Approach to Cancer-Related Fatigue
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DISCLOSURES
- I am a Colombian
- I speak fast
- I don’t mind repeating
- I have no financial disclosures

OVERVIEW
- Clinical aspects of fatigue: relevance, presentation and diagnosis
- Practical recommendations in the management of fatigue
- Goal is to provide a framework for your clinical practice
- Time for questions and discussion of experiences
TAKE HOME MESSAGES

- 5 take home messages in the talk
- You will be alerted at each of these
- They should be relevant to your clinical practice

WHAT IS CANCER-RELATED FATIGUE?

- Defined by the NCCN as “… a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that interferes with usual functioning.”
- Qualitatively and quantitatively different than fatigue in healthy individuals and less likely to be relieved by rest (Carr, et al., 2002)
WHAT DO PATIENTS REPORT

- Tiredness
- Exhaustion
- Lack of energy
- Heaviness
- Weakness
- Sleepiness

IMPACT

- Affects 77% of individuals with cancer (Van Lancker A, et al. 2014)
- Symptom that is most frequently reported, described as the most distressing than pain, and is associated with the most debilitating impact on functioning (Williams, et al., 2016)
- Up to ¼ of patients can experience fatigue for several years after completing cancer treatment (Bower, et al., 2006)
- Majority of patients and providers report that they have not talked to each other about fatigue (Passik, et al., 2002)

HYPOTHESIZED UNDERLYING MECHANISMS

- Elevated levels of pro-inflammatory cytokines (Miller AH, et al. 2008)
- 5-hydroxytryptophan (5-HT) dysregulation (Ryan, et al., 2007)
- Hypothalamic-pituitary-adrenal axis dysfunction (Miller, et al., 2008)
- Circadian rhythm disturbances (Mormont, et al., 2010)
- Autonomic nervous system dysregulation (Crosswell, et al 2014)
HOW DO WE APPROACH CANCER-RELATED FATIGUE?

NCCN GUIDELINES FOR THE MANAGEMENT OF FATIGUE

- Derived from consensus of a multidisciplinary team of experts
- Part of guidelines for supportive care, along with pain, nausea, and psychosocial distress
- First published in 2000, revised yearly
- Influenced ASCO 2014 Survivorship Guidelines for Fatigue
- Available free at NCCN website

3 PARTS TO GUIDELINES

- Screening
- Evaluation/ Diagnosis
- Interventions and recommendations
  - Active treatment
  - Post-treatment
  - End of life
SCREENING FOR FATIGUE

- Addresses multiple barriers to the management of fatigue
- Needs to be rapid and easy to use in busy clinical settings
- Should trigger further assessment of fatigue

RAPID SCREENING FOR FATIGUE

- NCCN recommends a one-item, 0-10 scale: “Since your last visit, how would you rate your fatigue on a scale of 0-10?”
- Scores are divided into severity categories: 0= no fatigue; 1-3= mild fatigue; 4-6= moderate fatigue; 7-10= severe fatigue
- NCCN recommends further assessment for scores of 4 or above

IS THERE EVIDENCE TO USE THIS SCALE?

- Some evidence to support this in studies of the Brief Fatigue Inventory (Mendoza, et al., 1999; Hwang, et al., 2002)
- Scores of 7 or above correlated with functional impairment on SF-36 (Piper, et al., 1997)
- It is highly correlated with validated instruments and is predictive of functional impairment.
TAKE HOME MESSAGE #1

The one-item, 0-10 fatigue screen is a good rough estimator of fatigue and its impact on functioning.

OTHER FATIGUE SCREENING INSTRUMENTS

- A variety of validated instruments exist for the measurement of fatigue
- Range from cancer-specific instruments to domains of quality of life instruments
- Common ones include: FSI, FACIT-F, BFI, Multidimensional Fatigue Index (MDFI), Piper Fatigue Scale
- Used primarily in research

DIAGNOSTIC CRITERIA FOR CANCER-RELATED FATIGUE

- Fatigue as syndrome, rather than symptom
- Proposed diagnostic criteria for ICD
- Criteria have a similar format to diagnostic criteria for psychiatric disorders in the DSM
- Meet criteria for diagnosis by having a minimum number of specified symptoms
PROPOSED DIAGNOSTIC CRITERIA

- Significant fatigue for 2 weeks and at least 5 other symptoms
  - Generalized weakness or limb heaviness
  - Diminished concentration or attention
  - Decreased motivation and interest
  - Anemia or hypersomnia
  - Unrefreshing or nonrestorative sleep
  - Perceived need to struggle to overcome inactivity
  - Marked emotional reactivity to fatigue
  - Difficulty completing daily tasks attributed to feeling fatigued
  - Perceived difficulties with short-term memory
  - Postexertional malaise lasting hours

- Symptoms cause clinically significant impairment in social, occupational, or other important areas of functioning

- There is evidence that symptoms are a consequence of cancer or cancer therapy

- The symptoms are not a consequence of comorbid psychiatric disorder

EVALUATION OF FATIGUE

- First step is to take a fatigue history:
  - Onset
  - Pattern
  - Duration and change over time
  - Description of a typical day
  - Associated and alleviating factors
  - Past interventions
  - Impact on relationships and social support

NCCN AREAS IN PRIMARY EVALUATION

- Assessment of concurrent symptoms and treatable contributing factors:
  - Anemia
  - Pain
  - Emotional distress
  - Sleep
  - Nutrition
  - Activity level
  - Other medical morbidity (thyroid function and medications)
TAKE HOME MESSAGE # 2
Make sure to cover the 7 areas recommended by the NCCN in your evaluation.

CANCER RELATED EMOTIONAL DISTRESS
- Periods of increased vulnerability
- Signs and symptoms of normal fear and worry of future and uncertainty
- Concerns about illness
- Preoccupation with thoughts of illness and death
- Sadness about loss of usual health
- Anger, feeling out of control
- Poor sleep, appetite, concentration

DISTRESS: DEPRESSION AND ANXIETY
- Fatigue is not psychological, but depression and anxiety make it worse
- ASCO guidelines for depression and anxiety:
  - Depression: PHQ-9
  - Anxiety: GAD-7
  - (www.phqscreeners.com)
- Consider referral to mental health professional
HOW TO DIFFERENTIATE BETWEEN FATIGUE AND DEPRESSION?

FATIGUE VS. DEPRESSION: EVIDENCE SLIDE

- Anhedonia found to discriminate depression (Reuter and Harter, 2003)
- Differences in temporal variation of fatigue severity (Donovan, et al., 2004)

FATIGUE VS. DEPRESSION: ART SLIDE

- Physical complaints such as limb heaviness more common in fatigue
- Past history of depression and/or family history of depression
- Supporting data from depression questionnaires (HADS)
- Clinical experience and diurnal pattern recognition
TAKE HOME MESSAGE # 3

Depression is more associated with anhedonia and worse fatigue in the morning. Past history and data from other instruments may be helpful in tipping the scale.

TREATMENT OF FATIGUE: STEPWISE APPROACH

1. Education and counseling of patient and family
2. Treat any contributing factors
3. Promote healthy exercise and sleep routines
4. Behavioral management
5. Medications

EDUCATION AND COUNSELING

- Validate the experience
- Give context for the fatigue
- Explore their beliefs and fears about the fatigue
- Give them a plan for the fatigue
EXERCISE: BASIC RECOMMENDATIONS

• Aerobic exercise is beneficial both during and post-cancer therapy (Cramp, et al. 2012)
• ASCO recommends moderate aerobic exercise (150 mins/week) and strength training 2-3x per week
• Start small and low intensity
• Physical therapy consultation can help design optimal exercise plans
• Motivate patients and make it fun

EXERCISE: PHYSICAL THERAPY

Specific issues that should trigger referral for physical therapy include:
• Cardiovascular and respiratory comorbidities
• Recent major surgery
• Specific functional or anatomical deficits
• Substantial deconditioning

EXERCISE: ROLE OF YOGA

Several controlled studies have demonstrated the efficacy of Yoga in the physical, mental and global burden of cancer related fatigue (Vadiraja, et al 2009,)
• Particularly helpful in older cancer patients (Sprod, et al., 2015)
• Benefits can be seen even with low to moderate intensity routines
• Prayanama (breathing exercises) has also demonstrated benefits (Chakrabarty, et al., 2015)
SLEEP

- Trouble falling asleep or staying asleep
- Feeling “sleepy” or “struggling to stay awake” are signs
- Less restful sleep: snoring, limb movements

SLEEP HYGIENE

- Sunlight exposure upon waking up
- Reduce total caffeine intake
- Optimize daytime naps
- Exercise
- Avoid late dinners
- First half of the night: Active stage
- One hour prior: Preparation for sleep
- Same bedtime every day
- Bed should be only used for sleep

SLEEP STUDY

- Monitored sleep in a lab
- Measures brain waves to tell when sleeping and how deeply
- Measures oxygen levels
- Analyzes body movements
# TREATMENTS FOR SLEEP DISORDERS

- Obstructive sleep apnea
  - CPAP
- Periodic limb movements during sleep
  - Medications: pramipexole, ropinirole

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## TAKE HOME MESSAGE # 4

Investing a few minutes in education about fatigue, exercise and healthy sleeping habits can go a long way.

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## BEHAVIORAL MANAGEMENT

- Energy conservation
- Energy management
- Cognitive behavioral therapy
- Mindfulness-based stress reduction
- Stress management strategies
ENERGY CONSERVATION
- Behavioral intervention to manage activity
- Based on people having a set amount of energy like a battery
- If all energy used up, you feel tired
- Focus on strategies to save energy
  - Delegate
  - Alternative ways to do things
  - Rest before you are fatigued

ENERGY MANAGEMENT
- Working with your body rhythms
- Identifying stamina level on a given day and planning activities appropriate to fluctuations
  - A-Day: > 75% stamina level
  - B-Day: 50 – 75% stamina level
  - C-Day: < 50% stamina level
- Find peak and low energy times

LOW ENERGY TIMES
- Don’t try doing hard things
- Do restorative activities
- No guilt (Acceptance/Action)
HIGH ENERGY TIMES

- Exercise
- Do things that take more energy and things that you need to accomplish
- Make a list and check it twice
- Plan over a week or a month

ENERGY MANAGEMENT PLAN

<table>
<thead>
<tr>
<th>6:00a</th>
<th>6:45a</th>
<th>9:00a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Take a bath, get dressed</td>
<td>Eat breakfast, read paper</td>
<td>Preapare and eat lunch while sitting or have someone prepare lunch</td>
</tr>
<tr>
<td>7:00a</td>
<td>7:30a</td>
<td>10:00a</td>
</tr>
<tr>
<td>Place dirty laundry in washing machine</td>
<td>Two collars in house</td>
<td>Ask spouse to place dirty laundry in washing machine</td>
</tr>
<tr>
<td>7:15a</td>
<td>8:00a</td>
<td>10:45a</td>
</tr>
<tr>
<td>Read a good book</td>
<td>Ask spouse to move laundry to dryer</td>
<td>Read a magazine article</td>
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<tr>
<td>7:30a</td>
<td>8:45a</td>
<td>11:00a</td>
</tr>
<tr>
<td>Prepare and eat lunch while sitting or have someone prepare lunch</td>
<td>Preapare and eat lunch</td>
<td>Read the mail and gather bills</td>
</tr>
<tr>
<td>8:00a</td>
<td>9:15a</td>
<td>11:30a</td>
</tr>
<tr>
<td>Eat breakfast, read paper</td>
<td>Write a letter or email to a friend</td>
<td>Go for a walk in the neighborhood</td>
</tr>
<tr>
<td>8:30a</td>
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STIMULANT MEDICATIONS

- 70% of patients report that they would rather have their fatigue treated without medications (Passik, et al., 2002)
- Mixed conclusions about benefit reported by meta-analyses and systematic reviews (Minton, et al 2010)
- Methylphenidate
- Modafinil
- Potentiate effects of narcotics for pain control and lessen the side effect of sedation
- Side effects can include constipation, anorexia, headache, and elevations in heart rate and blood pressure
WHEN DO I PRESCRIBE STIMULANTS?

- Persistent impairment in functioning after treating contributing factors
- Severe fatigue that would prevent participation in exercise or behavioral management
- Only in patients without medical or psychiatric contraindications

CAM AND OTHER MEDICATIONS

- Methylprednisolone: 16 mg bid in advanced cancer patients on opioids (Paulson, 2014)
- Wisconsin ginseng: 2000 mg qd (Barton, 2013)
- Acupuncture and Acupressure (Cheng, 2017)
- Infrared laser moxibustion (Mao, et al., 2016)

TAKE HOME MESSAGE # 5

Do not rely only on medications, behavioral interventions are equally important
MY RECOMMENDED APPROACH

1. Screen for fatigue at clinical encounters
2. If fatigue is present and at least moderate in severity, take a fatigue history that investigates impairment from the fatigue
3. Cover the seven areas recommended by the NCCN in your evaluation and provide relevant treatment
4. Provide patient education about fatigue
5. Consider exercise and behavioral interventions
6. Stimulant medications may be helpful for some patients