ETIOLOGY The multiple causes of fatigue in the terminally ill can be categorized as resulting from the underlying disease; from disease-induced factors such as tumor necrosis factor and other cytokines; and from secondary factors such as dehydration, anemia, infection, hypothyroidism, and drug side effects. Apart from low caloric intake, loss of muscle mass and changes in muscle enzymes may play an important role in fatigue of terminal illness. The importance of changes in the CNS, especially the reticular activating system, have been hypothesized based on reports of fatigue in patients receiving cranial radiation, experiencing depression, or having chronic pain in the absence of cachexia or other physiologic changes. Finally, depression and other causes of psychological distress can contribute to fatigue.

ASSESSMENT Like pain and dyspnea, fatigue is subjective. Objective changes, even in body mass, may be absent. Consequently, assessment must rely on patient self-reporting. Scales used to measure fatigue, such as the Edmonton Functional Assessment Tool, the Fatigue Self-Report Scales, and the Rhoten Fatigue Scale, are usually appropriate for research rather than clinical purposes. In clinical practice, a simple performance assessment such as the Karnofsky Performance Status or the ECOG's question "How much of the day does the patient spend in bed?" may be the best measure. In this 0–4 performance status assessment, 0 = normal activity; 1 = symptomatic without being bedridden; 2 = requiring some, but <50%, bed time; 3 = bedbound more than half the day; and 4 = bedbound all the time. Such a scale allows for assessment over time and correlates with overall disease severity and prognosis. A 2008 review by the European Association of Palliative Care also described several longer assessment tools with 9–20 items, including the Piper Fatigue Inventory, the Multidimensional Fatigue Inventory, and the Brief Fatigue Inventory (BFI).

INTERVENTIONS For some patients, there are reversible causes such as anemia, but for most patients at the end of life, fatigue will not be "cured." The goal is to ameliorate it and help patients and families adjust expectations. Behavioral interventions should be used to avoid blaming the patient for inactivity and to educate both the family and the patient that the underlying disease causes physiologic changes that produce low energy levels. Understanding that the problem is physiologic and not psychological can help alter expectations regarding the patient's level of physical activity. Practically, this may mean reducing routine activities such as housework and cooking or social events outside the house and making it acceptable to receive guests lying on a couch. At the same time, institution of exercise regimens and physical therapy can raise endorphins, reduce muscle wasting, and reduce the risk of depression. In addition, ensuring good hydration without worsening edema may help reduce fatigue. Discontinuing medications that worsen fatigue may help, including cardiac medications, benzodiazepines, certain antidepressants, or opioids if pain is well-controlled. As end-of-life care proceeds into its final stages, fatigue may protect patients from further suffering, and continued treatment could be detrimental.

There are woefully few pharmacologic interventions that target fatigue and weakness. Glucocorticoids can increase energy and enhance mood. Dexamethasone is preferred for its once-a-day dosing and minimal mineralocorticoid activity. Benefit, if any, usually is seen within the first month. Psychostimulants such as dextroamphetamine (5–10 mg PO) and methylphenidate (2.5–5 mg PO) may also enhance energy levels, although a randomized trial did not show methylphenidate beneficial compared with placebo in cancer fatigue. Doses should be given in the morning and at noon to minimize the risk of counterproductive insomnia. Modafinil, developed for narcolepsy, has shown some promise in the treatment of severe fatigue and has the advantage of once-daily dosing. Its precise role in fatigue at the end of life has not been determined. Anecdotal evidence suggests that L-carnitine may improve fatigue, depression, and sleep disruption. Similarly, some studies suggest ginseng can reduce fatigue.

PSYCHOLOGICAL SYMPTOMS AND THEIR MANAGEMENT

Depression • ***FREQUENCY*** Depression at the end of life presents an apparently paradoxical situation. Many people believe that depression is normal among seriously ill patients because they are dying. People frequently say, "Wouldn't you be depressed?" However, depression is not a necessary part of terminal illness and can contribute to needless suffering. Although sadness, anxiety, anger, and irritability are normal responses to a serious condition, they are typically of modest intensity and transient. Persistent sadness and anxiety and the physically disabling symptoms that they can lead to are abnormal and suggestive of major depression. Although as many as 75% of terminally ill patients experience emotional distress and depressive symptoms, <30% of terminally ill patients have major depression. Depression is not limited to cancer patients but found in patients with end-stage renal disease, Parkinson's disease, multiple sclerosis, and other terminal conditions.

ETIOLOGY Previous history of depression, family history of depression or bipolar disorder, and prior suicide attempts are associated with increased risk for depression among terminally ill patients. Other symptoms, such as pain and fatigue, are associated with higher rates of depression; uncontrolled pain can exacerbate depression, and depression can cause patients to be more distressed by pain. Many medications used in the terminal stages, including glucocorticoids, and some anticancer agents, such as tamoxifen, interleukin 2, interferon α, and vincristine, also are associated with depression. Some terminal conditions, such as pancreatic cancer, certain strokes, and heart failure, have been reported to be associated with higher rates of depression, although this is controversial. Finally, depression may be attributable to grief over the loss of a role or function, social isolation, or loneliness.

ASSESSMENT Diagnosing depression among seriously ill patients is complicated because many of the vegetative symptoms in the DSM-V (*Diagnostic and Statistical Manual of Mental Disorders*) criteria for clinical depression—insomnia, anorexia and weight loss, fatigue, decreased libido, and difficulty concentrating—are associated with the dying process itself. The assessment of depression in seriously ill patients therefore should focus on the dysphoric mood, helplessness, hopelessness, and lack of interest and enjoyment and concentration in normal activities. The single questions "How often do you feel downhearted and blue?" (more than a good bit of the time or similar responses) and "Do you feel depressed most of the time?" are appropriate for screening. Visual Analog Scales can also be useful in screening.

INTERVENTIONS Physicians must treat any physical symptom, such as pain, that may be causing or exacerbating depression. Fostering adaptation to the many losses that the patient is experiencing can also be helpful. Nonpharmacologic interventions, including group or individual psychological counseling, and behavioral therapies such as relaxation and imagery can be helpful, especially in combination with drug therapy.

Pharmacologic interventions remain the core of therapy. The same medications are used to treat depression in terminally ill as in non–terminally ill patients. Psychostimulants may be preferred for patients with a poor prognosis or for those with fatigue or opioid-induced somnolence. Psychostimulants are comparatively fast acting, working within a few days instead of the weeks required for selective serotonin reuptake inhibitors (SSRIs). Dextroamphetamine or methylphenidate should be started at 2.5–5.0 mg in the morning and at noon, the same starting doses used for treating fatigue. The dose can be escalated up to 15 mg bid. Modafinil is started at 100 mg qd and can be increased to 200 mg if there is no effect at the lower dose. Pemoline is a nonamphetamine psychostimulant with minimal abuse potential. It is also effective as an antidepressant beginning at 18.75 mg in the morning and at noon. Because it can be absorbed through the buccal mucosa, it is preferred for patients with intestinal obstruction or dysphagia. If it is used for prolonged periods, liver function must be monitored. The psychostimulants can also be combined with more traditional antidepressants while waiting for the antidepressants to become effective and then tapered after a few weeks if necessary. Psychostimulants have side effects, particularly initial anxiety, insomnia, and rarely paranoia, which may necessitate lowering the dose or discontinuing treatment.

Mirtazapine, an antagonist at the postsynaptic serotonin receptors, is a promising psychostimulant. It should be started at 7.5 mg before