# Depression, Anxiety, and Asthenia in Advanced Illness

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Depression, anxiety, and asthenia are frequently experienced by those suffering with an advanced (life-limiting) illness. Many caregivers may feel that it is "normal for patients in this condition to be depressed or anxious," and this misunderstanding may lead to missed opportunities to address a treatable condition. The role played by the yet more "normal" phenomenon of asthenia (ie, reduced energy or vitality) at the end of life also confounds treatment. Failure to recognize asthenia and to acknowledge depression in this population are exacerbated by the discomfort most physicians experience when they are confronted with a dying patient. A patient's terminal illness and accompanying psychological distress can remind physicians all too painfully of their treatment "failures" and their own mortality.

The objectives of this article are to help readers recognize clinical depression, anxiety, and asthenia in patients with advanced illness; become more aware of the need for active intervention; and gain a knowledge of the pharmacologic and nonpharmacologic approaches to treatment.

## DEPRESSION IN ADVANCED ILLNESS[1-3]

Although symptoms of grief and sadness at facing one's terminal diagnosis represent a common and expected response, they can also represent one end of a continuum with full clinical depression at the other end (Table 1). This has made it sometimes difficult to differentiate between stress reactions (adjustment disorders) and clinical depression (major depressive disorder) when defining the incidence of depression in the terminally ill. It has been estimated that about 50% of terminally ill cancer patients have no significant psychological distress.[4] The majority of those who do present with psychological distress have primarily depressive symptoms as part of an adjustment disorder with depressed mood. Among patients with cancer, approximately 5% to 15% meet criteria for major depressive disorder.[1] In any event, pervasive psychological distress that is persistent and interferes with a patient's functional status and quality of life warrants further investigation and treatment.

In general, it is thought that an interplay between psychosocial stressors and key physiologic pathways involved in regulating the organism's response to stress lead to depression. One major pathway that has been implicated is the hypothalamic-pituitary-adrenal axis (HPA).[5] It has been hypothesized that overactivity in this pathway can precipitate depression. Immune and inflammatory responses also interact with the HPA through cytokines (particularly interleukins-1 and 2). Interleukin-6 has also been recently reported to be elevated in cancer patients with depression.[6] Of real concern for cancer patients is the observation that natural killer cell activity can be decreased in depressed cancer patients. This, coupled with hyperactivity of the HPA, can have an overall immunosuppressive effect, weakening the host response to the neoplasm. So it is possible that a pathologic synergy might develop between an altered immune response and depression in depressed cancer patients, aggravating the depression and diminishing host defense against the cancer.

Risk factors for clinical depression in patients with advanced illness include age, earlier history of depression, poor social support, functional status, disease progression, uncontrolled physical symptoms, complications of the disease and its treatment, and existential distress. Cancer patients should be questioned about previous episodes of depression because such a history is a strong predictor of future problems. Poor or limited social support (eg, social isolation or homelessness) puts patients with advanced illness at greater risk for depression. As functional status declines with disease progression, the incidence of depression rises.[7,8] Uncontrolled

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**Table 1.** Major Depression Versus Adjustment Disorder

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|---|
| Essential features for a diagnosis of major depression |
| Depressed mood for at least 2 weeks |
| Anhedonia, ie, loss of pleasure in all or most of one's activities |
| Appetite changes often with loss of weight but occasionally weight gain |
| Sleep changes with insomnia or hypersomnia |
| Psychomotor retardation or agitation |
| Fatigue or loss of energy |
| Guilt that is inappropriate or feelings of worthlessness |
| Concentration impairment or diminished ability to think clearly |
| Suicidal ideation or recurrent thoughts of death |
| Impairment of functioning or significant distress from above symptoms |
| Essential features for a diagnosis of adjustment disorder |
| Emotional or behavioral symptoms that develop in response to an identifiable stressor, within 3 months of the onset of the stressor |
| Symptoms or behaviors are in excess of what would be typically expected from exposure to the stressor, or they cause significant social or occupational impairment |
| Symptoms cannot be explained better by another psychiatric disorder |
| If the stressor resolves, the symptoms do not persist more than an additional 6 months |
| Symptoms are termed "acute" if they are less than 6 months or "chronic" if longer than 6 months |
| Adjustment disorders can be seen with symptoms of depression, anxiety, mixed depression and anxiety, disturbance of conduct, or mixed disturbance of emotions and conduct |

(Adapted from: Diagnostic and Statistic Manual–DSM IV, with permission.)

physical symptoms (especially chronic unrelieved pain) can serve as potent triggers of depression.[9] If pain and other distressing physical symptoms are not addressed, standard antidepressant therapy will be of little benefit. Depressive symptoms can also be induced by complications of the disease and its treatment. (These would technically be classified in the Diagnostic and Statistic Manual–IV under mood disorder due to a medical condition.) For example, hypercalcemia, which can develop with several malignancies (especially lung and breast), can induce somnolence and depression. Although corticosteroid therapy can induce feelings of euphoria, it can also trigger depressive symptoms. Certain solid tumors are associated with a higher incidence of depression (eg, pancreatic cancer). Finally, existential distress coming from functional impairment and weakness can be at the heart of profound depression as patients struggle with a loss of meaning and purpose in their now sharply circumscribed existence.

The neurovegetative signs (eg, sleep disturbance with insomnia, or hypersomnia, decreased appetite, fatigue, and psychomotor retardation) typical of clinical depression are also common somatic complaints in patients with advanced illness.[10] This overlap becomes more pronounced as the disease progresses. Because of this overlap, greater emphasis is placed on assessing the patient's mood—is it consistently depressed? A very important feature of this assessment is determining whether the patient is anhedonic (unable to take pleasure in those things that normally have brought pleasure to the patient in the past). Even the patient who might be quite tearful and experiencing intense grief in response to a terminal diagnosis, if distracted, will usually be able to express pleasure about something. Another important question is to ask if the patient has a sense of hope. Feelings of hopelessness, unrelieved despair, and anhedonia are very suggestive of the diagnosis. In this context, the patient might also express a wish for death or request aid in suicide. If this is a persistent thought and is accompanied by a plan, this is an even stronger piece of evidence supporting the diagnosis of major depressive disorder. The relative risk of suicide in patients with advanced illness is twice that of the general population.[11] Finally, two useful and simple screening maneuvers are to ask the patient, "Are you sad or depressed?" and then record the impression the patient makes by virtue of appearance, body language, etc. If the patient makes the observer feel sad or depressed on observing him, this is a good sign that further investigation of depressive symptoms is in order.

Management of depression in the terminally ill is most effective if based on a relationship of trust between the primary caregiver and the patient. This is true even when a consultant is providing much of the direct management. A consultant might not be particularly effective without the endorsement of the physician (surgeon) with whom the patient has formed a trust relationship.

For patients experiencing an intense stress reaction (adjustment disorder) in response to their dysfunction or impending death, nonpharmacologic therapy (in the form of supportive counseling) is primarily indicated. This can include individual or group psychotherapy. Types of psychotherapy that can be helpful include biofeedback, relaxation training, and positive imagery (these behavioral methods can also be helpful in pain management); hypnotherapy; and cognitive and other

**Table 2.** Selected Medications to Treat Depression

| | Initial dose (mg) | Dose range (mg/d) | Half-life (h) |
|---|---|---|---|
| Tricyclics | | | |
| Desipramine (Norpramin) | 25–50 hs | 50–250 | 12–76 |
| Nortriptyline (Pamelor) | 25–50 hs | 50–150 | 13–88 |
| Selective serotonin reuptake inhibitor | | | |
| Citalopram (Celexa) | 10–20 qam | 10–60 | 35 |
| Fluoxetine (Prozac) | 10–20 qam | 10–60 | 24–96 |
| Paroxetine (Paxil) | 10–20 qam | 10–60 | 21 |
| Sertraline (Zoloft) | 25–50 qam | 25–200 | 24 |
| Stimulant | | | |
| Methylphenidate (Ritalin) | 2.5–5 bid | 10–40 | 2 |
| Other | | | |
| Mirtazapine (Remeron) | 15 hs | 15–45 | 20–40 |
| Trazodone (Desyrel) | 50–100 hs | 50–400 | 4–9 |

bid, twice daily; hs, bedtime; qam, every morning.
(From: Kaplan HI, Sadock BJ, eds. Comprehensive textbook of psychiatry/VI. Baltimore, MD: Williams and Wilkins; 1995, with permission.)

behavioral techniques. Complementary therapies, particularly art and music therapy can also be quite helpful for some patients.

Pharmacotherapy is the mainstay of therapy for patients meeting criteria for major depressive disorder. The nonpharmacologic approaches still play an important part in therapy once effective drug therapy has been established. Prognosis and time frame for therapy are very important when considering which types of agents to use. Based on the patient's functional status, tumor type, and stage, general estimates of time remaining can be made. If the patient is still largely independent in activities of daily living and has several months' projected survival, standard antidepressants should be initiated. If disease progression has occurred to the extent that activities of daily living are significantly restricted and fatigue and other somatic symptoms are prominent with weeks to 2 to 3 months' survival projected, a psychostimulant (eg, methylphenidate) might be appropriate. If the patient is bedfast and showing signs of actively dying within days to a week or so, anxiolytics, sedatives, and narcotics are more appropriate.

The type of antidepressant chosen for treatment should be considered in the context of the patient's symptoms and other medications (see Table 2). Tricyclic antidepressants (eg, amitriptyline) frequently produce many anticholinergic side effects including constipation, dry mouth, and urinary retention. Because these are also similar to side effects of narcotics and other agents commonly used in palliative care, most tricyclic antidepressants should be avoided. But nortriptyline and desipramine have fewer anticholinergic side effects and can be used effectively in this population. Cancer patients can respond to doses lower than the usual therapeutic range, so "start low and go slow" when starting these medications. Response to treatment has a latency from three to six weeks. The selective serotonin reuptake inhibitors have a much better profile of side effects when considering palliative care patients and are safer with respect to overdose than the tricyclics. They are usually started with dosing early in the day because they can cause insomnia, but many patients experience no effects on sleep. If sedation occurs, dosing later in the day is indicated. Other potential side effects include nausea, diarrhea, headache, and sexual dysfunction. They also have a several-week latency for therapeutic response. Newer antidepressants can have some advantages for certain patients. Mirtazapine has side effects of sedation and appetite stimulation that can be useful in some patients with advanced illness.[12] Psychostimulants (eg, methylphenidate) can help patients who have a depressed mood accompanied by asthenia who need rapid relief of symptoms.[13] It stimulates appetite at lower doses (but can suppress it at higher doses), increases a sense of well being, and helps reduce sedation secondary to narcotic analgesics. Its best effects tend to be shortterm because of tolerance, making it more useful for patients with a shorter expected survival (weeks to two to three months). Side effects relate to overstimulation (insomnia, anxiety, tremor, blood pressure elevation). It should be dosed early and midday so as not to

interfere with sleep. In the confused patient it may aggravate delirium.

## ANXIETY IN ADVANCED ILLNESS[14]

Anxiety is common in the population of patients with advanced illness. In one study, 16% of requests for psychiatric consultation were attributed to symptoms of anxiety.[15] Of those evaluated in that study, 25% were diagnosed with an anxiety disorder but 57% were diagnosed with a depressive disorder. In cancer patients, a mixture of anxiety and depressive symptoms is more common than pure anxiety alone.[16] As with the assessment of depressive symptoms, pain must first be addressed because uncontrolled pain is a common cause of anxiety and agitation.

Symptoms of anxiety can be manifest more as emotional distress or in the form of somatic symptoms. Existential concerns such as fear of pain and death, loss of autonomy, being a burden, and unfinished business can all weigh heavily on patients with advanced illness. Somatic symptoms of anxiety can often overlap with other symptoms of the physical illness or treatment modalities such as shortness of breath, tachycardia, diaphoresis, nausea, and shaking. Further, common end-of-life symptoms such as anorexia, insomnia, decreased libido, trouble staying focused, rumination, and irritability are seen frequently with depression as well.

Certain medical conditions are notorious for causing symptoms of anxiety. As stated above, uncontrolled pain is probably one of the most frequent. Situations that cause compromised breathing such as pneumonia, pulmonary embolism, lung metastasis, and malignant pleural effusion are another. Hormone-secreting tumors (eg, pheochromocytoma), though uncommon, can produce symptoms of anxiety. Abnormal metabolic and physiologic states (eg, electrolyte and glucose imbalance, severe constipation) can cause anxiety that can progress to frank delirium with agitation, disturbance of consciousness, and change in cognition, often with a fluctuating course. So, symptoms of anxiety that develop in a medically compromised patient can be early warning signs of impending delirium.

The role of medications and illicit substances in relation to anxiety should not be overlooked. Withdrawal states from alcohol, opioids, or benzodiazepines can all cause anxiety progressing to agitation and delirium. So a previous history of substance abuse, including alcohol, prescription drugs (which might have varied from the prescribed dosing), caffeine, and the use of illicit substances, must be assessed. Iatrogenic causes of anxiety can be frequently seen with corticosteroids, stimulants, bronchodilators, and other common medications used in patients with advanced illness. So effective assessment and management of anxiety in advanced illness involve eliminating primary causes (eg, metabolic derangements and withdrawal states), relieving distressing somatic symptoms (eg, good pain control), and finally, considering appropriate treatments for remaining symptoms.

Treatment of anxiety in advanced illness is most effective in the context of a supportive relationship of trust with caregivers. Too often, dying patients are shifted between different teams with the loss of trusted caregivers at the very time they need continuity the most. Dealing with the needs of this patient population takes time, which is often at a minimum in a busy medical practice. Having mental-health consultants experienced in end-of-life care working with the team is very helpful for caregivers, patients, and family. It is important that the primary caregivers endorse this consult and explain its importance to the patient, so that calling in a consultant does not feel like emotional abandonment. Educational efforts are helpful in relieving anxiety for both patients and families, often in the context of a family meeting. Discussions with the patient that address issues of dying, unfinished business, and spiritual concerns are important. Having chaplains available or helping patients connect with their own clergy can relieve a lot of existential suffering in patients with advanced illness.

Anxiolytic medications may be considered in patients with more severe symptoms. In one study, one-quarter to one-third of patients with advanced cancer received antianxiety medication sometime during their hospitalization.[17] Benzodiazepines are the first-line agents but must be used cautiously in this population. Excessive use can cause confusion, somnolence, and increase the risk of delirium. Too infrequent dosing can cause rebound anxiety or withdrawal between each dose. Benzodiazepines with active metabolites such as diazepam (Valium), chlordiazepoxide (Librium), clorazepate (Tranxene), and flurazepam (Dalmane) should be avoided because of escalating blood levels causing side effects (confusion, somnolence, slurring, staggering). Shorter half-life benzodiazepines such as lorazepam (Ativan), oxazepam (Serax), alprazolam (Xanax), and temazepam (Restoril) are preferred. Lorazepam and alprazolam can be useful for nausea and anxiety symptoms. Clonazepam

**Table 3.** Selected Medications to Treat Anxiety

| Medications | Initial dose (mg) | Dose range (mg/d) | Half-life (h) |
|---|---|---|---|
| Benzodiazepines | | | |
| Alprazolam (Xanax) | 0.25–0.5 tid | 0.5–4 | 6–27 |
| Clonazepam (Klonapin) | 0.25–1 bid-qd | 0.25–4 | 20–50 |
| Diazepam (Valium) | 5–10 bid-qd | 5–40 | 20–80* |
| Lorazepam (Ativan) | 0.5–2 bid-tid | 1–4 | 10–20 |
| Oxazepam (Serax) | 10–15 bid-tid | 20–90 | 5–20 |
| Other | | | |
| Buspirone (Buspar) | 5 tid | 15–30 | 2–3 |
| Neuroleptics | | | |
| Haloperidol (Haldol) | 0.5–1 bid-qd | 1–15 | |
| Olanzapine (Zyprexa) | 2.5–5 bid-qd | 5–20 | 21–54 |
| Risperidone (Risperidal) | 0.5–1 bid | 1–6 | 20 |

*Active metabolite desmethyldiazepam t½ 35–200 h.
(From: Kaplan HI, Sadock BJ, eds. Comprehensive textbook of psychiatry/VI. Baltimore, MD: Williams and Wilkins; 1995, with permission.)

can provide a smoother relief of anxiety with less frequent dosing but because of its long half-life, patients should be observed for signs of overmedication. In patients with compromised respiratory function, benzodiazepines should be avoided because of potential central respiratory suppression. Because of potential synergistic suppressive effects on respiratory drive, benzodiazepines should be used with caution in patients receiving substantial doses of narcotics. Buspirone may be considered in patients who have a potential for abuse, but it is not effective unless used consistently over several weeks, and even then might be less beneficial for some patients. Antidepressants will help address generalized anxiety and panic symptoms but can take up to a month to become effective. Neuroleptic medications should be reserved for patients with frank delirium or psychotic symptoms (see Table 3).

## ASTHENIA IN ADVANCED ILLNESS

Anxiety and depression are both underrecognized and undertreated. But asthenia is the most common symptom of cancer[18] and many other terminal conditions. Asthenia can be narrowly defined as reduced vitality, energy, or vigor. Asthenia has found a broader nosologic interpretation in the medical literature. Silas Weir Mitchell, one of the first physicians to restrict his practice to neurologic disorders, used the term *asthenia* to identify combat-stressed individuals in the American Civil War. Neurologists have gone on to enrich the meaning of asthenia by adding to the definition a reduction in amount of thought and action and a slowing of reaction time. Indifference to common social practices and lack of initiative and spontaneity are typical and accompanied by disinclination to deal with difficult or complex problems. Undue irritability, emotional lability, mental inertia, faulty insight, and reduced range of mental activity are further reflections of dysfunction in the long association fiber systems of the cerebral white matter and the thalamocortical connections to the reticular activating system. Victor and Ropper[19] have introduced the term *psychomotor asthenia*. MacCabe[20] has gone further to differentiate mental asthenia from depression.

Reduced vitality or asthenia must be differentiated from weakness, fatigue, depression, and anxiety. Weakness, in this context, refers to generalized loss of muscle strength or power rather than localized weakness, which characterizes neurologic disease. Fatigue is characterized by weariness or exhaustion resulting from physical or mental exertion. Weariness or exhaustion without physical or mental exertion is asthenia. In this sense chronic fatigue syndrome and combat fatigue are misnomers. Both syndromes occur in the absence of physical or mental exertion. Similarly, fatigue is differentiated from weakness because most people who complain of fatigue do not have true muscle weakness. Asthenia is more descriptive of chronic fatigue syndrome and the overused term combat fatigue. The depressed person shares many characteristics of the asthenic individual: lack of interest or pleasure, psychomotor retardation, loss of energy, inability to concentrate, and indecisiveness. The distinguishing qualities of a depressed person are pronounced hopelessness (often with suicidal ideation), overwhelming feelings of inadequacy or unworthiness,

**Table 4.** Treatable Causes of Asthenia

| |
|---|
| Dehydration |
| Chronic hypoxia–sleep disorders |
| Infection–eg, HIV, tuberculosis, hepatitis C |
| Anemia |
| Chronic pain |
| Metabolic or endocrinologic |
| Diabetes |
| Addison's disease |
| Hyponatremia |
| Hypokalemia |
| Hypomagnesemia |
| Hypercalcemia |
| Hypothyroidism |
| Medication (differentiated from sedation) |
| Chemotherapy |
| Narcotics |

and anhedonia. The anxious person may also have difficulty concentrating and be indecisive.

The asthenic patient begs a comparison with the cachectic individual. The clinical features of cachexia are weight loss and anorexia. The associated loss of muscle and fat is accompanied by anemia, hypoalbuminemia, and hypoproteinemia. Cancer cachexia is not reversed by adequate alimentation or hyperalimentation. Some of the pathophysiologic elements of asthenia are probably shared with cachexia. Cancer induces the production of cytokines that alter intermediary metabolism and cause muscle catabolism.

Treatable causes of asthenia are listed in Table 4. Other conditions associated with asthenia are manageable but not treatable: eg, paraneoplastic syndromes, chronic renal disease, chronic heart disease, and chronic pulmonary disease.

Management of asthenia begins with correcting the treatable causes. Just as important, the physiologic burden of chemotherapy and radiation therapy should be acknowledged and that measure of suffering validated for the patient. Physical activity must be balanced with rest. The demands of everyday living (eg, childcare, transportation, work-place stress) should be reduced. Finally, and perhaps least important, is the role of pharmacologic management. Methylphenidate has shown some promise in ameliorating asthenia.[18]

Surely weakness, fatigue, cachexia, depression, and anxiety overlap in the clinical setting. Fatigue can coexist with depression or anxiety, and the asthenic patient may be anxious. Communication with the patient is the first step in a patient-centered understanding of the disease or condition. It guides appropriate therapy and leads to innovations in treatment. Listening to the patient offers the guarantee of nonabandonment and engenders the trust and confidence necessary for successful care at the end of life.

## DISCUSSION

The following case summary illustrates the complex interrelationship and overlap between psychological distress, depression, and asthenia in advanced illness:

> *Mr L was a 63-year-old married man with recurrent prostate cancer now refractory to treatment and accompanied by severe cachexia. He faced the wall during the entire interview, complaining of very poor appetite, diminished sleep, low mood, irritability, tearfulness, low energy, weakness, anhedonia, and chronic uncontrolled pain. Initially, he was placed on an around-the-clock narcotic regime that diminished his pain significantly and improved sleep some, but his depressive symptoms did not change. He had been started on paroxetine 20 mg approximately 10 months earlier, when he first developed depressive symptoms, with initial good control of symptoms. Because of his very short life expectancy and an important upcoming visit from family, it was decided to start him on a psychostimulant medication (targeting asthenia symptoms and augmenting the antidepressant), rather than increasing the antidepressant and waiting several weeks for an effect. He was started on methylphenidate 5 mg twice a day at 8:00 AM and noon, increasing to 10 mg twice a day. He tolerated the dose escalation without side effects and with great improvement in mood, energy, and ability to interact with others. He was able to get his affairs in order, have a meaningful final visit with family, for which they were all grateful, and he died a few weeks later.*

There are several important concepts to be highlighted from the story of this unfortunate man. First, his symptoms of weakness, decreased appetite (with weight loss), and generalized exhaustion cannot easily be ascribed to either asthenia (secondary to his underlying cancer cachexia) or depression alone. Second, before being confident of a diagnosis of depression, his uncontrolled chronic cancer pain had to be addressed. Third, once his pain was adequately controlled, a reasonable assessment of his functional status revealed advanced progressive disease with a probable survival time of weeks to a

month or two. Longer-term interventions (eg, standard antidepressants) were unlikely to achieve full benefit, and agents with a more rapid onset of action (eg, psychostimulants) were necessary. Fourth, perhaps the most important issue is that of simplicity. For the sake of very ill patients, if a single intervention can safely and effectively address several distressing symptoms, it will be preferred over multiple modalities. In this example, methylphenidate fulfills this criterion by not only improving Mr L's mood, but also by increasing his energy level and decreasing the sedative effect of his narcotic analgesic.

In summary, effective medical interventions coupled with close followup and supportive therapy for patient and family can do much to alleviate the often intense psychological distress compounded by fatigue and asthenia experienced by patients with advanced illness.

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## Invited Commentary

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Surgeons are often the first health-care providers that patients see when they are diagnosed with cancer and enter the realm of a new reality. Frequently, it is the surgeon who is called on to deliver primary therapy in the case of solid tumors. For patients with advanced cancers, surgeons can provide palliative surgical procedures to alleviate symptoms of bleeding, obstruction, or pain. So it is the surgeon who patients look to for guidance and hope in the treatment of their disease. Throughout our training as surgical residents, we concentrate on learning to take care of the critically ill postoperative patient, and hone our technical skills and judgment in the operating room. But we are never given instructions to assess the patient's psychosocial needs.

The article by Dr Hinshaw and colleagues gives us some useful tips about depression, anxiety, and asthenia (or lack of vitality and vigor) in patients with advanced illness, particularly terminal cancer. As pointed out in the article, at least 50% of advanced cancer patients will manifest some aspect of these problems. An important take-home message is that there are therapeutic options available to address or alleviate these problems. But unless the patient's physician identifies them, appropriate steps cannot be taken. Chronic pain can exacerbate or contribute to the development of these symptoms, so