LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital (MGH) sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. Such consultations require the integration of medical and psychiatric knowledge. During their thrice-weekly rounds, Dr. Stern and other members of the Psychiatric Consultation Service discuss the diagnosis and management of conditions confronted. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

Dr. Gross is a clinical fellow in psychiatry at Harvard Medical School and a resident in psychiatry at MGH and McLean Hospital; Dr. Smith is an attending physician on the Psychiatric Consultation Service at MGH; and Dr. Stern is chief of the Psychiatric Consultation Service at MGH and a professor of psychiatry at Harvard Medical School.

Corresponding author and reprints: Anne F. Gross, M.D., Massachusetts General Hospital, Warren 6, 275 Charles St., Boston, MA 02114 (e-mail: afgross@partners.org).

Is Depression an Appropriate Response to Having Cancer? A Discussion of Diagnostic Criteria and Treatment Decisions

Anne F. Gross, M.D.; Felicia A. Smith, M.D.; and Theodore A. Stern, M.D.

Have you ever wondered if it is normal to be depressed after discovering that you have cancer? Have you puzzled over how to tell your patient that he or she has metastatic disease? Have you ever assumed that diminished energy, refusal to eat, and insomnia are consequences of chemotherapy? Have you wondered whether antidepressants are appropriate for someone who has terminal illness? If you have, then these questions and concerns faced by clinicians on a daily basis should focus our discussion. While typically trained in the diagnosis and treatment of medical issues associated with a chronic illness, physicians are often ill-prepared for the management of psychiatric and psychological ramifications of illness and its treatment. In this article, we will discuss the relationship between cancer and depression, including which patients are most likely to be affected, how the diagnosis of clinical depression is made in a medically ill patient, and what can be done to help someone suffering from both types of illness. We will argue that, while sadness and grief are normal responses to learning that one has cancer, major depressive disorder (MDD) is never normal; it is a significant complication that must be addressed. We will also attempt to empower clinicians when answering challenging questions with which they are confronted regarding psychiatric and psychological aspects of cancer.

Who Is Prone to Developing Depression After a Diagnosis of Cancer Is Made?

Depression develops in those with cancer in relation to the medical illness itself, to treatment-related factors, and to personal attributes. The frequency of depression is related to cancer type (i.e., pancreatic cancer is associated with the highest prevalence, followed by cancer of the lung, head and neck, and liver and leukemia).[1] The severity of disease is also a predictive factor, with metastatic disease leading to higher rates of depression as compared with cancers detected at earlier stages. Primary and metastatic brain tumors, as well as the presence of tumor cells in the cerebrospinal fluid, often lead to changes in mood.

The presence or absence of psychosocial supports and a person's ability to cope also contribute to the development of depression in cancer patients. Personal issues, including marital status, a supportive family, financial stability, involvement with a religion, and education, contribute to rates of depression. A history of substance abuse, past or present history of MDD, or the presence of other psychiatric/medical illness increases the risk of developing depression in this population.[2] Finally, a patient's age and the severity of illness are inversely related to psychological adjustments and to positive coping styles.[3]

How Often Is Depression Seen in People With Cancer?

Depression occurs in approximately 7% of the general population,[4] more often in women and the elderly. However, among those with cancer, the prevalence of depression is significantly higher, although the numbers vary greatly from study to study. Among inpatients with cancer, the rate of depression is approximately 25%[5]; the rate of psychological distress in inpatients with breast or gynecological cancer is approximately 10% higher than in outpatients with similar tumor status.[6] Clearly, not everyone with cancer develops depression; therefore, those patients who do develop depression merit special attention.

Why Does Having Cancer Predispose One to Depression?

While there is no clear causal relationship between having cancer and developing depression, several biological factors have been invoked. Primary lesions as well as metastatic disease of the brain and/or the presence of tumor cells within the cerebrospinal fluid are linked with mania and depression.[6] Moreover, the hormonal effects of several treatments can lead to changes in mood; chemotherapeutic agents associated with depression include vincristine, vinblastine, corticosteroids, interferon, interleukin (IL)-2, asparaginase, procarbazine, and tamoxifen.[5] Hypogonadal men, who have required either orchiectomy or a gonadotropin-releasing hormone agonist for treatment, are also at increased risk of depression,[7] while in women, the use of tamoxifen appears to lead to increased rates of depression.

Psychoneuroimmunologic studies have begun to investigate underlying biological factors (including changes in cortisol, IL-6, and natural killer cell activity in chronic inflammatory states like cancer), which may contribute to the development of depression.[8,9] Evidence suggests that chronic stress and depression may lead to hypothalamic-pituitary-adrenal axis activation, which in turn leads to the release of mediators that suppress normal immune responses. In cancers associated with viruses, this could initiate and promote development of disease.[8,9]

Why Should Depression in a Patient With Cancer Be Treated?

Depression diminishes one's quality of life, leads to a decrease in compliance with medical treatments, and predisposes one to both morbidity and mortality. With regard to morbidity and mortality, a recent study[10] assessed the risk of death in adults with and without cancer (and by cancer site) and found that, in patients with both depression and cancer, the mortality rate was higher than among nondepressed cancer patients. In this study, cancers of the gastrointestinal tract and lung had the highest hazard ratios (the proposed mechanism involves a decline in natural killer cell activity of depressed patients).[10] Thoughts of suicide and the desire for a hastened death are also common in the terminally ill and may further contribute to increased morbidity and mortality in this population.

How Can I Deliver Bad News in a Meaningful and Effective Manner?

Breaking bad news to patients is frequently difficult for physicians, in part, because this skill is not routinely taught during training. The moment that one receives a diagnosis of cancer will be a life-altering event for many patients, and the process by which a physician gives the information is often as important as the data regarding the diagnosis. Before breaking bad news, the physician should determine how much the patient knows and wants to know. Data support the idea that patients often want to know as much about their illness as possible.[11] Next, doctors should prepare their patients for bad news and take care with the delivery. This is accomplished by meeting with the patient in a private room, setting aside a block of time for the patient, using language that is easy for the patient to understand, making eye contact, and portraying compassion and empathy.[12] Information should be provided in clear and simple terms, in small amounts, and in a manner that is comfortable for the patient. After the information is given, the physician should offer support to the patient and encourage the patient to be involved in the decision-making process.[12] Very often, it is helpful to set up a second meeting to allow time for the patient to process information and to formulate questions.[12]

The specific types of questions that a patient will ask often depend on his or her stage of development but in general will be focused on issues related to loss of external and internal integrity. Patients will frequently be concerned about issues visible to others: deformity, hair loss, weight changes, functional impairment, and loss of fertility. Perhaps more importantly, questions about normal emotional responses (including feelings of anger, fear, and disbelief) will be asked, as will questions about morbidity and mortality: "Will I be in a lot of pain? Am I going to be alive to see my daughter's wedding? Will my parents forget me?" In the face of some of these difficult questions, the clinician must be honest about what he or she does and does not know while at the same time maintaining a sense of hope and offering support.

Is Depression Diagnosed in Someone With Cancer in the Same Way as in a Person Without a Major Medical Illness?

Depression is diagnosed by use of the same criteria whether comorbid illness is present or not. However, several neurovegetative signs (anorexia, fatigue, insomnia, and decreased appetite and weight) can be attributed to the illness (or the treatment). Diagnostic criteria for MDD, as

defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision, require the presence of a total of at least 5 symptoms, at least one of which must be depressed mood or anhedonia (a loss of pleasure); other potential symptoms include sleep disturbance (insomnia/hypersomnia), diminished interests, guilt or preoccupations of thought, decreased energy, decreased ability to concentrate, weight loss or change in appetite, psychomotor agitation or retardation, and suicidal ideation or thoughts of death (as recalled by the mnemonic SIG E CAPS [a prescription for energy capsules]).[13] Because many physicians discount some of these features as a consequence of illness or treatment, depression is often underdiagnosed in cancer patients.

To diagnose depression in the medically ill, a variety of strategies have been employed: some use the inclusive approach, in which every depressive symptom is counted (regardless of its etiology); others use the exclusive approach, in which commonalities between medical disease and depression are disregarded; and still others use the substitutive approach, in which additional depressive symptoms are exchanged for the neurovegetative symptoms. At Memorial Sloan-Kettering Cancer Center (New York, N.Y.), appetite loss and fatigue have been removed, and only 4 total criteria are needed.[14] Many advocate the emphasis of diagnosis based on the psychological symptoms of depression: dysphoria, sadness, lack of pleasure, hopelessness, social withdrawal, guilt, refusal of treatment, and even thoughts of suicide.[15]

Several studies have shown that the single best screening tool for depression in a cancer patient is simply asking the patient, "Are you depressed?"[16] If the patient answers "yes," then a more complete investigation is warranted.

A crucial part of the assessment for depression is to ascertain whether the patient is in pain; often, once pain is adequately addressed and treated, the patient's mood will improve dramatically. Clinicians must also always consider whether an underlying organic cause is contributing to the mood disorder. Metabolic disturbances (including thyroid abnormalities, adrenal insufficiency, hypercalcemia, and B_{12}/folate deficiencies) can lead to depressive symptoms, while tumor involvement in the central nervous system can also lead to both depressive and manic symptoms. Chemotherapeutic agents may also cause mood changes. It is a clinician's responsibility to address these organic causes of mood disturbances and attempt to correct the underlying cause. If, after attempting to correct these factors, the patient's depression persists, then an antidepressant trial is warranted.[5]

Is Depression an Appropriate Response to the Diagnosis of Cancer?

Physicians often think that it is normal to experience depression in response to the diagnosis of cancer. Feeling sad and depressed is an understandable reaction to learning that one has cancer, as these feelings are associated with the sense of loss accompanied with a cancer diagnosis. As with any grief process, these emotions can last days to weeks but will for the most part resolve with the support of family, friends, and a caring physician.[5] It is important to note, however, that this period of bereavement or grief is not characterized by anhedonia, feelings of intense hopelessness leading to treatment refusal or social isolation, or suicidal ideation, as with MDD. While the "blues" may be a common response to having cancer, the syndrome of MDD is never considered normal. This is a crucial distinction to make; if the patient has MDD, it should be treated.

How Do I Decide How to Treat?

Once it has been determined that a patient is suffering from depression, the clinician should decide how to treat the patient. Clinical experience supports both psychological and pharmacologic options for treatment; however, research-based evidence is still being developed.[14,17,18] A recent study showed that support groups are frequently joined by cancer survivors (1 in 4 cancer survivors), especially women with depression and anxiety.[19] Different formats for psychosocial support and therapy exist; these include psychoeducation, cognitive-behavioral therapy, supportive therapy, and individual therapy, each of which may be more useful depending on the stage of illness and the individual's attributes and circumstances. For example, psychoeducation might be most useful around the time of diagnosis, while individual and group therapy may be more meaningful at later stages of illness. The best-studied treatment modality is cognitive-behavioral therapy, which has been shown to improve coping, communication, and relaxation.[20]

While psychotherapy can be an effective treatment for depression in cancer patients, pharmacotherapy is frequently needed, as terminally ill patients often cannot participate fully in psychotherapy. Therefore, it is important for the primary care physician to understand the basics of psychopharmacology, especially in the context of medical illness. First, and foremost, the treatment must offer more benefit than harm to the patient. The treatment choice is highly dependent on the patient; further, the medication chosen must be selected in the context of the patient's underlying illness, the symptoms and side effects experienced, and other medications prescribed.

The specific antidepressant chosen is usually based on its side effect profile; in general, the newer antidepressants, including the selective serotonin reuptake inhibitors (SSRIs) and the mixed-action antidepressants, have fewer side effects and drug interactions than the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). SSRIs and mixed-action antidepressants

Table 1. Medications Used for the Treatment of Depression in Cancer Patients[a]

Medication Class	Pharmacokinetics	General Side Effects	Important Drug Interactions	General Comments
Selective serotonin reuptake inhibitors (SSRIs)	Metabolized by the liver, mostly by the cytochrome P450 2D6 (CYP2D6) isoenzymes of the P450 system; fluoxetine, fluvoxamine, and sertraline are associated with additional isoenzymes and thus have more drug interactions; fluoxetine has a long half-life due to active metabolite; citalopram is associated with fewer drug interactions	Nausea, vomiting, diarrhea, anxiety, sexual dysfunction	CYP2D6 inhibitors, including cimetidine, quinidine, and neuroleptics, may lead to increased levels of SSRIs; fluoxetine and paroxetine inhibit CYP2D6 activity, thereby interacting with neuroleptics, tramadol, antihistamines, antidepressants, and amphetamines; codeine, oxycodone, and hydrocodone are metabolized by CYP2D6, and therefore fluoxetine and paroxetine can block analgesic effect; fluvoxamine can lead to elevated levels of propranolol, warfarin, theophylline, and methadone; fluoxetine increases levels of haloperidol, diazepam, alprazolam, carbamazepine, digoxin, valproic acid, and phenytoin; associated with delirium when using clarithromycin; cimetidine and phenobarbital lead to decreased levels of paroxetine; sertraline can cause a decrease in tolbutamide and an increase in warfarin; may induce serotonergic syndrome with tramadol and may increase nausea after chemotherapy; doxorubicin and vinblastine may be cleared through CYP2D6 but have no documented interactions with SSRIs; several cases of serotonin syndrome when dextromethorphan was taken with fluoxetine or paroxetine	All equally effective in the treatment of depression; fluoxetine has longest half-life and therefore must be used with caution in those with liver failure; paroxetine has a short half-life and is associated with discontinuation syndrome; sertraline, citalopram, and escitalopram all have few drug interactions and therefore are useful in medically ill people; many are available in liquid format for people who cannot swallow pills; may not be appropriate for terminally ill patients, patients, as the medications take 2–4 weeks to have antidepressant effects
Mixed-action norepinephrine and dopamine reuptake inhibitor				
Bupropion	Undergoes extensive first-pass hepatic metabolism, and, thus, drugs that alter liver enzymes will affect metabolism; short half-life	Activating, appetite suppression, delirium at high doses		Few gastrointestinal side effects; causes constipation, not nausea, vomiting, or diarrhea; avoid in those with seizure disorders or organic brain disease, as it lowers seizure threshold; activating medication
Serotonin-norepinephrine reuptake inhibitors				
Venlafaxine	Undergoes renal excretion; short half-life and few drug interactions	Insomnia, anxiety, increase in diastolic blood pressure		Few drug interactions; helpful in the medically ill
Duloxetine	Metabolized by the liver through CYP2D6 and CYP1A2; half-life of 10–15 h	Nausea, decreased appetite, dizziness, small incidence of sexual dysfunction		Useful for pain syndromes associated with depression and peripheral neuropathy
Others				
Mirtazapine	Metabolized by several P450 enzymes; few interactions have been described	Drowsiness, increased appetite, weight gain		Associated with both sedation and appetite stimulation, which can be useful in cancer patients

(continued)

Table 1 (continued). Medications Used for the Treatment of Depression in Cancer Patients[a]

Medication Class	Pharmacokinetics	General Side Effects	Important Drug Interactions	General Comments
Others				
Tricyclic antidepressants (TCAs)	Act on multiple receptor systems; undergo first-pass hepatic metabolism; many drug interactions	Sedation, dry mouth, constipation, hypotension, cognitive impairment, arrhythmias	Most act as inhibitors of CYP2D6; increase the hypotensive effects of cardiac medications and the anticholinergic effects of neuroleptics or antihistamines and may increase the sedative effects of psychotropics; potentiation between opiates, benzodiazepines, and phenothiazines; increase levels of morphine; may prolong cardiac conduction when used with type 1A antiarrythmics; increase warfarin levels; most of clinically significant interactions occur with concurrent use of TCAs and SSRIs, leading to decreased clearance of TCAs; methadone and nonsteroidal anti-inflammatory drugs can lead to increased levels of desipramine; nortriptyline levels can be decreased with rifampin use; erythromycin has been shown to decrease metabolism of imipramine	Useful in cancer patients with neuropathic pain, especially since analgesic effects act more quickly than their effects on mood
Psychostimulants				
Methylphenidate	Rapid onset of action; peak effect at 2 h	Activating, associated anorexia, tachycardia, insomnia, hypertension		Useful in patients with limited life expectancy with depression; used to treat opiate-induced somnolence; useful in cognitive impairment, as it increases attention, concentration, and arousal

[a]Based on Berney[21] and Nemeroff and Schatzberg.[24]

are therefore considered first-line treatments for depression in cancer patients. The most common side effects associated with SSRIs are nausea, headache, sleep disturbances, sexual dysfunction, appetite suppression, and anxiety within the first few days of use.[21] All SSRIs are equally effective in the treatment of depression. There are important differences in these medications, including half-life, drug interactions, and individual side effect profiles; these factors are particularly relevant to the medically ill (see Table 1). Among chemotherapy agents, vinblastine and doxorubicin are metabolized by the same liver isoenzymes as are many SSRIs, although significant drug-drug interactions have yet to be reported with their use.[22] Many of these drugs are available in oral liquid preparations for those patients who cannot tolerate pills. However, some of these agents may not be ideal in the terminally ill, as they take at least 2 to 4 weeks for their antidepressant effects to begin.

The TCAs act on multiple receptor sites (including muscarinic, cholinergic, histaminic, and α-adrenergic), and their side effects include dry mouth, constipation, confusion, urinary retention, sedation, weight gain, and orthostatic hypotension. These medications can be very useful in cancer patients with neuropathic pain, since their analgesic and hypnotic effects act more quickly than their effects on mood. These agents must be used with caution, however, in patients prone to delirium and taking opiates.[21] The MAOIs are typically avoided in the medically ill due to their potential for generating hypertensive crisis from drug-drug (e.g., MAOI-sympathomimetic or MAOI-meperidine) and drug-food (e.g., MAOI–aged meat or cheese) interactions. The recently released selegiline patch offers a transdermal route of administration of an MAOI (which has potential benefit for cancer patients who experience nausea and vomiting); when prescribed at the lowest dose, this medication can also be used without dietary restrictions. Although there are limited data available for this new medication, the selegiline patch may be beneficial in select patient populations.

Psychostimulants, which have a rapid onset of action, are also emerging as an efficacious category of medication in cancer patients, especially in those with a limited life expectancy. They are used to overcome cognitive abnormalities (by increasing arousal, attention, and concentration) and diminished energy and appetite.[23] Research has shown that methylphenidate

is effective in treating depressive symptoms in cancer patients: up to 80% of terminally ill cancer patients feel better within 48 hours.[23] Psychostimulants also potentiate the effects of analgesics and reduce opiate-induced sedation.

Can Antidepressants Be Used as a Comfort Measure?

In the final stages of dying, patients and their families may request that the focus of treatment be changed from attempts at cure to symptom control and comfort. In this setting, antibiotics, daily medications, and blood draws are usually discontinued, whereas narcotics, anti-emetics, and other medications that focus on keeping the patient comfortable are maintained. Depression is distressing to a patient, it interferes with quality of life, and it may exacerbate pain; therefore, antidepressants should be seen as an appropriate agent for use in the comfort-measures-only setting.

Standard medications for the treatment of depression (e.g., SSRIs and TCAs) can be difficult to use in the comfort-measures-only setting, as their onset of action is often delayed.[23] If a patient has previously taken an antidepressant for the treatment of depression, then the medication should be continued as prescribed. In contrast, if the patient has not previously been taking an antidepressant, has a limited life expectancy, and has diminished mood and/or energy, then psychostimulants are often recommended. Psychostimulants also potentiate the analgesic effects of narcotic medications and counteract narcotic-induced sedation. Certain antidepressants, including trazodone and mirtazapine, are also used in the palliative care setting for their ability to induce sedation and stimulate appetite (effects that are noted soon after they are initiated).[25]

Conclusion

Feelings of grief, sadness, anxiety, disbelief, and fear are common in patients with cancer; such feelings are considered normal reactions to a stressful event and should improve over time with adequate support. Effective communication between patient and clinician is crucial to help alleviate distress. While it can be difficult for the physician to interpret whether changes in appetite, sleep, or weight are secondary to cancer or represent underlying depression, when a patient becomes anhedonic, socially isolated, or so hopeless that he or she refuses treatment or becomes suicidal, clinicians should suspect MDD. Depression can reduce the quality of life, decrease adherence with treatment, and increase the risk of mortality. Fortunately for patients, as well as clinicians, depression is treatable; both psychotherapy and psychopharmacology are efficacious treatments. Having a basic understanding of the diagnosis and treatment of depression in a cancer patient helps clinicians provide comprehensive care and alleviate suffering.

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