

Module: Fatigue and Insomnia

Learning Objectives

Attitudes

- Reflect on prior experiences with patients who have fatigue and insomnia.
 - Appreciate that fatigue and insomnia, particularly in life-limiting illness, are multifactorial and often require multi-modal treatment.
 - Recognize that fatigue and insomnia can markedly impact quality of life, function, recovery, and decision-making.
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Knowledge

- List common factors and comorbidities that can contribute to fatigue and primary insomnia.
 - Outline the potential benefits and limitations of non-pharmacologic treatments for fatigue and insomnia, with attention to patient-specific considerations.
 - Discuss the potential benefits and limitations of pharmacologic treatments for fatigue and insomnia, including key considerations for individual patient needs.
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Skills

- Develop an organized approach to the assessment of fatigue and insomnia.
- Demonstrate the ability to counsel patients on nonpharmacologic treatments for fatigue and insomnia.
- Create a care plan incorporating both non-pharmacologic and pharmacologic treatments for fatigue and insomnia.

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Fatigue

Fatigue is commonly reported as the most debilitating and prevalent symptom among both cancer and non-cancer patients with life-limiting illness (1).

Fatigue has broad effects, impacting physical function, cognition (e.g. memory and concentration), sleep (including both insomnia and hypersomnia), and emotional well-being.

Definition:

A persistent or profound sense of tiredness and lack of energy that is not relieved by rest and interferes with daily activities.

Additional features may include:

- Diminished concentration
 - Decreased motivation
 - Insomnia or hypersomnia
 - Nonrestorative sleep
 - Short-term memory deficits
 - Marked emotional reactivity
- Any of the above must be not primarily consequence of depression (2).

Differential Diagnosis:

- Cancer and cancer treatment
- Renal failure
- End-stage heart failure
- COPD and other chronic lung conditions
- Neurodegenerative diseases (e.g. multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's)
- HIV/AIDS
- Depression
- Substance use disorders
- Nutritional deficiencies
- Endocrine abnormalities
- Medication side effects
- Uncontrolled pain
- Medical conditions secondary to the above (e.g. anemia secondary to end-stage renal disease)

Evaluation:

Perform a history and physical examination. Identify potentially modifiable contributors to fatigue, such as anemia, medication effects, or poorly managed pain. Distinguish fatigue from physical weakness, such as progression of neurodegenerative disease.

Distinguishing Illness-Related Fatigue, vs. Depression-Related Fatigue (3-5).

- Illness-related fatigue and depression-related fatigue are *not* mutually exclusive.
- Screen for depression at each visit.
 - o Depression is common – 1 in 4 palliative care patients have depression
 - o Screening tools for depression include the PHQ-2, PHQ-9, Edinburgh Depression Scale, and Hospital Anxiety and Depression Scale.
 - o A positive screen should prompt further assessment or treatment

PHQ-2

1. "Are you feeling down, depressed, or hopeless most of the time over the last 2 weeks?"
2. "Have you found that little brings you pleasure or joy over the last 2 weeks?"

- Characterize *pattern of fatigue*.
 - o Illness-related fatigue: mood and energy may be better in the morning, improve with rest, and worsen late in the day.
 - o Depression-related fatigue: mood and energy often start low in the morning and may remain fixed or gradually improve throughout the day.

Management:Non-pharmacologic Strategies:

A multimodal approach including multiple of these strategies can reduce symptom burden, including fatigue (6).

Exercise

- Recommendations vary, on the type, frequency, and duration of exercise.
- Studies support benefits from aerobic, resistance, or mixed modality exercise.
 - o Low- to moderate-intensity yoga and strength training have demonstrated particular benefit for cancer-related fatigue (7).
- Regardless of modality or program length, exercise improves quality of life, fatigue, and endurance (8, 9).
- Consider recommending: 20-30 minutes of activity, at least three times per week (10).

Palliative Rehabilitation

- Designed to prevent functional decline or optimize existing capacity after permanent impairment.
- Provided in diverse settings (from acute care to hospice) and by various clinicians (physical therapists, occupational therapists, or speech and language pathologists) (11).

- Patients have reported reduced fatigue and improved quality of life while participating in these programs (9, 12, 13).
- May include strategies such as energy conservation, or a customized approach to treating fatigue in illnesses such as COPD, CHF, and neurodegenerative disease (14).

Nutrition (15-17)

- Malnutrition leads to increased fatigue.
- Early and multidisciplinary nutritional support can contribute to better quality of life.
- Patients with life-limiting illness are at increased risk for malnutrition and should be screened and counselled appropriately.

Pharmacologic Strategies:

Class and Examples	Clinical Pearls	Suggested Dosing
Psychostimulants (18, 19): Dextroamphetamine Methylphenidate Modafinil	<ul style="list-style-type: none"> - Mixed evidence: some studies show significant improvement in fatigue; others show no benefit over placebo (20, 21). - Generally well tolerated across patient populations - Side effects: palpitations, anxiety - Short-acting or extended-release forms - May have less benefit in patients with life expectancy less than 4 weeks (22). - Modafinil is a non-amphetamine psychostimulant, with similarly mixed results 	Dextroamphetamine 2.5-5mg PO QAM (starting dose) Methylphenidate 2.5-5mg PO BID (dose am and noon) Modafinil 100mg PO QAM (starting dose)
Corticosteroids (23): Dexamethasone Prednisone Methylprednisolone	<ul style="list-style-type: none"> - May improve cancer-related fatigue, nausea, anorexia, and pain - Side effects: insomnia, agitation - Avoid long-term use due to risks including hyperglycemia, adrenal suppression, and GI bleeding (especially with NSAID use) - Cannot be used concurrently with many immune-based systemic cancer treatments due to their immunosuppressive effects – consult with patient's oncologist. 	Use the lowest effective dose. Discontinue within 5-7 days, especially if ineffective, to avoid need to taper.

<p>Supplements (24):</p> <p>Ginseng</p>	<ul style="list-style-type: none"> - Traditionally used across cultures for a variety of symptoms - Some studies show reduction in cancer-related fatigue (25-27) - Use caution with warfarin – ginseng can reduce warfarin's efficacy 	<p>More research needed to establish specific dosing</p>
<p>Supplements (24):</p> <p>Vitamin D</p>	<ul style="list-style-type: none"> - High prevalence of vitamin D deficiency among palliative patients - Preliminary studies suggest potential benefits in reducing fatigue and improving pain (28-30) 	<p>More research needed to establish specific dosing</p>

Insomnia

Disordered sleep is common in the general population, including in the elderly, and the terminally ill. Sleep deprivation can worsen pain, increase fatigue, and diminish quality of life (31).

Definition:

Primary Insomnia – Dissatisfaction with sleep quantity or quality, associated with one or more of the following:

- Difficulty initiating sleep
- Difficulty maintaining sleep
- Early morning awakening with inability to return to sleep

Diagnostic criteria also include:

- Persistent symptoms occurring at least 3 nights per week, for at least 3 months.
- Occurs despite adequate opportunity for sleep.
- Leads to significant functional impairment during the day.
- Sleep disturbance *cannot* be better explained by another sleep-wake disorder, mental disorder, medical condition, or the physiologic effects of a substance (32).

Differential Diagnosis:

New-onset primary insomnia, or short-term insomnia, may be triggered by acute stressors, such as: bereavement, changes in environment, uncontrolled pain, and illness.

- These episodes of insomnia can resolve once the underlying stressor is addressed.
- Contributing factors may include:
 - excessive caffeine use (often in response to excessive daytime hypersomnolence)
 - increased screen time prior to bed
 - poor sleep hygiene

Persistent (chronic) insomnia may begin at a young age. Contributing factors include:

- acute stressors (as in new-onset insomnia)
- genetic predisposition
- circadian rhythm disorders
 - i.e., disrupted sleep-wake patterns including shift work or excessive napping (31, 33, 34).

Alternative sleep disorder etiologies:

- *Sleep-related breathing disorders*, e.g. obstructive sleep apnea, central sleep apnea, sleep-related hypoventilation disorders
- *Central disorders of hypersomnolence*, e.g. narcolepsy
- *Parasomnias*, e.g. nightmare disorders, sleep terrors, sleepwalking

- *Sleep-related movement disorders*, e.g. restless legs syndrome, periodic limb movement disorder

Consider other causes of secondary insomnia:

- *Medication- or substance-related*: caffeine, alcohol, nicotine, bronchodilators, clonidine, corticosteroids, diuretics
- *Other medical conditions*: COPD, nocturia, GERD, other uncontrolled symptoms
- *Mental health disorders*: anxiety, depression

Evaluation:

- Perform a complete history and physical examination to identify or rule out contributing factors and other causes.
- Obtain a sleep history from the patient (and, when possible, from a bed partner). Consider asking the patient to complete a one-week sleep diary.

Key components of a sleep history include (31):

- *Sleep hygiene*: bedtime routines, use of sleep aids, and screen use prior to sleep
- *Sleep chronology*: sleep onset, pattern, and duration; difficulties initiating sleep or staying asleep; experiencing early awakening
- *Sleep environment*: assess noise, light, temperature, and odors; document alcohol and caffeine intake
- *Physical symptoms*: e.g. pain, dyspnea/cough, nausea
- *Associated medical conditions and current medications*
- *Spiritual concerns or existential distress*, which may interfere with sleep

Validated assessment tools include: Insomnia Severity Index (ISI), the Pittsburgh Sleep Quality Index (PSQI), and the Athens Insomnia Scale (AIS) (33, 34).

Management:

Non-pharmacologic Strategies:

Non-pharmacologic interventions are considered **first line** treatments for insomnia (35). These include:

- *Sleep hygiene*:
 - maintain a consistent sleep schedule
 - limit modifiable factors such as caffeine and alcohol intake
 - avoid long daytime naps
 - minimize screen time, especially in the evening
 - reduce light and noise levels in the sleep environment
- *Stimulus control therapy*: Reinforces the connection between the bed and sleep by:
 - limiting bedtime stimuli such as television or other devices

- using the bed and bedroom only for sleep
- going to bed only when sleepy
- getting out of bed if unable to fall sleep
- *Sleep restriction:*
 - limit total time in bed to match actual sleep duration (as assessed via sleep diary)
 - gradually increase time in bed
 - can enhance sleep drive and improve sleep quality (36).
- *Relaxation techniques:*
 - Practice prior to bedtime, to promote sleep onset and improve quality (37)
 - Examples include:
 - yoga
 - meditation
 - guided imagery
 - progressive muscle relaxation
- *Exercise:* Improves sleep quality and efficiency, and reduces daytime dysfunction. Most evidence is in older individuals (38, 39).
- *Other supportive strategies:*
 - Treat comorbid medical conditions and symptoms (e.g. pain, dyspnea)
 - Deprescribe medications that may disrupt sleep, if possible
 - Explore and address spiritual and existential concerns

Many patients benefit most from a combination of the above strategies.

Pharmacologic Strategies:

Before initiating pharmacologic treatment for insomnia, consider adjusting or optimizing medications for other uncontrolled physical symptoms that may be disrupting sleep (40).

Class and Examples	Clinical Pearls	Suggested Dosing
Melatonin (41)	<ul style="list-style-type: none"> - Available over the counter; sold as a supplement, not FDA-regulated - Fast-release vs. extended-release forms - Insufficient evidence in primary insomnia, multiple studies showing no effect on sleep onset, latency, or efficiency (42, 43) - May be effective in circadian rhythm disorders, e.g. jet lag - Use caution post-organ transplant 	Melatonin Wide dose range from 0.3mg-20mg PO QHS (commonly 3mg-15mg)
Melatonin Receptor Agonists Ramelteon	<ul style="list-style-type: none"> - FDA-approved for insomnia - May reduce sleep latency and increase total sleep time, especially in older adults - Side effects: headache, somnolence, sore throat - No evidence of abuse, dependence, rebound insomnia, or withdrawal - May reduce delirium risk in hospitalized patients - Use caution post-organ transplant 	Ramelteon 8mg PO QHS
Atypical antidepressants Mirtazapine (44, 45)	<ul style="list-style-type: none"> - Targets multiple neurotransmitters – effect on insomnia likely due to antihistamine properties - Also used for mood disorders, pruritis, anorexia, nausea - Higher doses may worsen insomnia - Dose-reduce in renal or hepatic impairment - Takes up to one week to reach steady state - Side effects: drowsiness, dizziness, weight gain, constipation, dry mouth 	Mirtazapine 5-15 mg PO QHS
Atypical antipsychotics Olanzapine (46)	<ul style="list-style-type: none"> - May improve sleep efficiency and sleep quality, especially when combined with SSRI in depressed patients; some studies also report increased sleep time and slow-wave sleep. - Anti-emetic is added benefit, esp. for chemotherapy-induced nausea/vomiting (47) - Use caution in liver dysfunction - Side effects: somnolence, weight gain 	Olanzapine 2.5-10mg PO QHS

	<ul style="list-style-type: none"> - Black box warning (as with all anti-psychotics) of increased mortality risk in elderly dementia patients (48) 	
<p>Dual Orexin Receptor Antagonists (DORAs) (49)</p> <p>Suvorexant Lemborexant Daridorexant</p>	<ul style="list-style-type: none"> - Newest class for insomnia; Schedule IV substances - Can be cost-prohibitive - Preliminary data, most only compared to placebo - Improve sleep latency, sleep efficiency, and total sleep time (50, 51) - Suvorexant specifically approved for insomnia in mild-to-moderate Alzheimer's dementia, as it did not demonstrate worsening of cognition - Low abuse and overdose potential - Use caution in severe renal impairment - Side effects: somnolence, nasopharyngitis, and headache 	<p>Suvorexant 5-20mg PO QHS</p> <p>Lemborexant 5-10mg PO QHS</p> <p>Daridorexant 25-50mg PO QHS</p>
<p>Antihistamines</p> <p>Diphenhydramine</p>	<ul style="list-style-type: none"> - Available over the counter - Not recommended in elderly due to anticholinergic properties and drug interactions - Diphenhydramine may increase sleep duration but not quality 	<p>Diphenhydramine 25-100mg PO QHS</p>
<p>Benzodiazepines</p> <p>Temazepam Estazolam Triazolam Quazepam Flurazepam</p>	<ul style="list-style-type: none"> - These specific benzodiazepines are FDA-approved for insomnia - Intended for short-term use only (<7-10 days), and not daily - Controlled substances - Abrupt discontinuation, especially after chronic use, can cause withdrawal, which can be life-threatening - High incidence of amnesia and rebound insomnia - May cause paradoxical agitation, increased fall risk, especially in the elderly - Additive neurologic and respiratory effects when used with other sedating drugs, additional drug-drug interactions 	<p>Temazepam 7.5mg PO QHS</p> <p>Estazolam 0.5mg PO QHS</p> <p>Triazolam 0.125mg PO QHS</p> <p>Quazepam 7.5mg PO QHS</p> <p>Flurazepam 15 mg PO QHS</p>
<p>Benzodiazepine Receptor Agonists</p> <p>Zolpidem Zaleplon Eszopiclone</p>	<ul style="list-style-type: none"> - Rapid onset, hepatic metabolism, no active metabolites - Low abuse and dependence potential compared to other classes - Do not cause rebound insomnia - May be useful for middle-of-the-night awakenings 	<p>Zolpidem 5-10mg PO QHS</p> <p>Zaleplon 10-20mg PO QHS</p> <p>Eszopiclone 1-2mg PO QHS</p>

Herbal Remedies and Supplements (24) Valerian	<ul style="list-style-type: none">- Conflicting evidence- May be as effective as mild hypnotics- Side effects: hepatotoxicity, cardiotoxicity, and delirium	Valerian 400-900mg PO QHS
Herbal Remedies and Supplements (24) Tart cherry concentrate	<ul style="list-style-type: none">- Mixed and limited evidence- Use caution due to high sugar content	Tart cherry concentrate 2Tbsp in 8oz water daily

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Pre/Post Test Questions

1. List three common secondary causes of fatigue, in patients with life-limiting illness.

2. List one non-pharmacologic and one pharmacologic treatment for fatigue.

3. Name one defining characteristic of primary insomnia.

4. List three components of an evaluation for a patient with insomnia.

Answers

1. Any three of: Cancer and cancer treatment, renal failure, heart failure, chronic lung disease, neurodegenerative disorders, HIV/AIDS, depression, substance use disorders, nutritional deficiencies, endocrine abnormalities, medication side effects, uncontrolled pain, anemia.
2. One of: Exercise, rehabilitation programs, nutritional support, and one of: psychostimulants, corticosteroids, or select supplements
3. Any of: Dissatisfaction with sleep quantity or quality, difficulty initiating or maintaining sleep, early morning awakening with inability to return to sleep, or associated functional impairment
4. Any three of: History and physical; Sleep history from both patient and bed partner; Sleep hygiene, chronology and environment; Screening for other physical symptoms; Review comorbidities and medications; Assess for spiritual concerns; Sleep diary

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Case 1

A 56-year-old female with coronary artery disease, depression, and end-stage renal disease presents to clinic following a recent one-week hospitalization for adhesive small bowel obstruction. She reports **progressively worsening fatigue** over the last few months, noting that it has significantly intensified since hospital discharge. She receives dialysis on Mondays, Wednesdays, and Fridays, but missed her most recent session due to feeling too fatigued to get out of bed. She also describes episodes of feeling her heart racing. Additionally, she reports that she has not been following up with her primary care physician for refills of her antidepressant medication.

Questions

1. What potential factors may be contributing to this patient's fatigue?
2. For each identified factor, is there an appropriate treatment or management strategy?
3. Develop a care plan addressing this patient's fatigue.
4. What barriers might interfere with this patient's ability to follow through with this care plan?

Case 2

A 38-year-old male with coronary artery disease, obesity (BMI 54), and ulcerative colitis presents to your clinic. He has recently-diagnosed metastatic colon cancer and underwent hyperthermic intraperitoneal chemotherapy and tumor debulking. He is here for his postoperative visit, with primary concerns of diarrhea and **difficulty falling asleep**, which began after his diagnosis 3.5 months ago. He reports a history of occasional poor sleep prior to diagnosis, but now rarely experiences restful sleep. He is also having particular difficulty initiating sleep, since his surgery.

Questions

1. What factors may be contributing to this patient's difficulty initiating sleep?
2. What non-pharmacologic and pharmacologic interventions could be recommended?
3. What additional referrals might be helpful to address this patient's insomnia?
4. Discuss the contributors to insomnia for patients with multiple comorbidities and acute stressors.