Palliative Care Review

Fatigue in the Seriously Ill

Fatigue is among the most prevalent symptoms experienced by patients with chronic serious illness.[1] Most studies indicate that more than 50% of patients report fatigue that interferes with usual functioning.

It is associated with multiple conditions and is found in about 60-90% of patients with advanced cancer; 69-82% in end-stage renal disease (ESRD) patients on hemodialysis; 54-85% in advanced AIDS populations; 68-80% in COPD; and in 20% of patients attending a general medical clinic.[2] Although most studies of fatigue have focused on the cancer population, there is increasing attention on the impact of this symptom in other chronic illnesses.

Definition and Pathophysiology

Fatigue is defined by the National Comprehensive Cancer Network as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning."[3] The key elements in this definition include persistence over time, a poor relationship to activity or rest, and a multidimensional impact on the patient.

Fatigue is itself multidimensional. Patients may describe it as "feeling tired," "feeling weak," "feeling exhausted," and "lacking energy." Clinicians will translate these as "asthenia," "lethargy," "fatigue," general weakness," or "tiredness." The ICD-10 billing code (R53.83) includes the following terminology: exhaustion, general fatigue, lack of energy, lethargy, overstrained, overworked, prostration, tiredness, lack of vitality.

From a clinical perspective, patients with chronic fatigue may emphasize a physical component (weakness, sleepiness), a cognitive component (decreased attention or concentration), or a mood component (dysthymia). It is possible that fatigue is a common final pathway for a variety of pathophysiologies that may involve different neural and metabolic processes.

Presumably, patients with serious chronic illnesses may experience fatigue as a result of multiple conditions (such as the primary illness, comorbidities and complications, and centrally acting drugs) and multiple

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pathophysiologies (such as chronic inflammatory processes with increased cytokine production, malnourishment with impaired energy metabolism, increased catabolism related to the primary illness, and others). Other sources of symptom distress, such as depressed mood, sleep dysfunction, and anorexia, may be involved in the development or persistence of fatigue.

Despite growing research interest, the pathophysiology of fatigue remains inadequately understood, and the ability to determine the nature of the problem in individual patients is challenged by the complex array of biological and psychological disturbances that characterize chronic illness.

Assessment

The work-up in patients with advanced illness will need to be prioritized in relation to the prognosis and goals of care. A self-report verbal or numeric scale can be used to screen for significant fatigue. Clinical assessment may identify potential etiologies that may be treatable (e.g., depression or unnecessary medications).

In the clinical setting, it is useful to obtain specific information about the patient's experience by asking about fatigue severity, temporal features, exacerbating or palliative factors, direct impact on the patient's life, and associated distress. In the research setting, any of a variety of validated self-report scales can be used, such as Brief Fatigue Inventory (BFI), Functional Assessment of Cancer Therapy (FACT-F), or Piper Fatigue Scale (PFS).

Management

If potentially treatable etiologies are identified, and treatment is consistent with the goals of care, management of fatigue begins with the attempt to mitigate the impact of these factors. This may include the treatment of pain or depression, a sleep disorder, anemia, deconditioning, metabolic disturbances, or may involve deprescribing of unnecessary drugs.

Symptomatic therapies can be nonpharmacological or pharmacological. There is some evidence to suggest that physical therapy or gentle exercise, cognitive behavioral therapy, and acupuncture can benefit some patients.

A Cochrane Review[4] highlights the limited data pertaining to drug therapies. A glucocorticoid such as dexamethasone (e.g., 1-2 mg BID) is commonly tried in the setting of advanced cancer. There are very limited data supporting a potential role for psychostimulants (see table on page 3). The latter drugs must be used cautiously in the setting of advanced illness due to a side-effect profile that includes anxiety, anorexia, and insomnia.

References

1. Yennurajalingam S, Bruera E. Fatigue and asthenia. (2015) *Oxford Textbook of Palliative Medicine*, 5th ed., chap 8.1, pp 409-420.
2. Solano JP, Gomes B, Higginson I. (2006). A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. Journal of Pain and Symptom Management, 31:1:58-69.
3. Berger AM, Abernethy AP, Atkinson A, et al. (2010). NCCN Clinical Practice Guidelines Cancer-related fatigue. Journal of the National Comprehensive Cancer Network, 8, 904-31
4. Peuckmann V, Elsner F, Krumm N, Trottenberg P, and Radbruch L. (2010). Pharmaceutical treatments for fatigue associated with palliative care. Cochrane Database of Systematic Reviews, 11, CD006788.

Fatigue: Pharmacological Approach*

Drug	Dosage	Comments/ADRs
Dexamethasone	4 mg BID	Potent anti-inflammatory agent being evaluated for fatigue in pts with advanced cancer.
Methylphenidate (Ritalin)	2.5 mg/day (start) Titrate up to 54 mg/day (27 mg D-isomer)	CII. High fat meals may increase AUC. Peak concentration 102 hrs after ingestion. Don't use with MAOIs (hypertensive crisis). Antidepressants that increase norepinephrine can cause increased amphetamine ADRs. Concomitant use with SSRI can increase SSRI concentrations.
Modafinil (Provigil)	50-100 mg (start) 100-200 mg QAM	CIV. Avoid operating machinery. Don't take HS. Peak concentration in 2-4 hrs. Food slows absorption by about 1 hr but doesn't affect bioavailability. Decreases efficacy of birth control.
Armodafinil (Nuvigil)	50 mg (start) 25-250 mg QAM	CIV. Avoid operating machinery. Don't take HS. Peak concentration in 2 hrs if fasting, slowed to 4 hrs if fed, but food doesn't affect bioavailability. Decreases efficacy of birth control.

*Anecdotal experience includes the use of other psychostimulants, such as dextroamphetamine and amphetamine, and the use of bupropion, an antidepressant that may be activating.

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