Cancer-Related Fatigue (CRF) Management During and Following Cancer Treatment: Moving the Evidence into Practice

Sandra A. Mitchell, PhD, CRNP, AOCN, FAAN

Research Scientist and Program Director; Outcomes Research Branch;
Division of Cancer Control and Population Sciences and
Oncology Nurse Practitioner; Experimental Transplantation and Immunology Branch

National Cancer Institute
Rockville, MD
mitchlls@mail.nih.gov

March 11, 2016
Disclosures

• Nothing to disclose
Objectives

At the end of this session, the participant will be able to:

- Describe the strength of the evidence for three interventions to manage fatigue during and following stem cell transplantation
- Identify two instruments that can be used for screening or outcomes assessment in patients or survivors with cancer-related fatigue
- Name two evidence-based guidelines that can be used to improve clinical outcomes for patients at risk for or experiencing fatigue
Scope of the Problem

- Prevalence of fatigue during and following transplant:
  - 35% of respondents had moderate/severe fatigue immediately pre-transplant and Day +30
  - 50% have moderate to severe fatigue at nadir
  - 30-50% bothered ‘a lot’ or ‘extremely’ by fatigue at 6, 12 and 24 months post transplant
  - 5 years post-transplant fatigue was significantly higher than age- and gender-matched healthy comparison samples
- Fatigue has consequences for physical, vocational, cognitive and social functioning; mood; treatment adherence, psychological and spiritual distress, and possibly for long-term survival outcomes
Scope of the Problem

- Single item assessments of fatigue are common in the literature; comparatively fewer prospective studies using multi-dimensional fatigue measures.
- Variety of self-report measures used makes comparisons between studies difficult.
- Strong correlations between measures of fatigue and depression.
- Small convenience samples; high rates of missing data.
- Identifying the biologic factors contributing to fatigue across the transplant trajectory is challenging.
Fatigue—Definition

- Cancer related fatigue (CRF) is a multifaceted condition characterized by an usual, persistent and subjective sense of tiredness that is not proportional to recent activity and interferes with usual functioning.
- May be accompanied by generalized weakness, diminished mental concentration, insomnia or hypersomnia, and emotional reactivity.
ICD-10 Criteria for Cancer-Related Fatigue

A. Six (or more) of the following symptoms have been present every day or nearly every day during the same two-week period in the past month, and at least one of the symptoms is significant fatigue (A1)

A1. Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level
A2. Complaints of generalized weakness or limb heaviness
A3. Diminished concentration or attention
A4. Decreased motivation or interest to engage in usual activities
A5. Insomnia or hypersomnia
A6. Experience of sleep as unrefreshing or nonrestorative
A7. Perceived need to struggle to overcome inactivity
A8. Marked emotional reactivity (e.g. sadness, frustration, irritability) to feeling fatigued
A9. Difficulty completing daily tasks attributed to feeling fatigued
A10. Perceived problems with short-term memory
A11. Postexertional malaise lasting several hours

ICD-10 Criteria for Cancer-Related Fatigue

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

C. There is evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer or cancer therapy

D. The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delirium
Features

- Clinical expression of CRF is multidimensional
- Fatigue may be experienced and reported differently by each individual
- May occur as an isolated symptom or as one component within a cluster (pain, fatigue, depression, sleep disturbances)
- Qualitative studies of fatigue show:
  - CRF experience is unlike other fatigue
  - Unpredictability and refractoriness to self-management contributes to distress
- Personality and coping style may also influence the experience of CRF
Variability in Manifestations of CRF

- Central features: loss of efficiency, mental fogginess, inertia, and sleep that is not restorative
- Peripheral features: excessive need to rest, an inability to recover promptly from exertion, muscle heaviness and weakness
  - Variable features of fatigue?
  - Fatigue subtypes?
  - Cause or sequelae of fatigue?
- Challenging to distinguish CRF from depression, cognitive dysfunction, or asthenia
  - Overlapping symptoms?
  - Shared neurophysiologic mechanisms?
What do we need to be doing better?

- Studies suggest:
  - fatigue screening and evaluation is suboptimal
  - fatigue is undertreated
  - health care professionals may not fully appreciate the degree of distress and functional loss that fatigue produces

- Fatigue communication barriers:
  - Inadequate knowledge of effective treatments, including non-pharmacologic treatments which some patients may prefer
  - Tendency to be stoic about fatigue in order to avoid being labeled as a ‘complainer’
Etiology and Risk Factors

- Inconsistent relationships to treatment-related variables (chemotherapy, radiation therapy, anemia, neutropenia, and time since treatment completion)

- Inconsistent relationships with age, gender, marital status and employment status
Etiology and Risk Factors

- Advanced/metastatic disease or cancer recurrence
- Cancer treatment (chemotherapy, radiation, surgery, biologic agents, hormonal agents, molecularly targeted agents)
- Anemia
- Neutropenia
- Hypothyroidism
- Adrenal Insufficiency
- Hypogonadism
- Infection
- Malnutrition
- Depletion of vitamins B1, B6 and B12
- Electrolyte disturbances (calcium, magnesium, phosphorus)
- Cardiopulmonary, hepatic or renal dysfunction
- Sarcopenia, asthenia, deconditioning
Etiology and Risk Factors

- Proinflammatory cytokine expression/generalized inflammation
- Medications with sedating side effects (e.g. narcotics, anxiolytics, antiemetics, antidepressants), or medications with fatigue as part of the side effects profile (e.g. beta-blockers) of medications
- Concurrent symptoms (e.g. pain, dyspnea, nausea, diarrhea)
- Impaired sleep quality
- Psychological distress (depression, anxiety)
- Accumulating evidence also suggests a role for gene polymorphisms, altered circadian rhythmicity, immune dysregulation, abnormal cortisol secretion, elevated body mass index, and metabolic syndrome
- In any one individual, the etiology of CRF likely involves the interaction of several physiologic and psychobehavioral mechanisms
Psychophysiologic Models of CRF

- **Energy Balance/Energy Analysis Models**
  - energy intake, metabolism, and expenditure are major explanatory variables

- **Fatigue as a Stress Response Models**
  - tiredness, fatigue, and exhaustion represent a continuum of stress response

- **Neuro-Endocrine Based Regulatory Fatigue Models**
  - fatigue explained by neuro-immuno-endocrine dysregulation
Organizing Framework for Understanding Cancer-Related Fatigue

Approaches to Measuring Cancer-Related Fatigue

- Single items that gauge fatigue severity
- Single items or subscales that measure relevant aspects of the fatigue experience that have been drawn from measures of quality of life (e.g. FACIT-Fatigue), psychosocial adjustment, mood, or self-reported health status (e.g. vigor, vitality)
- Instruments designed specifically to evaluate CRF from a multidimensional perspective (e.g. Multidimensional Fatigue Inventory; Piper Fatigue Scale; PROMIS Fatigue Measures)
- Neurophysiologic and performance-based measurements of fatigue, including muscle force, endurance time, muscle reserve, neuromuscular-junction impulse propagation, and functional performance
Measurement Considerations

- Fatigue is a multidimensional construct:
  - *sensory* dimension (fatigue severity, persistence)
  - *physiologic* dimension (e.g. leg weakness, diminished mental concentration)
  - *affective* dimension (sadness, depression, fear)
  - *behavioral* dimension (reduction in the performance of needed or valued activities)

- Multidimensional measures provide information about this full range of characteristics beyond fatigue presence and intensity

- Weakness, tiredness or the absence of vigor or vitality, may not necessarily be equated with fatigue
Measurement Considerations for Research Purposes

- Reliability, validity, specificity, sensitivity to change, and recall period

- Respondent burden, translation in multiple languages, the complexity of scoring algorithms, and the availability of normative values and other interpretive guidance (e.g. minimal clinically important difference)

- Should possess the capacity to discriminate cases from non-cases with an acceptable level of sensitivity and specificity
Measurement Considerations for Research Purposes

- Contemporary advances:
  - item-banks, computerized-adapted testing, and other digital formats will improve efficiency, precision, and ease of interpretation of screening measures for CRF (e.g. PROMIS)

- Ecological momentary assessment
  - elicits a repeated, real-time measurement of behaviors or experiences as they occur in the naturalistic setting of an individual’s day to day life

  - may overcome methodologic limitations including recall bias and the influence of current context on self-report of fatigue
Fatigue Screening and Evaluation in the HSCT Recipient

Screening

- Brief measures to screen for fatigue are sensitive, and they can be applied efficiently in the clinic to identify individuals who would benefit from more systematic evaluation.

- Every patient be screened for the presence of fatigue at regular intervals. If present, fatigue should be assessed quantitatively on a 0-10 scale (0= no fatigue and 10= worst fatigue imaginable).

- Those with a severity of more than 4 should be further evaluated by history and physical examination.
Evaluation of the HSCT Recipient with Fatigue $>4$

- presence, intensity, and pervasiveness of fatigue
- course over time
- factors that exacerbate or relieve fatigue
- impact of fatigue on functioning and level of distress
- impact on self-esteem, mood, and the ability to perform activities of daily living, fulfill important roles as parent, spouse and worker, and relate to family and friends
- self-management interventions the patient has tried for fatigue and their effectiveness can be helpful in tailoring recommendations for fatigue management
Etiologic Factors That May Amplify Fatigue

- Hypothyroidism
- Hypogonadism
- Adrenal insufficiency
- Cardiomyopathy
- Pulmonary dysfunction
- Infection
- Anemia, neutropenia
- Sleep disturbances
- Malnutrition

- Sarcopenia, asthenia
- Inactivity and deconditioning
- Fluid and electrolyte imbalances
- Emotional distress (anxiety, depression)
- Uncontrolled concurrent symptoms
- Disease progression or recurrence
Medication Side Effects Profile May Intensify Fatigue

- Medications that may produce daytime sleepiness and fatigue
  - opioid analgesics, sedative-hypnotics, benzodiazepines, anxiolytics
  - antidepressants, antiemetics, antihistamines, and anticonvulsant agents
  - cardiac medications such as beta-blockers may contribute to fatigue by causing bradycardia
  - corticosteroids may cause fatigue by disrupting sleep or generating proximal muscle weakness
General Principles of CRF Management

- Typically several different causes in any one patient, treatment plan must be multidimensional and individually tailored
- Work with the patient and family to improve the assessment of fatigue and identify management strategies
- Open communication among patient, family, and health care team will facilitate discussion about the experience of fatigue and its effects on daily life
- General supportive care recommendations:
  - Optimize nutritional status and prevent weight loss
  - Balance rest with physical activity
  - Encourage attention restoring activities such as exposure to natural environments and pleasant distractions like music
Interventions for Cancer Related Fatigue—General Principles

- More than 300 empiric studies of pharmacologic and non-pharmacologic interventions to reduce or manage CRF, and more than 75 meta-analyses or systematic reviews

- For some interventions, there is strong and consistent evidence to support effectiveness, while for other interventions only preliminary data are available

- Many of the interventions for fatigue have not been studied in HSCT recipients or long-term survivors of HSCT
Exercise is effective in managing fatigue during and following cancer treatment in patients with breast, prostate or colorectal cancer, patients undergoing chemotherapy, radiation or HSCT; survivors with solid tumor or hematologic malignancy, and following HSCT.

Possible mechanisms:
- Improves aerobic capacity, and ameliorates muscle loss and deconditioning
- Favorable effects on sleep, mood, self-efficacy, body composition, and the immune system and cytokine

Exercise modalities differ in:
- content (walking, cycling, swimming, resistive exercise, or combined exercise)
- frequency (ranging from two times per week to two times daily)
- intensity
- degree of supervision (fully supervised group versus self-directed exercise)
- duration (from two weeks up to one year)
Referral to a rehabilitation professional such as a physiatrist or physical therapist can be helpful in providing specific and detailed recommendations about the type, intensity, and frequency of exercise in which the patient should engage.

Ongoing follow-up by rehabilitation professionals contributes to strengthening motivation and adherence, and to advancing the exercise program as functional capacity improves.

Research is needed to:

- systematically assess the safety of exercise (both aerobic exercise and strength training)
- tailor the intensity, frequency, duration and type of exercise prescribed for different sub-populations of patients (e.g. tumor types, phase of treatment and follow-up)
Experts recommend that patients with fatigue be screened for the following treatable etiologic factors and managed as indicated:

- Concurrent distressing symptoms including pain, nausea and depression
- Hypothyroidism
- Hypogonadism
- Cardiomyopathy
- Adrenal insufficiency
- Pulmonary dysfunction
- Anemia
- Sleep disturbance
- Fluid and electrolyte imbalances
- Emotional distress
- Sedation secondary to specific classes of medications (e.g. opiates, antidepressants, antiemetics, antihistamines) or due to drug-drug interactions, and manage as indicated
Energy Conservation and Activity Management

- A nurse-delivered intervention focused on energy conservation and activity management (a multi-component intervention designed to help patients develop skills in planning, delegating, setting priorities, pacing, resting, and planning high-energy use activities at times of peak energy) had a modest but significant effect in a large, multi-site randomized clinical trial with patients (mostly breast cancer) initiating chemotherapy or radiation.

Education/Information Provision

- Four meta-analyses and 12 RCTs indicate that educational interventions (including teaching, counseling, support, anticipatory guidance about fatigue patterns, coping skills training, and coaching in fatigue self-management have a role in supporting positive coping in patients with fatigue, and contribute to reductions in fatigue levels.
- Interventions incorporate anticipatory guidance about fatigue patterns, the importance of exercise and sleep, and coaching and emotional support to promote goal setting and enhance self-efficacy.
**Likely to Be Effective**

### Measures to Optimize Sleep Quality

- Studies indicate a multi-component cognitive-behavioral intervention designed to optimize sleep quality may also improve fatigue.
- Cognitive behavioral intervention generally includes:
  - relaxation training
  - sleep consolidation strategies (avoiding long or late afternoon naps, limiting time in bed to actual sleep time)
  - stimulus control therapy
    - go to bed only when sleepy,
    - use bed/bedroom for sleep and sexual activities only
    - consistent time to lie down and get up,
    - avoid caffeine and stimulating activity in the evening)
  - reducing cognitive-emotional arousal
    - keep at least an hour to relax before going to bed
    - establish a pre-sleep routine to be used every night
Likely to Be Effective

Relaxation
- In six RCTs, progressive muscle relaxation training or relaxation breathing and yoga-like positioning delivered in a series of sessions to patients with cancer were found to be effective in lowering fatigue scores.

Yoga Practices
- Significantly improved fatigue outcomes in breast cancer.
- Effects of yoga on fatigue outcomes has not been established across a wide range of cancer patient populations.
- High risk of bias across studies with respect to sampling, inconsistent methods, blinding of participants and outcomes assessors and duration of follow-up.
Structured Multidimensional Rehabilitation

- Eight RCTs in patients with a range of solid tumors, including advanced disease
- Structured combination of physical training, psychoeducation, and nutritional counselling, mudpacks, massage and manual lymph drainage
- Some therapies delivered during an inpatient hospital stay
- Improves fatigue as well as mood, physical function and nutritional status

Mindfulness-Based Stress Reduction and Cognitive-Behavioral Stress Mgmt

- Significantly improved fatigue outcomes in 5 RCTs in breast cancer, and one RCT in patients with mixed tumor sites
- Three other RCTs however showed no effects on fatigue outcomes
Cognitive-Behavioral Therapy (CBT) for Fatigue, Depression and Pain

- Six RCTs in patients with a range of solid tumors and severely fatigue survivors and patients with advanced cancers
- Consistently favorable effects on fatigue outcomes

Management of Concurrent Symptoms including Pain, SOB, Insomnia and Depression

- APN intervention to systematically evaluate and manage symptoms
- Palliative care clinic consultation to address concurrent symptoms
Benefits Balanced With Harms

Correction of Anemia

- Seven recent meta-analyses or systematic reviews suggest that patients receiving erythropoiesis stimulating agents to correct anemia less than 10 g/dL may experience increased vigor and diminished fatigue.
- There is only limited evidence that ESAs improve fatigue when anemia is less severe.
- Data suggest that a target hemoglobin level of 11 to 12 g/dL will produce the greatest gains in fatigue and other quality of life outcomes.
- Use of these agents *specifically for fatigue* is relatively contraindicated due to safety issues:
  - Increased risk of thrombotic events, hypertension
  - Epoietin may support or extend tumor growth in certain tumor types
- National practice guidelines (*NCCN, 2010*) and FDA guidance should direct patient management including:
  - Decisions about monitoring
  - Treatment thresholds
  - Dose reductions and treatment discontinuation
  - Use of supplemental iron; transfusion support instead of ESAs
- *FDA* mandated a risk evaluation and mitigation strategy (REMS) requiring all prescribers of ESAs to register and receive training.
Low-dose Dexamethasone

- Dexamethasone 4 mg BID x 2 weeks improved CRF in advanced cancer in a small randomized, placebo-controlled trial
- Adverse events were comparable in dexamethasone and placebo groups
- Caveat: systemic corticosteroids may have prominent adverse effects in specific subpopulations (e.g. at end of life)
Effectiveness Not Established

**Acupuncture, acupressure and self-acupuncture**
- 6 meta-analyses of randomized trials published in the last 2 years
- Many studies demonstrate a positive effect on fatigue outcomes
- Interventions are feasible, well-accepted and safe
- Interpretation of study outcomes is complicated by high risk of bias including short duration of follow-up, single acupuncturists and non-blinding of outcome assessors
- All reviews urge additional study using rigorous trial designs

**Morning exposure to bright light**
- Small RCT showed positive effects in terms of preventing fatigue during chemotherapy for breast cancer and in cancer survivors with mixed diagnoses
- Evidence suggests that exposure to bright light may protect recipients from circadian rhythm desynchronization during cancer treatment

**Qigong or Tai Chi**
- Three RCTs showed favorable effects of Qigong on fatigue outcomes
- Tai chi improved fatigue in a small single arm trial
- Recent meta-analysis concluded that study results should be interpreted cautiously
**Effectiveness Not Established**

### Nutritional Supplements and Herbal Remedies
- Agents studied include vitamin supplements, levocarnitine, lectin-standardized misteltoe, omega-3 fatty acid, guarana, valerian, and Chinese herbal medicines
- Many studied as part of a multi-component regimen
- Improvements in fatigue endpoints was inconsistent
- High risk of bias given the open label, non-randomized study designs, small samples, and testing of multiple secondary endpoints

### Massage and biofield therapies such as Reiki, healing touch
- Multiple small RCTs or quasi-experimental studies
- Modalities examined as single interventions or as part of a multicomponent intervention
- Preliminary evidence suggests these may be effective, although efficacy results are mixed, and studies have a high risk of bias
- Continued testing and refinement is needed

### Complementary Approaches
- Expressive writing, art, music, dance, or animal-assisted therapy, exposure to nature and green space, distraction-virtual reality immersion, and aromatherapy with lavender foot soak and reflexology
- Open label and/or uncontrolled study designs and small sample sizes make it difficult to draw conclusions
Paroxetine

- Evidence of effectiveness in treating fatigue during and following cancer treatment is mixed
- In two large randomized trials, paroxetine 20 mg po daily did not have an effect on fatigue, although improvements in depression and overall mood were noted in the paroxetine treatment group
- Two small trials show a possible benefit for paroxetine in treating fatigue in women with hot flashes and in patients receiving interferon alpha

Methylphenidate

- Several small open label, single arm trials and 3 RCTs have reported improvements in fatigue in most of their participants as a result of the methylphenidate (5-10 mg BID) intervention

Donepezil

- Donepezil (5 mg every morning) evaluated in a blinded RCT and two single arm open label trials
- RCT showed no benefit on fatigue outcomes; fatigue was improved in the open label trials
**Bupropion Sustained Release**

- Bupropion Sustained Release (dose of 100-150 mg/day) evaluated in an uncontrolled, open-label trial in 15 patients with marked fatigue
- Most participants reported an improvement in their level of fatigue within two to four weeks of therapy
- Controlled trials needed to establish the efficacy of this intervention, and to determine whether this effect of bupropion is separate from its action as an antidepressant

**Modafinil**

- Several trials also suggest that modafinil at a dose of 100 mg BID may be effective in treating fatigue and improving daytime wakefulness and cognitive function in patients during and following cancer treatment
**Effectiveness Not Established**

**Venlafaxine**
- Small RCT (n=57) showed no improvement in fatigue outcomes

**Sertraline**
- Large RCT (n=189) in patients with advanced cancer showed not significant effect on fatigue in the absence of depression
Expert Opinion

- Work with patient and family caregivers to improve assessment of fatigue and identify management strategies.
- Promote open communication between patient, family and caregiving team to facilitate discussions about the experience of fatigue and its effects on daily life.
- Consider attention restoring activities such as exposure to natural environments, and pleasant distractions such as music.
- Encourage a balanced diet with adequate intake of fluid, calories, protein, carbohydrates, fat, vitamins, minerals.
Case Study

- Beatrice M is a 54 year old high school art teacher with AML in 1st remission. She is day +45 status post related allogeneic HSCT with her course complicated by acute GVHD of upper GI tract (nausea and anorexia), and pruritic erythematous skin rash.

- She continues on immunosuppression with tacrolimus and is on a tapering dose of steroids. Due to poor oral intake, she has continued to lose weight (BMI now 22), and she requires daily visits to the day hospital for fluids and magnesium supplementation.

- She has mild anemia which she tearfully admits causes her some concern about her remission status, however donor chimerism is 100%.

- On review of systems she has periodic waves of nausea, a limited appetite, and has been sleeping poorly for more than month since starting steroids. She often cat-naps throughout the day and early evening, with the result that she finds it difficult to sleep at night. In addition to the cutaneous findings for acute GVHD of the skin, on examination she has mild proximal muscle weakness.
Your Approach

- Screen for fatigue using a 0-10 scale
- Fatigue is a 5
- Evaluate for contributing fatigue contributing factors:
  - Anemia
  - Emotional distress
  - Proximal muscle weakness
  - Sarcopenia and weight loss
  - Concurrent symptoms (pruritis, nausea, anorexia)
  - Poor sleep quality
  - Dehydration/electrolyte imbalances
Your Approach

- Anticipatory guidance about possible reasons for fatigue (anemia, proinflammatory cytokine activity with acute GVHD, sarcopenia, proximal muscle weakness, concurrent symptoms, sleep quality) and options for self-management
- Teach energy conservation strategies
- Refer to physical therapy for proximal muscle strengthening and a gentle exercise program
- Supportive therapy to help manage anxiety
- Nutrition consultation to attenuate weight loss
- Multiple vitamin supplement; folic acid
- Consider medication to improve sleep quality
- Topical agents to relieve pruritis
Case Study

- Gina M. is a married, 56 year old African American female who is 2 1/2 years postmatched-unrelated donor hematopoietic stem cell transplantation for acute lymphocytic leukemia (ALL). She was conditioned with Bu/Cy/TBI. Her post-transplant course has been complicated by chronic graft-versus-host disease (GVHD) requiring treatment with immunosuppressants, including prednisone 40 mg daily.

- Comorbidities include neuropathic pain (NP), depression, weight gain, and osteoporosis. She has been post-menopausal since her remission induction chemotherapy.

- Gina has returned to part-time work, with adjusted responsibilities due to her physical and cognitive fatigue and to allow her to keep frequent medical appointments. However she is worried these accommodations will not be offered to her indefinitely.

- Although Gina was prepared to feel fatigue for at least a year post-transplant, she has become very discouraged by its persistence, and she is tearful as she discusses her concerns.
Case Study

- Due to multiple psychological stresses as well as neuropathy, she has difficulty falling asleep most nights, and often lies awake due to pain. Although she has had trouble sleeping for several years, this has worsened with the initiation of prednisone.

- She rates her fatigue severity as 6 or 8 on a 0-10 scale and is fatigued on most days. Her muscles feel weak and she frequently experiences daytime sleepiness, difficulty concentrating, and short term memory problems.

- These have all caused her to limit her social interaction and recreational pursuits. She often goes straight to bed after work, spending the evening napping and watching TV.

- On examination she is obese with a BMI of 32; CBC and basic metabolic panel are normal.
Your Approach

- Comprehensive assessment of fatigue and sleep-wake patterns
- Evaluate for contributing factors such as hypothyroidism (given conditioning with TBI)
- TSH and reduced free-T4 consistent with hypothyroidism
- You also note depression, sarcopenia, and suboptimal management of neuropathic pain.
- She is not engaged in a program of regular exercise
Your Approach

- Pharmacotherapy to address pain, depression, and hypothyroidism
- Referral to physical therapy to improve strength, aerobic conditioning, and muscle mass
- Amitriptyline hydrochloride at hs is selected for painful neuropathy, and its sedating side-effects may also have a beneficial impact on sleep
- To improve sleep quality you also recommend
  - progressive muscle relaxation with imagery
  - behavioral measures including regular bedtime and get-up times, using the bedroom only for sleep and sexual activity, and initiating a calming pre-sleep routine
Your Approach

- You discuss with Gina several causes of her fatigue during survivorship and how chronic GVHD and its treatment with corticosteroids may amplify her fatigue and sleep problems through an altered cytokine milieu and disrupted immune-neuro-endocrine stress response.

- You also provide coaching to encourage goal setting and self-management.

- At the weekly team conference you suggest administering prednisone in the morning to limit the effects on sleep and/or moving to an every-other day steroid dosing, as tapering proceeds.

- At her follow-up appointment 8 weeks later, Gina rates her fatigue as a 3 (0-10) and reports her sleep and daytime functioning are gradually improving.

- The team encourages her to continue the positive steps she has taken to reduce her symptom distress and recommends follow-up assessments every month to modify the care plan and consider referrals.
Implications for Practice

- Ongoing periodic screening is an essential component of care quality

- 10 point scale for screening is efficient and sensitive; moderate to severe fatigue 4-10 (on 10 point scale) warrants further evaluation and treatment

- Use national guidelines (NCCN and ONS-PEP) to:
  - Examine your practice and expand the repertoire of interventions recommended for a specific patient based on efficacy

- Emphasis has been on fatigue in patients with solid tumors who are on treatment and cancer survivors
Implications for Practice

- Attention to treating comorbidities (e.g. deconditioning, impaired sleep quality, concurrent symptoms, mood disturbances)

- Multimodal approach addressing both central and peripheral fatigue:
  - exercise
  - psychoeducational interventions to optimize fatigue self-management
  - manage concurrent symptoms (especially depression, pain and stress)
  - improve sleep quality
  - judicious use of medications such as modafinil, methylphenidate to improve daytime dysfunction
  - complementary therapies such as relaxation, massage, healing touch, or acupuncture
Implications for Practice

- Screen for correctable contributing factors: anemia, thyroid dysfunction, hypogonadism, cardiomyopathy, adrenal insufficiency, pulmonary dysfunction, sleep disturbances, fluid and electrolyte imbalances

- Provide patients with anticipatory information about fatigue prior to initiation of treatment, and as they transition to survivorship phase

- Develop plan to prevent/manage fatigue

- Systematic evaluation of fatigue at baseline and prospectively, to evaluate outcome of intervention
# Recommendations for Cancer-Related Fatigue in Adults: National Guidelines

<table>
<thead>
<tr>
<th>Interventions Identified as Recommended for Practice by NCCN, ONS, CPAC/CAPO, ASCO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address Treatable Contributors to Fatigue</td>
</tr>
<tr>
<td>Manage Concurrent Symptoms</td>
</tr>
<tr>
<td>Physical Activity/Exercise</td>
</tr>
<tr>
<td>Comprehensive rehabilitation</td>
</tr>
<tr>
<td>Psychoeducational Interventions, including Energy Conservation</td>
</tr>
<tr>
<td>Meditation, mindfulness-based stress reduction, cognitive-behavioral stress management</td>
</tr>
<tr>
<td>Relaxation</td>
</tr>
<tr>
<td>Cognitive-behavioral therapy for fatigue, depression, and pain</td>
</tr>
<tr>
<td>Cognitive-behavioral therapy for sleep</td>
</tr>
<tr>
<td>Yoga</td>
</tr>
</tbody>
</table>
**FATIGUE SURVIVORSHIP CARE PLAN**

**DEFINITION:**
- Fatigue is one of the most common side effects of treatment and almost 50 percent of cancer survivors report fatigue that persists for months and even years after treatment.
- Fatigue is a feeling of weakness, tiredness or exhaustion that can include a loss of physical and/or emotional energy.
- Fatigue is felt on different levels with some survivors experiencing low energy, others feeling totally wiped out or unable to concentrate, and some feeling depressed or frustrated.

**EVALUATE ALL PATIENTS FOR FATIGUE:**
- Screen all patients for fatigue at regular intervals. On a scale of 0-10 where zero is no fatigue and 10 is the worst fatigue imaginable, how would you rate your fatigue over the past 7 days?
- If moderate (4-6) or severe (7-10), evaluate onset, pattern, duration, change over time, contributing factors, interference with function, and self-management strategies, and develop a tailored fatigue plan.

**INTERVENTIONS TO MANAGE FATIGUE:**
- Exercise: With permission from your health care team, begin a program of physical activity such as walking, stretching, and cycling. Begin with 5 or 10 minutes a day and increase the time by 1 minute a day. Do not be tempted to overdo it, but rather strive for consistency.
- Consider referral to physical therapy, occupational therapy, exercise physiologist, or physiatrist to develop, tailor, or sustain an exercise program.

**Gain information About Fatigue:**
- Offer anticipatory guidance on possible patterns of fatigue onset/occurrence (e.g. in association with muscle weakness/conditioning, bowel, excess activity, impaired sleep quality, escalating medications, or stress).
- Differentiate levels of the fatigue experience (fatigue, tiredness, weakness, low energy, cognitive slowing).
- Keep a journal or diary of activities, fatigue severity, associated feelings and emotions, and evaluation of self-care actions.
- Visit National Cancer Institute (NCI) on Fatigue: www.cancer.gov/cancerinfo/understandingfatigue/fatigueintestinal/basics/

**SLEEP-WAKE SURVIVORSHIP CAREPLAN**

**INTERVENTIONS TO IMPROVE SLEEP:**
- Go to bed only when you truly feel sleepy and wake up to a regular time each night.
- Get out of bed and go to another room whenever you are unable to fall asleep; return to bed only when sleepy again.
- Limit the use of the bed to sleep and sex only.
- Maintain a regular rising time each day.
- Avoid daytime napping. If needed, limit to 20-30 minutes and complete first 5 behavioral hours before bedtime.
- Create a bedtime routine. Start by winding down 1-2 hours before bedtime. Use a preferred relaxation technique such as taking a warm bath or shower, reading, listening to soft music, or receiving a massage.
- Avoid stimulants such as caffeine after noon and nicotine or alcohol prior to bedtime; complete dinner 3 hours before bedtime, do not go to bed hungry (a protein snack is preferred).
- Create a comfortable sleep environment. Replace mattresses every 10-12 years and pillows more frequently; keep the bedroom dark, cool and quiet, and use light covers, do not watch television in the bedroom.

**SCREEN ALL PATIENTS FOR SLEEP-WAKE DISTURBANCES**

** Insomnia Severity Index (ISI)**
- Circle the number that best describes your current (last 2 weeks) sleep pattern.

<table>
<thead>
<tr>
<th>ISI Score</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Difficulty falling asleep &lt; 30 minutes</td>
</tr>
<tr>
<td>2</td>
<td>Time taken to fall asleep 30-60 minutes</td>
</tr>
<tr>
<td>3</td>
<td>Problem waking too early</td>
</tr>
</tbody>
</table>

**How satisfied/disatisfied are you with your sleep pattern?**
- How satisfied/disatisfied are you with your sleep pattern?

**How noticeable to others are your sleeping problems in terms of impairing the quality of your life?**
- How noticeable to others are your sleeping problems in terms of impairing the quality of your life?

**Add the scores for all items = total score**

**Note:**
- ISI score of 6 or higher indicates significant insomnia.
- ISI score of 6-10 (mild insomnia)
- ISI score of 11-15 (moderate insomnia)
- ISI score of 16-18 (severe insomnia)
- ISI score of 20-29 (clinical insomnia; severe)

**Follow-up Assessment: Repeat 6-8 weeks later; if NPI score #2 or higher, initiate interventions**
- Follow-up Assessment: Repeat 6-8 weeks later; if NPI score #2 or higher, initiate interventions.
- Consult with registered nurse, primary care provider, or sleep specialist.

**For further consideration:**
- With permission from your home care team, begin a program of physical activity such as walking, stretching, and cycling. Avoid exercising within 2 hours of bedtime.
- Consider mindfulness based stress reduction, relaxation and guided imagery, progressive muscle relaxation, supportive-expressive group therapy, expressive writing, massage, yoga, and music therapy.

**Patient:**

**Clinician initials:**

**Date:**

Implications for Research

- Many of the fatigue interventions have had only limited study—many were uncontrolled trials or pilot work
- Few interventions have been tested in transplant recipients and survivors
- Randomized trials are indicated
  - Further development of interventions that have shown promise (eg. massage, rehabilitation)
  - Evaluate therapies where there were mixed results (eg. acupuncture, methylphenidate; modafinil) to develop more tailored indications for use