not enjoy and that consume energy
	Attend to 1 activity at a time	
	Engage labor saving devices	<ul style="list-style-type: none"> • Reaching tools for grasping items beyond reach • Wheelchairs for long distances or as needed • Electric household equipment for household tasks, etc
	Practice good sleep hygiene, including limiting naps to less than 1 h a day to avoid interfering with nighttime sleep	
(3) Teach patient to use distraction	Games Music Reading Socializing	
(4) Help patient find meaning in current situation	Emphasize meaningful interaction and tasks Promote patient dignity	<ul style="list-style-type: none"> • Help patients identify things that bring them joy

described further in the section on psychosocial interventions and in Table 1.

NONPHARMACOLOGIC INTERVENTIONS FOR CRF

We describe the nonpharmacologic interventions most commonly recommended in the treatment of CRF, as well as the current state of evidence pertaining to each intervention. We have graded the level of evidence for each intervention in Table 2. The nonpharmacologic interventions that are best supported by evidence include physical activity (exercise) and psychosocial interventions, including educational interventions and cognitive-

behavioral therapy (CBT). In addition, there are data supporting the benefit of mindfulness-based stress reduction (MBSR), yoga, and acupuncture for the treatment of CRF. Further research is needed to better understand the effect of massage, music therapy, Reiki, and Qigong on CRF.

Physical Activity

Multiple studies and meta-analyses have demonstrated the benefit of physical activity on CRF. The most recent meta-analysis included 70 studies, 27 of which included cancer patients following active treatment.¹³ For these 27 studies, the average age was 55 years, and the majority of patients were women with a

TABLE 2. Overview of the Evidence for Nonpharmacologic Interventions for CRF

Intervention	Level of Evidence
Exercise	Strong
Psychosocial*	Strong
Yoga	Moderate
MBSR	Moderate
Acupuncture	Moderate
Massage	Limited
Reiki/therapeutic touch	Limited
Qigong	Limited
Hypnosis	Limited
Music therapy	Limited

Level of evidence key: Strong—evidence from multiple properly designed randomized controlled trials, meta-analysis; moderate—evidence of benefit from at least one properly designed randomized controlled trial; limited—evidence of benefit from small number of studies, requires further investigation.

*Includes education, counseling, CBT, support groups, journaling.

history of breast cancer. The median time from treatment completion was 16.3 months (range, 1.0–75.0 months). It was reported that exercise significantly reduced CRF following treatment with a mean effect size of 0.38 (95% confidence interval [CI], 0.21–0.54). In addition, exercise reduced CRF in patients currently receiving active cancer treatment with a mean effect size of 0.32 (95% CI, 0.21–0.43). A variety of exercise programs with different schedules and activities have been evaluated for the treatment of CRF. Aerobic, resistance, and mixed training programs all have been shown to improve CRF.^{14,15} It remains unclear if one form of exercise is superior to others.^{14,16} Limited evidence suggests a benefit for shorter exercise programs and those that are supervised instead of home based.^{14,17}

How can care providers incorporate exercise into their care plan for cancer patients? Guidelines published by the American Society of Clinical Oncology recommend that patients engage in moderate levels of physical activity including moderate aerobic exercise (150 minutes per week) and strength training (2–3 times per week).⁹ Previous guidelines propose that exercise prescriptions vary based on the level of fatigue, with patients with mild fatigue prescribed progressive aerobic exercise program, 20- to 30-minute sessions, 3 to 5 days per week, as well as resistance exercises including 8 to 10 exercises for major muscle groups to be done 2 to 3 days per week. Alternatively, those patients with severe fatigue are encouraged to participate in frequent sessions of low-intensity exercise, 5 to 10 minutes in duration spaced throughout the day and to consider referral to physical therapy to start resistance-type exercise.¹⁵

According to the American College of Sports Medicine, most patients can independently initiate an exercise program that includes walking, flexibility, and resistance training. However, referral to an exercise specialist may be required for patients beginning a moderate or vigorous aerobic exercise program and for patients who have treatment or cancer-related complications affecting their ability to exercise such as significant lymphedema, neuropathy, or cardiac disease.^{9,18} Many patients perceive significant barriers to initiating an exercise program including both disease-specific and individual barriers, such as the perception of being “too busy” or having “no willpower.”¹⁹ Motivational interviewing has been shown to help overcome such barriers and could be used in the clinic setting.²⁰

Psychosocial Interventions

Psychosocial interventions include education, counseling, CBT, and support groups. Overall, evidence from meta-analyses and reviews has shown limited efficacy for psychosocial interventions for the treatment of CRF during and after cancer therapy, with effects sizes ranging from 0.10 to 1.07. However, 2 types of psychosocial interventions have shown benefit: educational therapies and CBT. Educational therapies include providing general education about fatigue and introducing the concepts of energy conservation, self-care, and coping techniques.²¹ Multiple studies have demonstrated the benefit of educational interventions for patients with CRF undergoing cancer treatment.^{10–12} A recent study included 273 cancer survivors with CRF and randomly assigned them either to an intervention group or a control group receiving routine care. The intervention group received a 12-week Web-based, tailored educational program focusing on 6 areas including energy conservation, physical activity, nutrition, sleep hygiene, pain control, and distress management. Patients in the intervention group had an improvement in fatigue demonstrated by a significantly greater decrease in Brief Fatigue Inventory global score (–0.66 points; 95% CI, –1.04 to –0.27) and Fatigue Severity Scale total score (–0.49; 95% CI, –0.78 to –0.21), as compared with the routine care group.²²

Cognitive-behavioral therapies have also been shown to have benefit in the treatment of CRF. Cognitive-behavioral therapy has been found helpful in treating CRF both in patients undergoing cancer treatment and in cancer survivors.²³ A study involving 112 cancer survivors randomized to CBT or waitlist control suggested a lasting benefit for CBT. The CBT was adapted for each patient but focused on 6 factors of postcancer fatigue, including insufficient coping with the experience of cancer, fear of disease recurrence, dysfunctional cognitions concerning fatigue, dysregulation of sleep, dysregulation of activity, and low social support/negative social interactions. Patients who received CBT had a greater decrease in fatigue as compared with the waitlist group (difference, 13.3; 95% CI, 8.6–18.1), and these positive effects were maintained 2 years after completing the CBT.^{24,25}

Supportive expressive therapies including support groups, counseling, and journal writing have some positive evidence as well in the treatment of CRF.³ Overall, it has been recommended that cancer survivors should be referred to psychosocial service providers who specialize in cancer and these interventions.⁹

Mind-Body Interventions

Yoga

Yoga is a mind-body practice that unites stretching, postures, deep relaxation, breathing, and meditation. Studies, predominantly conducted in the breast cancer population, have shown that yoga can have beneficial effects on CRF. A small study demonstrated the benefit of Iyengar yoga on fatigue in breast cancer survivors.²⁶ In addition, a study of 31 breast cancer survivors who were randomly assigned either to yoga or to health education reported that fatigue severity significantly declined from baseline to postintervention in the yoga group, an improvement that persisted over the 3-month period of follow-up in the yoga group.²⁷ Another study included 63 overweight and obese (body mass index, ≥ 24 kg/m²) breast cancer survivors who were randomly assigned to a 6-month yoga intervention or a waitlist control group. There appeared to be an improvement in quality of life and fatigue in the yoga group, although this was not statistically significant.²⁸ Other studies have been completed in patients actively undergoing treatment and have shown a benefit as well.^{29,30}

One of the main concerns regarding the previous studies was that the control group was often a waitlist or standard care, leaving the question of placebo effect. More recently, a study was published of breast cancer patients undergoing radiotherapy, which included a stretching group as well as yoga and waitlist control groups. By the end of radiotherapy, both the yoga and stretching groups had a significant reduction in fatigue; however, the yoga group had a greater improvement in physical functioning.³¹ Further research needs to be done to define the specifics of the yoga intervention, such as type of yoga and duration. Trials are needed specifically in the cancer survivor population and in tumor types other than breast cancer.

Mindfulness-Based Stress Reduction

Mindfulness-based stress reduction is a multimodal stress reduction program that includes mindfulness, relaxation, meditation, yoga, and group discussions. Mindfulness-based stress reduction has been investigated for cancer-related symptoms, and multiple trials reported improvements in CRF.³² A study involving 84 breast cancer survivors randomized to a 6-week MBSR program or usual care demonstrated a statistically significant reduction in fatigue.³³ Another study performed in cancer survivors with a variety of cancers included 100 subjects who were randomized to a 9-week MBSR intervention or waitlist. This study again showed an improvement in mean fatigue score.³⁴ The largest study was performed in 229 women who completed treatment for breast cancer who were randomly assigned to the 8-week MBSR program or standard care. There were statistically significant improvements in the intervention group compared with control group for fatigue, as well as improvement in other symptoms, including mood disturbance, vigor, and confusion.³⁵

Acupuncture

Multiple studies have investigated the role of acupuncture for CRF with mixed results. A recent meta-analysis included 7 trials involving 689 subjects. The 7 trials included 3 studies comparing acupuncture with sham acupuncture, 2 studies comparing acupuncture with no treatment or waitlist control, and 2 studies comparing acupuncture with another treatment, such as acupressure or self-acupuncture. In these studies, it appeared that the reduction in CRF favored acupuncture; however, only 2 of the studies showed significant differences in fatigue, with a standardized mean difference of -2.12 (95% CI, -3.21 to -1.03).³⁶ One of the 2 studies included 302 breast cancer patients who had completed chemotherapy and compared 75 patients who received usual care (fatigue information booklet) with 227 patients who received usual care plus 6 acupuncture sessions over 6 weeks. The difference in mean general fatigue score was -3.11 (95% CI, -3.97 to -2.25 ; $P < .001$).³⁷ The other study was a pilot trial performed in breast cancer survivors comparing acupuncture plus an education intervention to usual care. There was an improvement in fatigue in the intervention group; however, this study was very small, with only 6 patients randomized to treatment.³⁸ Moreover, it is impossible to know whether it was the acupuncture, the education, or both that led to the improved fatigue scores. Therefore, although studies of acupuncture appear promising, they are limited by the small size and high risk of bias. Further large, placebo-controlled trials are needed to discern the impact of acupuncture in fatigue.³⁹

Massage

A large study of 230 cancer patients receiving chemotherapy was performed to determine the effectiveness of therapeutic

massage and healing touch compared with presence alone (therapist sat with the participant but did not perform massage) or standard care. For the 164 patients who completed the study intervention, the healing touch cohort had a statistically significant improvement in fatigue, whereas the massage effect on fatigue was close to significance.⁴⁰ Another study was performed in cancer patients after treatment and included 86 women randomized to receive classic massage biweekly for 5 weeks or control. A decrease in fatigue was noted in the massage group at the end of the intervention (mean difference, -6.8 ; $P = 0.06$).⁴¹ Overall, evidence for massage appears promising, but studies are limited by sample size and differences in intervention. Further investigation is warranted to determine the potential benefit of massage in CRF.

Other Interventions

Reiki is a Japanese technique used for stress reduction and relaxation that involves the laying on of hands by a practitioner with a goal to promote healing. A small pilot study demonstrated potential benefit of Reiki on CRF in 16 patients who had completed treatment for a variety of cancers.⁴² Qigong is a form of mind-body traditional Chinese medicine that involves a combination of coordinated gentle exercise and relaxation through meditation and breathing. A recent review examines the role of Qigong in the treatment of cancer patients. Although most studies are small and have methodological limitations, it appears that there may be a benefit of Qigong on CRF.^{43,44} Hypnosis has shown promise in the treatment of CRF. A small study showed its potential benefit on fatigue in breast surgery patients.⁴⁵ A recent trial of 200 women with breast cancer undergoing radiotherapy randomized participants to CBT plus hypnosis versus attention control. The CBT and hypnosis group had significantly lower levels of fatigue at the end of follow-up ($z = 6.98$; $P < .001$).⁴⁶ Music therapy has shown mixed results for CRF, with some studies reporting benefit, but others showing potential worsening of fatigue.^{47,48} In addition, a Cochrane review including 3 trials that examined the effect of music therapy on fatigue showed no benefit.⁴⁹

CONCLUSIONS

Cancer-related fatigue is a common yet underappreciated problem with a significant detrimental impact on daily activities and quality of life. Practice guidelines mandate that all cancer patients and survivors be screened for CRF at diagnosis, throughout treatment, and at regular intervals during the survivorship period. Comorbidities that could contribute to fatigue should be treated, and patients with moderate to severe fatigue should undergo a comprehensive evaluation.

Nonpharmacologic interventions are important tools to combat CRF and should be incorporated into routine practice. Physical activity, educational interventions, and CBT have the most supportive data and can be recommended to patients with confidence. From a practical standpoint, general education on CRF is something that most care providers can readily offer patients as part of routine care. Other interventions that appear promising include MBSR, yoga, and acupuncture. Reiki, Qigong, hypnosis, and music therapy are interventions that may be worthy of further investigation.

It is important to note that the fatigue associated with active cancer treatment may differ from that experienced by cancer survivors. However, most nonpharmacologic interventions have been studied in both patient populations. In addition, the majority of research on the management of CRF has been performed in the breast cancer population, and further studies are needed in more diverse cancer patient populations. Ultimately, the treatment of

CRF may require a multimodal therapeutic approach and needs to be individualized to incorporate a patient's health status, goals of care, and personal preferences.

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