NIH NATIONAL CANCER INSTITUTE

Depression (PDQ®)–Health Professional Version

Go to Patient Version

Overview

Depression is a comorbid, disabling syndrome that affects up to approximately 25% of cancer patients.[1-3] This prevalence significantly exceeds the prevalence in the general population.[4] However, most patients do not receive potentially effective treatments, and only 5% see a mental health professional.[2]

In contrast to depression in the general population, depression in people with cancer is believed to affect men and women equally.[5] Individuals and families who face a diagnosis of cancer experience varying levels of stress and emotional upset. Depression in patients with cancer not only affects the patients themselves, but also has a major negative impact on their families.

Definitions: Depression is suspected when a number of specific symptoms such as low affect, sleep disturbance, and distorted thought patterns are observed. These are specified in the categorization of psychiatric/behavioral disorders in the *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition.[6]

Normally, a patient's initial emotional response to a diagnosis of cancer is brief, extending over several days to weeks, and may include feelings of disbelief, denial, or despair. This normal

response is part of a spectrum of depressive symptoms that range from normal sadness to adjustment disorder with depressed mood to major depression.[6] Other syndromes described include the following:

- Dysthymia: a chronic mood disorder in which a depressed mood is present on more days than not for at least 2 years.
- Subsyndromal depression (also called minor depression or subclinical depression): an acute mood disorder that is less severe (some, but not all, diagnostic symptoms present) than major depression.

Possible Causes of Depressive Symptoms in People With Cancer

- Experience of loss or anticipated loss.
- Uncontrolled pain.[7][Level of evidence: II]
- Metabolic abnormalities:
    - Hypercalcemia.
    - Sodium/potassium imbalance.
    - Anemia.
    - Vitamin B12 or folate deficiency.
    - Fever.
- Primary or metastatic central nervous system tumors.
- Disruption of sleep due to medical treatments.
- Endocrine abnormalities:
    - Hyperthyroidism or hypothyroidism.
    - Adrenal insufficiency.
- Medications:[8];[9][Level of evidence: II];[10]
    - Steroids.
    - Endogenous and exogenous cytokines, i.e., interferon-

alfa and aldesleukin (interleukin-2 [IL-2]).[11]

- Methyldopa.
- Reserpine.
- Barbiturates.
- Propranolol.
- Some antibiotics (e.g., amphotericin B).
- Some chemotherapeutic agents (e.g., procarbazine, asparaginase).
- Hormone therapy (e.g., androgen deprivation therapy). [12][Level of evidence: III]

A survey in England of women with breast cancer showed that among several factors, depression was the strongest predictor of emotional and behavioral problems in their children.[13] Fear of death, disruption of life plans, changes in body image and self-esteem, changes in social role and lifestyle, and financial and legal concerns are significant issues in the life of any person with cancer, yet not everyone who is diagnosed with cancer experiences serious depression or anxiety. However, many patients with cancer can experience moderately severe depression and anxiety. For example, in a study of 256 women who underwent chemotherapy treatment for early breast cancer, 26% and 41% of study participants reported moderately severe depression and anxiety, respectively. This treatment phase warrants close monitoring of patients' psychological well-being.[14]

The use of hormone therapy or second-generation antiandrogen therapy is also associated with increased risk of depression. In a retrospective study of 210,804 patients with prostate cancer identified from the Surveillance, Epidemiology, and End Results–Medicare (SEER-Medicare) and Texas Cancer Registry–Medicare linked databases, 3% of patients received second-generation

antiandrogen therapy.[12][Level of evidence: III] Using a multivariable Cox proportional hazards model, patients who received second-generation antiandrogen therapy had a greater increased risk of depression, compared with a no-hormone-therapy group (hazard ratio [HR], 2.15; 95% confidence interval [CI], 1.79–2.59; $P < .001$) and with a traditional-hormone-therapy group (HR, 2.26; 95% CI, 1.88–2.73; $P < .001$).[12][Level of evidence: III] While this secondary analysis was a limitation of this study, the large sample size merits consideration for monitoring for depression in patients undergoing hormone therapy, particularly second-generation antiandrogen therapy.

In a study of 149 women with nonmetastatic breast cancer, 40% reported at least mild depression at the end of chemotherapy.[15] Up to 5.6 years postchemotherapy, 23% had received a new psychiatric diagnosis, 62% were prescribed a psychotropic medication, and 21% engaged in mental health specialty care.

Just as patients require ongoing evaluation for depression and anxiety throughout their course of treatment, so do family caregivers. In a study of family caregivers of patients in the palliative phase of illness, both male and female caregivers experienced significantly more anxiety than did a sample of noncaregivers, while there was an increased incidence of Hospital Anxiety and Depression Scale–defined depression among women.[16]

Some people may have more difficulty adjusting to the diagnosis of cancer than others do and will vary in their responses to the diagnosis. Sadness and grief are normal reactions to the crises faced during cancer. All people will experience these reactions periodically. Because sadness is common, it is important to distinguish between normal degrees of sadness and depressive disorders. An end-of-life care consensus panel review article describes details regarding this important distinction and illustrates the major points using case vignettes.[17] A critical

part of cancer care is the recognition of the levels of depression present and determination of the appropriate level of intervention, ranging from brief counseling or support groups to medication and/or psychotherapy. For example, relaxation and counseling interventions have been shown to reduce psychological symptoms in women with a new diagnosis of gynecological cancer.[18]

Major depression, which is more common in cancer patients than in the general population,[3] has recognizable symptoms whose diagnosis and treatment are essential because they have an impact on quality of life.[19] Major depression may also impact survival. In a large study of 20,582 patients treated for breast, colorectal, gynecological, and prostate cancers across Scotland, United Kingdom, across all cancer diagnoses, having major depression was associated with worse survival (pooled HR, 1.41; 95% CI, 1.29–1.54; $P < .001$).[20][Level of evidence: II] Similarly, in a population-based study of 13,244 individuals with diffuse large B-cell lymphoma identified through the SEER-Medicare database,[21][Level of evidence: III] compared with patients with no mental health disorders, those with depression had the highest 5-year mortality rate (HR, 1.37; 95% CI, 1.28–1.47), followed by those with co-occurring depression and anxiety (HR, 1.23; 95% CI, 1.08–1.41) and those with anxiety alone (HR, 1.17; 95% CI, 1.06–1.29).

Further, disparities in cancer care have been identified among individuals who have preexisting major depression and/or other severe mental illnesses. A large systematic review and meta-analysis (N = 299,193) [22][Level of evidence: III] found that individuals with breast cancer with preexisting major depression, schizophrenia, and/or bipolar disorder received delayed and discordant care, compared with individuals with cancer without these disorders. Given the high prevalence of depression among patients with cancer, this health care disparity warrants attention.

Depression is also an underdiagnosed disorder in the general population. Symptoms evident at the time of a cancer diagnosis may represent a preexisting condition and warrant separate evaluation and treatment.

Depression and anxiety disorders are common among patients receiving palliative care and contribute to a greatly diminished quality of life in these patients.[23] In the Canadian National Palliative Care Survey, patients receiving palliative care for cancer (N = 381) were evaluated for depressive and anxiety disorders and for the impact of these disorders on quality of life. The primary assessment tool was a modified version of the Primary Care Evaluation of Mental Disorders. A significant number of participants (24.4%; 95% CI, 20.2%–29.0%) were found to fulfill diagnostic criteria for at least one depressive or anxiety disorder (20.7% prevalence for depressive disorder and 13.1% for anxiety disorder).

Participants diagnosed with a depressive or anxiety disorder had the following characteristics:

- Were significantly younger than the other participants (P = .002).
- Had lower performance status (P = .017).
- Had smaller social networks (P = .008).
- Participated less in organized religious services (P = .007).

They also reported more severe distress about physical symptoms, social concerns, and existential issues, suggesting significant negative impact on other aspects of their quality of life.[23]

The importance of psychological issues was underscored by another study conducted in terminally ill cancer patients (n = 211) with life expectancies of less than 6 months.[24]

Investigators evaluated patient “sense of burden to others” and its correlation with physical, psychological, and existential issues, using specific validated psychometrics (e.g., visual analog scale). The variables most highly correlated with sense of burden to others included:

- Depression ($r = 0.460$, $P < .0001$).
- Hopelessness ($r = 0.420$, $P < .0001$).
- Outlook ($r = 0.362$, $P < .0001$).

In multiple regression analysis, four variables predicted perception of burden to others:

- Depression.
- Hopelessness.
- Level of fatigue.
- Current quality of life.

No association between sense of burden to others and actual degree of physical dependency was found, implying that this perception is mainly mediated through psychological distress and existential issues. A subanalysis of patient groups from different settings suggested that these findings were consistent across the inpatient and outpatient settings, with some minor variations.[24]

The emotional response to a diagnosis of cancer (or cancer relapse) may begin as a dysphoric period marked by increasing turmoil. The individual will experience sleep and appetite disturbance, anxiety, ruminative thoughts, and fears about the future. Epidemiological studies, however, suggest that at least one-half of all people diagnosed with cancer will successfully adapt.

Strategies to promote psychological adjustment to a diagnosis of

cancer and other chronic diseases include the following:[25]

- Remaining as active and engaged in life as possible.
- Expressing emotions in a way that helps to achieve insight.
- Self-management (including healthy diet and exercise).
- Focusing on potential positive outcomes of illness.

Some studies suggest an association between maladaptive coping styles and higher levels of depression, anxiety, and fatigue symptoms.[26,27] Examples of maladaptive coping behaviors include the following:

- Avoidant or negative coping.
- Negative self-coping statements.
- Preoccupation with physical symptoms.
- Catastrophizing.

One study conducted in a group of 86 mostly late-stage cancer patients suggested that maladaptive coping styles and higher levels of depressive symptoms are potential predictors of the timing of disease progression.[27] Another study examining coping strategies in women with breast cancer (n = 138) concluded that patients with better coping skills such as positive self-statements have lower levels of depressive and anxiety symptoms.[26] The same study found racial differences in the use of coping strategies, with African American women reporting and benefiting more from the use of religious coping strategies such as prayer and hopefulness than did White women.[26]

Preliminary data suggest a beneficial impact of spirituality on associated depression, as measured by the Functional Assessment of Chronic Illness Therapy—Spiritual Well-Being questionnaire and the Hamilton Depression Rating Scale.[28]

The following indicators may suggest a need for early intervention:

- A history of depression.
- A weak social support system (not married, few friends, a solitary work environment).
- Evidence of persistent irrational beliefs or negativistic thinking regarding the diagnosis.
- A more serious prognosis.
- Greater dysfunction related to cancer.

As shown by a study of adult cancer patients (n = 48) and their adult relatives (n = 99), family functioning is an important factor that impacts patient and family distress. Families that were able to act openly, express feelings directly, and solve problems effectively had lower levels of depression, and direct communication of information within the family was associated with lower levels of anxiety.[29] Depressive symptoms in spouses of patients with cancer can also have a negative impact on their marital communication. A preliminary study investigated 19 potential predictors of depression in spouses (n = 206) of women with nonmetastatic breast cancer.[30] Spouses were more likely to experience depressive symptoms if they:

- Were older.
- Were less well-educated.
- Were more-recently married.
- Reported heightened fears about their spouse's well-being.
- Worried about their job performance.
- Were more uncertain about their future.
- Were in marriages that were less well-adjusted.

Risk factors may be different, especially pain and other physical

symptoms.[31] When the clinician begins to suspect that a patient is depressed, he or she will assess the patient for symptoms. Mild or subclinical levels of depression that include some, but not all, of the diagnostic criteria for a major depressive episode can cause considerable distress and may warrant interventions such as supportive individual or group counseling, either by a mental health professional or through participation in a self-help support group.[32]

Evidence-based recommendations have described various approaches to the problems of cancer-related fatigue, anorexia, depression, and dyspnea.[33] Even in the absence of any symptoms, many patients express interest in supportive counseling; clinicians can accommodate these patients with referrals to qualified mental health professionals. However, when symptoms are more intense, longer lasting, or recurrent after apparent resolution, treatment to alleviate symptoms is essential.[19,34,35] Anxiety and depression in early treatment are good predictors of these same problems at 6 months.[36] In a study of older women with breast cancer, a recent diagnosis of depression was associated with both a greater likelihood of not receiving definitive cancer treatment and poorer survival.[37]

In this summary, unless otherwise stated, evidence and practice issues as they relate to adults are discussed. The evidence and application to practice related to children may differ significantly from information related to adults. When specific information about the care of children is available, it is summarized under its own heading.

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Assessment and Diagnosis

Symptoms and Risk Factors

There are two major classifications of symptoms for major depression: neurovegetative and emotional-cognitive. In cancer patients whose neurovegetative symptoms may be affected by the disease process or treatment, assessing the emotional-cognitive symptoms of their depression is likely to be more diagnostic and prevent false-positive results. Symptoms include the following:

- A depressed mood for most of the day and on most days.
- Diminished pleasure or interest in most activities.
- Significant change in appetite and sleep patterns.
- Psychomotor agitation or slowing.
- Fatigue.[1]
- Feelings of worthlessness or excessive, inappropriate guilt.
- Poor concentration.
- Recurrent thoughts of death or suicide.

Cognitive symptoms may express themselves as repeated and ruminative thoughts such as “I brought this on myself,” “God is punishing me,” or “I’m letting my family down,” and as fatalistic expectations concerning prognosis, despite realistic evidence to the contrary. Such thinking may predominate or may alternate with more realistic thinking yet remain very stressful. Some individuals will share negativistic thoughts freely, and family members may be aware of them. Other patients will not volunteer such thinking but will respond to brief inquiries such as the following (other examples are listed in Table 2):

- “Many people find themselves dwelling on thoughts about their cancer. What kinds of thoughts do you have?”
- “Do you find yourself ever thinking, ‘I brought this on myself. God is punishing me’? How often? Only a few times a week, or all the time? Do you believe these thoughts are true?”
- “In spite of these thoughts, are you still able to go on with your life and find pleasure in things? Or, are you so preoccupied that you can't sleep, or feel hopeless?”

It is possible for a physician or nurse to ask these types of questions without becoming engaged in providing counseling themselves. Merely asking these questions will express concern and increase the likelihood that the patient will be receptive to suggestions for further counseling.

These questions can be followed by a statement such as, “Many people with cancer sometimes have these feelings. You are not alone. But talking to someone else about them can greatly help. I'd like to suggest that you consider doing that. Would you be willing to talk to someone who has a lot of experience helping people cope with the stress of having cancer?”

It is preferable at this time both to encourage patients to seek out someone already known to them and to inform them about

other resources in the community. Particularly for patients who have completed cancer treatment and who have manageable physical symptoms, higher perceived availability of social support has been associated with fewer depressive symptoms.[2] In some instances, referral to a cleric or therapist may also be appropriate. Most therapists can address general issues of grief or fears about death; some will specialize in clinical health psychology, medical social work, or even working primarily with cancer patients. For the hesitant patient, suggesting multiple resources will increase the likelihood that some assistance will be sought. For other patients, a formal direct referral may be appropriate.

Evaluation of depression in people with cancer includes careful assessment of the following:

- Symptoms.
- Treatment effects.
- Laboratory data results.
- Physical status.
- Mental status.

Although the etiology of depression in patients with cancer is largely unknown, many risk factors for depression have been identified. The major risk factors for cancer-related depression include psychological and social factors. Preexisting mental health issues and impaired social support carry the highest risk.[3] Certain comorbidities, such as fatigue, pain, and lower physical functioning, can also increase depression risk. Cancer-related risk factors such as cancer type, stage, and treatment may play a role, but they carry a lower risk than psychological and social factors.[3] However, certain cancers—such as head and neck cancers and pancreatic cancer—carry a high risk of depression. Cancer-related risk factors can be divided into four

broad categories, as shown in Table 1.

Table 1. Risk Factors for Cancer-Related Depression

Type of Risk Factor	Specific Risk Factors
Psychological	History of depression or other mental illness[a], neuroticism[a], dysfunctional coping behaviors[b]
Social, sociodemographic, and socioeconomic	Impaired social support[a], single/separated/widowed[a], female gender[a], lower socioeconomic status[b], lower educational level[b]
Comorbidities	Pain[a], fatigue[a], overall symptom burden[a], lower physical functioning[b]
Cancer and cancer treatment	Specific cancer types (pancreatic, head and neck)[a], advanced cancer[b]

[a]High risk.

[b]Moderate risk.

For patients with head and neck cancer treated with curative intent, the following eight pretreatment variables can be used to predict which patients are likely to become depressed up to 3 years after treatment:[4,5]

- Tumor stage.

- Sex.
- Depressive symptoms.
- Openness to discussing his/her cancer with family members.
- Perceived available support.
- Received emotional support.
- Tumor-related symptoms.
- Size of the informal social network.

Screening and Assessment for Depression

Because of the common underrecognition and undertreatment of depression in people with cancer,[6] screening tools can be used to prompt further assessment.[7] Among the physically ill, in general, instruments used to measure depression have not been shown to be more clinically useful than an interview and a thorough examination of mental status. Simply asking the patient whether he or she is depressed may improve the identification of depression.

The following screening tools are commonly used:

- A single-item interview. In people with advanced cancer, a single-item interview question has been found to have acceptable psychometric properties and can be useful. One example is to ask “Are you depressed?”[8] Another example is to say, “Please grade your mood during the past week by assigning it a score from 0 to 100, with a score of 100 representing your usual relaxed mood.” A score of 60 is considered a passing grade.[9]
- The Hospital Anxiety and Depression Scale (HADS). The HADS may be useful in the assessment of depression and anxiety in patients who have comorbid neurovegetative symptoms due to their disease or treatment, helping to avoid false-positive results on the scale caused by these symptoms.

[10-12]

- The nine-item Patient Health Questionnaire (PHQ-9).[13]
- The Psychological Distress Inventory.[14]
- The Edinburgh Depression Scale.[15]
- The Brief Symptom Inventory.[16]
- The Zung Self-Rating Depression Scale.[17]
- The Distress Thermometer.[18]

One study of women with newly diagnosed breast cancer (n = 236) successfully used brief screening instruments such as the Distress Thermometer and the PHQ-9 to identify women requiring further assessment to detect clinically significant levels of distress and psychiatric symptoms.[19]

In a study of 321 women with newly diagnosed stage I to stage III breast cancer, the ability of the single-item Distress Thermometer to specifically predict depression, as measured by a self-report questionnaire of the nine *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM-IV) symptoms for major depressive disorder, was investigated. Sensitivity and specificity characteristics were evaluated, and the optimal cutoff score of 7 was identified, resulting in a sensitivity of 0.81 and a specificity of 0.85 for detecting depression. Therefore, individuals scoring 7 or above will undergo a more thorough psychosocial evaluation.[20]

The Impact Thermometer, a modification of and accompaniment to the Distress Thermometer, has improved specificity for the detection of adjustment disorders and/or major depression, as compared with the Distress Thermometer. The revised tool has a screening performance comparable to that of the HADS and is brief, potentially making it an effective tool for routine screening in oncology settings.[21] The Mood Evaluation Questionnaire, a cognitive-based screening tool for depression, has moderate

correlation with the structured clinical interview for the DSM, 3rd revised edition (DSM-III-R) and good acceptability in the palliative care population. With further validation, it may become a useful alternative in this population because it can be used by clinicians who are not trained in psychiatry.[22]

It is important that screening instruments be validated in cancer populations and used in combination with structured diagnostic interviews.[23] A pilot study of 25 patients used a simple, easily reproduced visual analog scale suggesting the benefits of a single-item approach to screening for depression. This scale consists of a 10-cm line with a sad face at one end and a happy face at the other end, on which patients make a mark to indicate their mood. Although the results do suggest that a visual analog scale may be useful as a screening tool for depression, the small patient numbers and lack of clinical interviews limit conclusions. Furthermore, although very high correlations with the HADS were reported (r = 0.87), no indication of cutoffs was given. Finally, it is emphasized that such a tool is intended to suggest the need for further professional assessment. However, if validated further, this simple approach could greatly enhance assessment and management of depression in cognitively intact advanced-cancer patients.[24,25]

In a study of 2,141 German cancer patients, the HADS and the PHQ-9 had similar sensitivity (89% and 83%, respectively) and specificity (43% and 61%, respectively) for detecting DSM-IV major depressive disorder at suggested cutoffs based on receiver operating characteristic curves.[26]

Other brief assessment tools for depression can be used. To help patients distinguish normal anxiety reactions from depression, assessment includes discussion about common symptoms experienced by cancer patients. Depression is reassessed over time.[27] Because of the increased risk of adjustment disorders and major depression in cancer patients,

routine screening with increased vigilance at times of increased stress (e.g., diagnosis, recurrences, progression) is recommended.[28] General risk factors for depression are noted in the list above. Other risk factors may pertain to specific populations, for example, patients with head and neck cancer [4] and women at high risk of developing breast cancer.[29]

Clinical interview

Table 2. Suggested Questions for the Assessment of Depressive Symptoms in Adults With Cancer[a]

Question	Symptom
Depressive symptoms	
How well are you coping with your cancer? Well? Poorly?	Well-being
How are your spirits since diagnosis? During treatment? Down? Blue?	Mood
Do you cry sometimes? How often? Only alone?	Mood
Are there things you still enjoy doing, or have you lost pleasure in things you used to do before you had cancer?	Anhedonia
How does the future look to you? Bright? Black?	Hopelessness
Do you feel you can influence your care, or	Helplessness

is your care totally under others' control?	
Do you worry about being a burden to family/friends during cancer treatment?	Guilt
Do you feel others might be better off without you?	Worthlessness
Physical symptoms (evaluate in the context of cancer-related symptoms)	
Do you have pain that isn't controlled?	Pain
How much time do you spend in bed?	Fatigue
Do you feel weak? Fatigue easily? Rested after sleep? Any relationship between how you feel and a change in treatment or how you otherwise feel physically?	Fatigue
How is your sleeping? Trouble going to sleep? Awake early? Often?	Insomnia
How is your appetite? Food tastes good? Weight loss or gain?	Appetite
How is your interest in sex? Extent of sexual activity?	Libido
Do you think or move more slowly than usual?	Psychomotor slowing

[a]Adapted from Roth et al.[30]

Organic Mood Syndromes or Mood Syndromes Related to

Another Medical Condition (MSRAMC), as they are referred to in the DSM, 5th edition (DSM-5),[31] often mimic the mood syndromes in their presentation. The assumption is made (perhaps based on their time course or laboratory data) that an organic or medical factor has a role in the etiology of the syndrome. The DSM-5 suggests that prominent cognitive abnormalities may be accompanying factors and therefore are useful in making the diagnosis. Consideration should be given to obtaining laboratory data to assist in detection of electrolyte or endocrine imbalances or the presence of nutritional deficiencies. Clinical experience suggests that pharmacotherapy is more advantageous than psychotherapy alone in the treatment of depression that is caused by medical factors, particularly if the dosages of the causative agent(s) (i.e., steroids, antibiotics, or other medications) cannot be decreased or discontinued.[32]

Diagnosis

To make a diagnosis of depression, the clinician confirms that these symptoms have lasted at least 2 weeks and are present on most days. The diagnosis of depression in people with cancer can be difficult because of the problems inherent in distinguishing biological or physical symptoms of depression from symptoms of illness or toxic side effects of treatment. This is particularly true of individuals who are receiving active treatment or those with advanced disease.

The following cognitive symptoms are probably the most useful in diagnosing depression in people with cancer:

- Guilt.
- Worthlessness.
- Hopelessness.
- Helplessness.
- Thoughts of suicide.

- Loss of pleasure in activities.

One German study comparing cancer patients who had a current affective disorder with those who had a single depressive symptom found loss of interest, followed by depressed mood, to yield the highest power of discrimination between the two groups on multivariate analysis.[33]

The evaluation of depression in people with cancer also includes:

- Careful assessment of the person's perception of the illness.
- Medical history.
- Personal or family history of depression or thoughts of suicide.
- Current mental status, and physical status, as well as treatment and disease effects.
- Concurrent life stressors.
- Availability of social supports.

More than 90% of patients indicate that they prefer to discuss emotional issues with their physician, but more than one-quarter of patients feel that the physician must initiate any discussion of that topic.[34]

Suicidal ideation is not uncommon among patients with cancer and, when it occurs, is frightening for the individual, the health professional, and the family. In one study of 354 health care providers working with oncology patients in Germany, 83.3% reported that they had at least one patient with suicidal ideation in the past year, and 59% reported having one to three suicidal patients annually. This experience was distressing for 88.1% of providers. In addition, over 20% of providers reported feeling overwhelmed when confronted with a suicidal patient.[35][Level of evidence: II]

Suicidal statements may range from an offhand comment resulting from frustration or disgust with a treatment course—"If I have to have one more bone marrow aspiration this year, I'll jump out the window"—to a reflection of significant despair and an emergent situation—"I can no longer bear what this disease is doing to all of us, and I am going to kill myself." Exploring the seriousness of the thoughts is imperative. If the suicidal thoughts are believed to be serious, it is imperative that a referral to a psychiatrist or psychologist is made immediately and attention is given to the patient's safety.[34] For more information, see the Suicide Risk in Cancer Patients section.

The most common form of depressive symptomatology in people with cancer is an adjustment disorder with depressed mood, sometimes referred to as reactive depression. This disorder is manifested when a person has a dysphoric mood that is accompanied by the inability to perform usual activities. [36][Level of evidence: II] The symptoms appear to be prolonged and in excess of a normal and expected reaction but do not meet the criteria for a major depressive episode. When these symptoms significantly interfere with a person's daily functioning, such as attending to work or school activities, shopping, or caring for a household, they are treated in the same way that major depression is treated (i.e., with crisis intervention, supportive psychotherapy, and medication, especially with drugs that quickly relieve distressing symptoms). Basing the diagnosis on these symptoms can be problematic when the individual has advanced disease and the illness itself is undermining functioning.

It is also important to distinguish between fatigue and depression, which are often interrelated and can be part of a symptom cluster. The different mechanisms that give rise to these conditions can be treated separately.[1] In more advanced illness, focusing on despair, guilty thoughts, and a total lack of enjoyment of life is helpful in diagnosing depression. For more

information, see Symptom Clusters in Cancer and Adjustment to Cancer: Anxiety and Distress.

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Intervention

The decision to initiate therapy for depression depends on the probability that the patient will recover spontaneously in the next 2 to 4 weeks, the degree of functional impairment, and the severity and duration of the depressive symptoms.[1] It is important to assess the nature of emotional distress and factors contributing to the depression symptomatology (e.g., psychosocial factors, demoralization, and comorbid symptoms such as pain or fatigue). Decisions about interventions depend on the severity of depression and on factors driving depression symptomatology.[2] Studies have shown that treatment of severe major depression is optimized by a combination of

pharmacotherapy and psychotherapy.[2] Thus, even if a primary care physician or oncologist undertakes the treatment of depressive symptoms pharmacologically, a referral for psychotherapy or supportive counseling should be considered.

For the following reasons, referral of individuals for a psychiatric consultation should be considered:[3,4]

- The primary care physician or oncologist does not feel competent treating the patient for depression because of specific clinical features in the presentation (i.e., if prominent suicidal tendencies are present).
- The depressive symptoms treated by the primary physician are resistant to pharmacological interventions after 2 to 4 weeks of intervention.
- The depressive symptoms are worsening rather than improving.
- Initiating treatment with antidepressant drugs, titrating drug doses, or continuing treatment is interrupted or made problematic by adverse effects attributable to the medication.
- The depressive symptoms are interfering with the patient's ability to cooperate with medical treatment.

In addition, among patients who have completed treatment for cancer and have comorbid depression, the use of antidepressants may decrease the risk of cancer recurrence. For example, in a population-based study, men with prostate cancer with documented depression disorder (n = 10,017) were followed for over 20 years. The researchers found that those who took antidepressants had lower rates of prostate cancer recurrence than those who did not take antidepressants.[5] While this evidence is intriguing, prospective, confirmatory trials and investigations are needed to better understand these

findings and the underlying mechanisms.

Pharmacological Intervention

Overview

There is a dearth of randomized, placebo-controlled trials assessing the risks and benefits of antidepressants in patients with cancer and depression or depressive symptoms. Furthermore, these studies are limited by methodological challenges and a lack of broad representation of children, adolescents, older adults, and minority groups.[6] However, a systematic review and meta-analysis of the available studies suggest that antidepressants, regardless of their class (e.g., selective serotonin reuptake inhibitors [SSRIs] or tricyclic antidepressants [TCAs]), are more effective than placebo in treating depression in patients with cancer.[7] Evidence also suggests that the efficacy of antidepressant treatment is related to the presence of clinically significant depression symptomatology,[8] suggesting that antidepressants be reserved for patients presenting with clinical depression.

A survey of prescribing patterns in outpatient oncology settings over a 2-year period found that antidepressants were prescribed for about 14% of patients.[9] In a systematic review of newer pharmacotherapies for depression in adults, the response rate for treatment of depression with antidepressants was found to be approximately 54%.[10] The efficacy of the newer pharmacotherapies is similar to that of older antidepressants for general medical patients, including older adults and those with medical or psychiatric comorbidities.[10] The rates of dropout due to adverse effects are approximately 11% for newer antidepressants and 16% for older antidepressants.[10]

Because of the relative paucity of data regarding antidepressant use in oncology settings, there is considerable variability in practice patterns related to prescribing antidepressants for

cancer patients. Although studies generally indicate that about 25% of all cancer patients are depressed, one study found that only 16% of cancer patients were receiving antidepressant medication.[11] However, among depressed patients with advanced cancer who had an unplanned hospitalization, patients who were treated with a prescribed antidepressant had shorter hospitalizations than did patients who were not treated.[12]

Antidepressant classes

Antidepressants are divided into several classes on the basis of their underlying mechanisms. Most inhibit uptake of neurotransmitters; some also have a direct impact on cell receptors (see Table 3).

Table 3. Antidepressant Medications[a] and Adjunctive Pharmacological Treatments

SSRIs			
Medication	***Starting Dose (mg/day)***	***Maintenance Dose (mg/day)***	***Co***
Citalopram	10–20	20–40	Be tol pro oth ant
			Pot QT pro (do lim pat car

Escitalopram	5–10	10–20	Bet tol pro oth ant
Fluoxetine	10–20	20–60	Mi ser dis syr to
			Sig inh CYI
Fluvoxamine	25–50	100–300	Bet pro oth
			Sig inh CYI CYI
Paroxetine	10–20	20–60	Hig ser dis syr
			Mo ant pro
			Sig inh CYI
Sertraline	25–50	100–200	Hig

			sid
			Do dep inh CYI
Vilazodone	10	20–40	Ris eff
			Pos of dys evi inc
SNRIs[b]			
Medication	***Starting Dose (mg/day)***	***Maintenance Dose (mg/day)***	***Co***
Desvenlafaxine	50	50–100	Pos on
Duloxetine	30	30–60	Firs tre pat cor ner pai hig
			Hig sid hyp
			Ris hep

Levomilnacipran	20	40–120	Mo no eff act eff
			Us co co pa
			Inc ca sid sw uri he
Venlafaxine (IR and XL)	37.5–75	150–225	Fir tre pa co fla
			Hi se di sy

TCAs

Medication (only most commonly used TCAs included below)	***Starting Dose (mg/day)***	***Maintenance Dose (mg/day)***	***Co***
Amitriptyline	10–25	150–300	Ma se an eff

			We
			Ort hyp
			Diz
Clomipramine	25	100–250	Mo ser eff sec fev ant eff oth
Desipramine	25–50	100–300	Mil
			Mi ant eff
Doxepin	10–25	75–300	Ma sec ant eff
			We
			Ort hyp
			Diz
Imipramine	25–50	75–300	Mo sec

			We
			An eff
			Ort hyp
			Diz
Nortriptyline	10–25	90–150	Mil
			Mo ant eff

NDRIs

Medication	***Starting Dose (mg/day)***	***Maintenance Dose (mg/day)***	***Co***
Bupropion (IR, SR, and XL)	100–150 (SR and XL)	150–450	Sti eff of dys
			Do dep sei (ra hea we
			SR cor

			to anx eff hig risk wit

Atypical antidepressants

Medication	*Starting Dose (mg/day)*	*Maintenance Dose (mg/day)*	*Co*
Mirtazapine	7.5–15	30–45	Fre in pat cor ins cac Kn ant eff
			De elir eld
			Sec gai diz
			Ris hep and ner
Trazodone	25–50	50–200	Pri as oth ant Us cor

Questions?

			ins an
			Ma sec an eff
			Ris ort hyp diz pri
MAOIs/Psychostimulants as adjunctive treatments to antidepressants/Other adjunctive treatments	See the text below for more informati		

CYP = cytochrome P450 enzyme; GI = gastrointestinal; IR = immedic
MAOI = monoamine oxidase inhibitor; NDRI = norepinephrine-dopar
inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; SR = su
release; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic
antidepressant; XL = extended release.

[a]All antidepressants carry a boxed warning about the risk of suicida
behavior, risk of mania, and risk of drug-drug interaction when com
MAOIs (for more information, see the MAOIs section).

[b]For more information about side effects associated with SNRIs, see
Serotonin-norepinephrine reuptake inhibitors (SNRIs) section.

The following sections describe the major antidepressant classes, their underlying mechanisms of action, their safety/tolerability profiles, and their potential use in cancer patient populations.[7,13]

Selective serotonin reuptake inhibitors

SSRIs are most commonly used in patients with cancer because

they have better safety-tolerability profiles than other antidepressants. SSRIs block the reabsorption of serotonin (also called 5-hydroxytryptamine or 5-HT) by the presynaptic neurons by blocking the serotonin transporters. This causes more serotonin to be available to bind to the receptors of the postsynaptic neuron. Medications such as citalopram, escitalopram, and paroxetine work primarily by serotonin transporter blockade. Other SSRIs have additional mechanisms underlying their antidepressant effects. For example, fluoxetine binds to a specific serotonin receptor called the 5-HT_{2c} receptor, sertraline blocks dopamine transporters, and vilazodone has partial agonism at the 5-HT_{1a} serotonin receptor. The drugs in this class are similar in terms of their effectiveness. The most common side effects associated with this class of medications include:

- Gastrointestinal (GI) side effects (e.g., nausea, diarrhea, constipation).
- Sexual dysfunction (e.g., delayed ejaculation, anorgasmia, decreased libido).

However, the drugs differ in severity of these side effects and can have additional effects related to their impact on other neurobiological systems such as:

- Anticholinergic effects (e.g., cognitive difficulties, confusion, dry mouth, dry skin, constipation, blurred vision, urinary retention).
- Sedation.
- Insomnia.

SSRIs generally undergo hepatic metabolism, renal elimination, and differ significantly in terms of their half-lives. The half-life of the specific SSRI depends on the half-lives of the parent compound and the metabolite. The serotonin discontinuation

syndrome, a syndrome associated with abrupt discontinuation of SSRIs, is related to the half-life of the SSRI and its active metabolites. The shorter the half-life of the SSRI and its metabolites, the higher the risk of serotonin discontinuation syndrome. For more information, see the Serotonin discontinuation syndrome section.

Serotonin-norepinephrine reuptake inhibitors (SNRIs)

SNRIs increase levels of both 5-HT and norepinephrine (NE) in the synapse by blocking reuptake of these neurotransmitters by their respective transporters. SNRIs differ in their blockade of 5-HT and NE transporters, depending on their affinity for these transporters. Venlafaxine is primarily serotonergic at lower dosages, with mixed 5-HT and NE effects at higher dosages. Duloxetine and desvenlafaxine are known to block both 5-HT and NE transporters at low dosages, while levomilnacipran has the highest noradrenergic effects at lower dosages, compared with other SNRIs. These different 5-HT and NE effects may be associated with differential efficacy and side effect profiles in different patient populations. For example, serotonergic effects may be more beneficial in the treatment of depression with comorbid anxiety, while noradrenergic effects may be more beneficial in the treatment of depression with atypical features such as hypersomnia, lack of energy, and lack of motivation.

Many of the SNRIs are also known for their positive impact on pain syndromes, including neuropathic pain associated with chemotherapy. Like SSRIs, SNRIs can cause GI side effects and sexual side effects. Other side effects associated with SNRIs result from their anticholinergic and antihistamine properties and include the following:

- Sedation.
- Dry mouth.
- Constipation.

- Dizziness (due to orthostatic hypotension).
- Blurred vision.
- Urinary retention.

The precise underlying mechanisms of these side effects remain unknown. Other side effects of SNRIs include dose-related diastolic hypertension and increased risk of cardiovascular side effects, primarily resulting from their noradrenergic effects. For this reason, a baseline electrocardiogram (ECG) is recommended in some cases. SNRIs are also associated with increased risk of headaches and excessive sweating. Certain SNRIs, specifically venlafaxine and desvenlafaxine, are known to treat hot flashes associated with menopausal symptoms. Similar to SSRIs, SNRIs also carry a risk of serotonin syndrome and serotonin discontinuation syndrome with abrupt discontinuation.

Tricyclic antidepressants

Similar to SNRIs, TCAs also increase levels of both 5-HT and NE in the synapse by blocking reuptake of these neurotransmitters by their respective transporters. TCAs are converted to secondary amine metabolites by demethylation in the liver. Both the primary amines and their secondary amine metabolites are active compounds. The secondary amine active metabolites of imipramine (desipramine) and amitriptyline (nortriptyline) are much more potent NE reuptake inhibitors.

TCAs are not commonly used as first-line agents due to high risk of cardiotoxicity and neurotoxicity, including risk of seizures. Use of TCAs requires extreme caution because overdoses of even small amounts can be fatal. A baseline ECG is recommended to evaluate for preexisting cardiac conduction abnormalities. Other side effects include risk of weight gain and anticholinergic effects. These side effects are more prominent with TCAs than SNRIs.

TCAs are primarily used as adjuncts in the treatment of refractory depression and in the treatment of comorbidities such as headaches, neuropathy, and insomnia. TCAs also carry a risk of serotonin syndrome and serotonin discontinuation syndrome with abrupt discontinuation.

Serotonin discontinuation syndrome

A discontinuation syndrome has been associated with stoppage of serotonergic antidepressants, both SSRIs and SNRIs.[14] This syndrome is particularly associated with abrupt discontinuation of these medications but can occur in certain cases even with gradual taper. The syndrome includes symptoms such as:

- Dysphoric mood.
- Anxiety.
- Headaches.
- Dizziness.
- Confusion.
- Agitation.
- Sensory disturbances (such as paresthesia).
- Insomnia.
- Autonomic instability and seizures in rare cases.

The syndrome is generally self-limiting but in rare cases requires medical attention. The treatment may include re-initiation of serotonergic medications at lower dosages, with gradual taper of these medications over a longer period. Gradual tapering of all serotonergic medications, especially medications with short half-lives such as paroxetine, is strongly recommended to avoid discontinuation syndrome. When taper schedules are recommended, it is also critical to consider individual patient factors such as history of discontinuation syndromes.

Serotonin syndrome

Serotonin syndrome [15] can result from a high dose of one serotonergic medication. More frequently, it is caused by inadvertent concomitant use of two or more serotonergic medications (e.g., serotonergic antidepressants with tramadol, fentanyl, triptans, St. John's wort, or monoamine oxidase inhibitors [MAOIs]). This syndrome may include the following:

- GI symptoms (e.g., nausea, vomiting, and diarrhea).
- Neuromuscular symptoms (e.g., rigidity, tremors, myoclonus, and hyperreflexia).
- Autonomic instability in extreme cases (e.g., labile blood pressure, tachycardia, hyperthermia, and flushing).
- Mental status changes in extreme cases (e.g., agitation, delirium, and coma).

Careful review of all medications is recommended before any serotonergic medication is added to a patient's medication regimen.

Norepinephrine-dopamine reuptake inhibitors

Bupropion is the only medication with this mechanism of action. It blocks the dopamine transporter while its primary metabolite, 6-hydroxybupropion, is a potent NE reuptake inhibitor. Bupropion may be more effective in the treatment of atypical depression (i.e., depression with fatigue and hypersomnia). It is a unique alternative to SSRIs and SNRIs for treating persons with depression and cancer, especially when depression is accompanied by fatigue. Unlike serotonergic antidepressants, bupropion is not associated with sexual dysfunction; therefore, it may be useful in treating patients who wish to remain sexually active and those who have experienced sexual dysfunction with other antidepressants.

Bupropion is available in three formulations based on frequency of administration:[16]

- Immediate release (three times daily).[17]
- Sustained release (twice daily).[18]
- Extended release (once daily).[19]

The sustained- and extended-release formulations are used more frequently because of the ease of administration and less risk of certain side effects, such as anxiety and seizures. The risk of seizures with bupropion is low but can be increased substantially by predisposing factors such as the following:[16-19]

- History of seizures.
- Head trauma.
- Brain tumor.
- Eating disorders.

Bupropion should be avoided in patients with malignant diseases involving the brain and histories of cranial trauma or seizure disorder,[16] **and it is contraindicated in people with a history of bulimia.**[20][Level of evidence: II] Other potential side effects with bupropion include anxiety and insomnia.

Antidepressants with mixed pharmacological properties

The antidepressants in this category have multiple pharmacological properties, including combinations of blockade of monoamine transporters and direct receptor agonist or antagonist properties.[7,13]

Mirtazapine

Mirtazapine is an alpha-2 adrenergic receptor antagonist, blocks

several serotonin receptors (5-HT_{2a}, 5-HT_{2c}, and 5-HT_3), and is a potent H_1 histamine receptor antagonist. Its blockade of presynaptic alpha-2 adrenergic receptors causes the release of NE which, in turn, causes the release of 5-HT. This increase in NE and 5-HT and blockade of 5-HT_{2c} and 5-HT_3 receptors have been associated with mirtazapine's antidepressant effects. The potent antihistaminic effects of mirtazapine can cause significant sedation; in addition, its blockade of histaminic and 5-HT_{2c} receptors has been associated with increased appetite/weight gain, and its blockade of 5-HT_3 receptors causes mild antiemetic effects. Mirtazapine has minimal risk of drug-drug interactions because it does not have significant impact on cytochrome P450 enzymes. The sedation and increased appetite/weight gain side effects can be beneficial in patients with cancer struggling with insomnia and cachexia.

Mirtazapine is frequently used for cancer patients, specifically for the treatment of depression with comorbid insomnia and weight loss. It is also useful in this patient population because of the following:

- Minimal risk of drug-drug interactions.
- Mild antiemetic effects.
- Minimal impact on sexual function.

Mirtazapine is associated with agranulocytosis/neutropenia and increased liver enzymes in rare cases. Monitoring of blood counts and liver enzymes is necessary, especially when patients are at risk of these side effects because of comorbid conditions and other cancer treatments. In rare cases, mirtazapine carries the risk of serotonin syndrome, primarily when taken in combination with other potent serotonergic medications; it is not associated with serotonin discontinuation syndrome. For more information, see the Serotonin syndrome section.

Trazodone

Trazodone is a 5-HT_{2a} and 5-HT_{2c} receptor antagonist and weak serotonin reuptake inhibitor. It can be very beneficial as an adjunct in the treatment of depression with comorbid insomnia and anxiety. It has potent sedative effects even at low dosages because of its blockade of histamine, 5-HT_{2c} receptors, and alpha-1 receptors. Trazodone is primarily used at low dosages (25–150 mg) to treat insomnia with or without depression/anxiety. Only high dosages (150–600 mg) of trazodone are associated with antidepressant effects. However, such high dosages carry a high risk of side effects, especially risk of significant daytime sedation, dizziness due to orthostatic hypotension, and other cardiovascular risks.

MAOIs

MAOIs increase all three monoamines (dopamine, serotonin, and NE) simultaneously because of their inhibition of MAO enzymes. The older MAOIs cause irreversible inhibition of both MAO-A and MAO-B enzymes. These medications can be highly effective, especially in the treatment of refractory depression and anxiety symptoms. However, MAOIs are primarily used as last resort because of their risk of serious side effects, multiple drug-drug interactions, and the significant dietary restrictions patients must adhere to when using these medications.

Several classes of medications are contraindicated or used with extreme caution with MAOIs because of the risk of serious and even lethal interactions due to serotonin syndrome and hypertensive crisis. Such classes of medications include the following:

- Sympathomimetics.
- Anesthetics.
- Other noradrenergic agents.

- Serotonergic agents.
- Dopaminergic agents.

Opioids with serotonergic properties, such as meperidine and methadone, should also be avoided with MAOIs. Patients taking MAOIs must follow strict dietary restrictions to avoid potentially fatal hypertensive crises. Avoiding foods that contain significant amounts of tyramine (e.g., aged cheese and meats) is critical when these medications are taken. The hypertensive crisis with MAOIs is related to the rapid increase in NE levels because of lack of tyramine processing by the MAO enzymes. Other common side effects include orthostatic hypotension, dizziness, anticholinergic side effects, and headaches.

MAOIs include selegiline, phenelzine, and tranylcypromine. Selegiline, a reversible MAOI, is available as a transdermal patch. At low dosages, it is primarily a selective MAO-B inhibitor and therefore does not require dietary restrictions (up to 9-mg doses). Because of selegiline's transdermal delivery, at higher doses it still bypasses most of the MAO-A enzyme in the gut while inhibiting both MAO-A and MAO-B in the brain needed for antidepressant effects. However, patients receiving high doses are required to follow dietary restrictions because of the potential for inhibition of MAO-A enzyme in the gut. Higher doses carry warnings for drug-drug interactions and other side effects similar to those for older MAOIs.

In patients with cancer, the use of MAOIs is limited to highly refractory cases due to additional cancer and cancer treatment–related risk factors (e.g., cardiovascular comorbidities due to certain cancer treatments and the use of pain medications such as tramadol and methadone). In most cases, MAOIs are prescribed and managed by psychiatric clinicians in this patient population because of the multiple risks noted earlier. At a minimum, significant involvement of psychiatric prescribers and

pharmacy consultation are strongly recommended during initiation and management of MAOIs.

Augmentation strategies

A patient may show improvement with the primary antidepressant treatment, but this improvement may be inadequate from a clinical standpoint because of significant residual symptomatology affecting the patient's well-being and functioning. In such cases, certain augmentation strategies may be helpful.[21] However, before any augmentation strategies are considered, it is critical to ensure the adequacy of the primary antidepressant, especially in terms of dosing and duration. Selection of the augmentation strategy is driven by residual or comorbid symptomatology. The following sections describe certain augmentation agents and strategies.

Benzodiazepines

Benzodiazepines can be used to effectively treat the anxiety that may be associated with depression. In patients receiving antidepressant medications and benzodiazepines concomitantly, the latter drugs may be discontinued after patients' depressive symptoms begin to abate; however, both agents can be continued safely if needed. Benzodiazepines cannot be stopped abruptly because withdrawal symptoms with possible seizures may occur. The dose of benzodiazepines is tapered slowly, at a rate of approximately 25% every 3 to 4 days.

Psychostimulants

Clinical experience suggests that analeptic agents (e.g., methylphenidate and dextroamphetamine) are useful at low doses for patients whose symptoms include the following:[22] [Level of evidence: II]

- Depressed mood.
- Apathy.

- Decreased energy.
- Poor concentration.
- Weakness.

These agents are usually prescribed at low dosages and as adjuncts to antidepressants. Analeptic agents are particularly useful for patients with advanced cancer who have a limited life expectancy (weeks to a few months). Psychostimulants often demonstrate antifatigue effects within a few days of starting treatment. They can be helpful in countering the sedating effects of opioids.

Adverse effects associated with analeptic agents include neuropsychiatric side effects such as insomnia, mood lability, anxiety, agitation, anorexia, and even psychotic symptoms. They are also associated with adverse cardiovascular effects such as hypertension and arrhythmia. A baseline ECG is recommended. These medications can also lower the seizure threshold. Finally, there is a risk of developing tolerance, misuse, and dependence on these medications. Considering risks and benefits is critical when the use of these medications is being contemplated. These medications, in appropriate cases and when used in optimal dosages, can have a significant positive impact on a patient's quality of life, especially for those with advanced cancers.

Adjunctive medications to treat medical and psychiatric comorbidities

Medical and psychiatric comorbidities (e.g., neuropathy, menopausal symptoms, and trauma symptoms) may play a role in depression severity. Such conditions frequently have a bidirectional interaction with depression, with one exacerbating the other and vice versa. Medications other than antidepressants that can treat medical/psychiatric comorbidities may play a crucial role in the management of depression in patients with psychiatric comorbidities. For example, gabapentin

can be used as an adjunct to antidepressants to target comorbid neuropathic pain, menopausal symptoms, and anxiety symptoms.

Adjunctive medications in treatment-refractory cases

Evidence from the noncancer (general psychiatry) literature suggests a role for other medications and medication classes as adjuncts to antidepressants in treatment-refractory cases.[21] Such medications and medication classes include the following:

- Antipsychotic medications.
- Thyroid hormone.
- Lithium.
- Buspirone.
- Certain combination strategies for different antidepressant classes.

Buspirone is primarily used as an adjunct to treat comorbid anxiety symptoms. Some of these medications (e.g., antipsychotic medications and lithium) are associated with a significant burden of side effects. Referral to and/or extensive involvement of psychiatric clinicians is strongly recommended for treatment-refractory cases, especially if these medications and medication classes are considered as adjuncts.

Antidepressant medication selection and management

Several general, cancer-related, and cancer treatment–related factors play an important role in the choice and management of antidepressants in cancer patients.[23,24] The general risks-benefits-alternatives principle is even more crucial in the selection of depression treatment for this patient population. Furthermore, full informed consent and patients' active involvement in decisions about their treatments is critical in the

selection and management of depression treatment and for the success of any antidepressant trial.

Targeting symptoms

The predominance or lack of specific symptoms of depression (e.g., fatigue, insomnia, and cognitive difficulties) and related psychiatric comorbidities (e.g., anxiety disorders) play a role in the selection of an antidepressant.[24] For example, patients with fatigue as the predominant part of their depressive symptomatology may benefit from a trial of bupropion. The side effects of antidepressants may be clinically advantageous in some cases. For example, the sedation and weight gain associated with mirtazapine or certain TCAs may benefit depressed patients with comorbid insomnia and weight loss.

Avoiding side effects

Patients with cancer frequently struggle with multiple physical and psychological adverse effects related to their cancer and cancer treatments. It is critical to select antidepressants to avoid further worsening of their health status, either by addition of side effects due to antidepressants or exacerbation of existing issues. For example, patients with cancer may be struggling with issues concerning their sexual function. Antidepressants exacerbating sexual dysfunction can heighten distress, which can worsen depression. Some patients may struggle with the GI side effects of their cancer and cancer treatments. Certain antidepressants with known risks for significant GI side effects such as nausea and diarrhea (e.g., sertraline and duloxetine) may need to be avoided in these patients.

Medical comorbidities

The presence or absence of certain medical comorbidities can drive antidepressant selection.[24] For example, medications such as citalopram, which carries a warning about QTc prolongation, or potent noradrenergic antidepressants such as

levomilnacipran may need to be avoided in patients with significant cardiovascular comorbidities. In patients with depression with comorbid chemotherapy-related neuropathy, duloxetine may be beneficial because it targets both depression and neuropathic symptoms. Similarly, patients with depression and menopausal symptoms may benefit from a trial of venlafaxine because it is known to treat both.

Antidepressant pharmacology

Antidepressants, even from the same class, can have significant pharmacological differences. They can differ in their absorption; half-lives, including half-lives of their active metabolites; and metabolism via an impact on different cytochrome P450 enzymes. These differences can play an important role, depending on cancer types and cancer treatments.

Concomitant medications

Consideration of pharmacodynamic and pharmacokinetic interactions with concomitant medical and psychiatric medications is critical when an antidepressant is being contemplated. For example, highly sedating antidepressants, such as mirtazapine, are not desirable in combination with sedating concomitant medications, such as opioids and benzodiazepines. Potent 2D6 cytochrome P450 enzyme inhibitors, such as paroxetine and duloxetine, are not recommended for patients receiving tamoxifen because of concerns about their impact on the efficacy of tamoxifen (because of the inhibition of tamoxifen's conversion to endoxifen, its active metabolite).

Antidepressant trials for patient and biological family members

Information collected from patients and family members about experience with antidepressants (i.e., positive responses or negative experiences such as side effects) can be crucial in the

selection of an antidepressant. Genetic background (e.g., serotonin transporter polymorphism) shared by the patient and biological family members may play a role in responsiveness to specific medications or medication classes. Information about successful or failed antidepressants for biological family members can play an important role in antidepressant selection.

Formulations

The availability of antidepressant formulations may play a crucial role in antidepressant selection for certain patient populations with cancer. For example, patients with head and neck cancers may have difficulty swallowing because of the disease, its treatment, or both. In such cases, the use of antidepressants in liquid form (e.g., citalopram and fluoxetine) or parenteral form (e.g., amitriptyline injection) may be necessary.

Bioavailability

Certain cancers can affect medication absorption (e.g., GI cancers) or metabolism (e.g., liver and kidney cancers). Antidepressant selection may therefore be driven by the pharmacokinetic profile of individual antidepressants to circumvent any issues. In some cases, antidepressant dosages may need to be adjusted beyond recommended guidelines to derive maximum therapeutic benefit.

Initial titration and management

Generally, there is a long latency period (3–6 weeks) from initiation of antidepressant medications to the onset of a therapeutic response.[13] Antidepressant treatment begins at low doses, followed by a period of gradual dose titration to achieve an optimum individualized response. Initial low doses may help to avoid initial side effects, but dose escalation may be required to produce therapeutic effects. For some agents, there is a therapeutic window during which plasma concentrations correlate with a patient's response to the antidepressant (e.g.,

nortriptyline). For patients receiving these agents, serial drug concentration monitoring guides therapy and helps provide an adequate therapeutic trial because plasma concentrations lower and higher than the defined therapeutic ranges are associated with treatment failure, suboptimal responses and, in the case of high drug concentrations, unnecessary toxicity.

It is recommended that an antidepressant be continued for at least 1 year for a major depressive episode. Continuation of an antidepressant beyond 1 year depends on several factors, including a patient's psychological status at that time, their psychiatric history, their cancer and cancer treatment status and, more important, their thoughts about and experience with the antidepressant. As in the initiation, decisions are individualized according to the risks-benefits-alternatives principle and patient choice.

Switching or discontinuing antidepressants

Switching from one antidepressant to another or discontinuing antidepressants is frequently indicated because of intolerable adverse effects or lack of treatment response. Several factors play a role in the strategies employed during switching or stopping an antidepressant. These factors are primarily driven by the risk of serotonin syndrome (see the Serotonin syndrome section for more information) and serotonin discontinuation syndrome (see the Serotonin discontinuation syndrome section for more information). Such factors include antidepressant-dependent factors and patient- or illness-related factors:[25,26]

Antidepressant-dependent factors

- Half-life of the antidepressant (i.e., shorter half-life is associated with higher risk of withdrawal symptoms).
- Antidepressant dose (i.e., higher dose needs a longer taper period).

- Duration (i.e., longer duration of antidepressant use may need a longer taper period).

Patient- or illness-related factors

- History of withdrawal symptoms with discontinuation of antidepressants.
- History of heightened sensitivity to medication side effects.
- Severity of psychiatric symptomatology (i.e., more caution is needed with higher severity).
- Medical and physical comorbidities.
- Concomitant medications.

Generally, when antidepressants are switched, either (1) discontinuing one antidepressant followed by initiating the new one or (2) gradual cross-tapering between the two antidepressants is recommended. However, given the lack of controlled evidence, the switching strategy is highly individualized and driven by the pharmacological properties of both antidepressants and specific patient- and illness-related factors.[27] There are differing opinions about the exact duration and schedule of dose titration because of the lack of evidence from controlled trials in this area.[27]

Switching from a serotonergic antidepressant with a longer half-life (or one that has an active metabolite with a longer half-life, e.g., fluoxetine) to another serotonergic antidepressant may carry the risk of developing serotonin syndrome, depending on when one medication is stopped and the second one is started. The risk of serotonin syndrome in these cases will also depend on the doses of both medications and the schedule of cross-taper.[27] For more information, see the Serotonin syndrome section.

For the discontinuation of serotonergic antidepressants, it is

strongly recommended that antidepressants be tapered gradually to minimize the risk of serotonin discontinuation syndrome. For more information, see the Serotonin discontinuation syndrome section.

As with switching antidepressants, specific medication-related factors and patient- or illness-related factors need to be considered when patients are tapered off antidepressants, but the precise taper strategy is highly individualized. The half-life of antidepressants is a critical factor in stopping antidepressants. Generally, the shorter the half-life of an antidepressant, the higher the risk of discontinuation syndrome. See Table 4 for a list of antidepressants and the risk of serotonin discontinuation syndrome.

Table 4. Antidepressants and Risk of Serotonin Discontinuation Syndrome

Agent	Risk[a]	Comment(s)
SSRIs		
Citalopram	++	
Escitalopram	++	
Fluoxetine		Very long half-life; generally, no taper required
Fluvoxamine	++	
Paroxetine	+++	

Sertraline	++	
Vilazodone	++	
SNRIs		
Desvenlafaxine	+	~2% risk
Duloxetine	++	
Levomilnacipran	++	
Venlafaxine	+++	
TCAs		
Clomipramine	++	Most serotonergic TCA
Other TCAs	+	
Other antidepressants		
Bupropion		Minimal to no risk
MAOIs		
Mirtazapine		Minimal to no risk

Trazodone		Doses <150 mg/d carry minimal to no risk

MAOI = monoamine oxidase inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; + = low risk; ++ = moderate risk; +++ = high risk.

[a]Risk based on half-life of antidepressant.

Educating patients about what to expect, close clinical monitoring, and frequent reassurance are crucial during the switching or discontinuing of antidepressants. Consultation with pharmacy or psychiatric services is generally recommended for switching or stopping. In a minority of cases, despite gradual tapering, patients may experience severe withdrawal symptoms, sometimes lasting several weeks. In such cases, immediate consultation with psychiatric services is strongly recommended.

Interferon-related depression

Most antidepressant prescribing is directed at the treatment of an existing depressive disorder or significant depressive symptoms. However, one study supports the use of antidepressants to prevent depression in patients receiving high-dose interferon for adjuvant therapy of malignant melanoma. [28][Level of evidence: I] The rationale for this approach is that treatment with high-dose interferon is associated with a particularly high rate of depression in this patient population, and proinflammatory cytokines implicated in the biological changes that result in depression may be directly reduced by antidepressants.

In a double-blind study of patients receiving high-dose interferon, 2 of 18 patients in the paroxetine group developed depression during the first 12 weeks of therapy, compared with 9 of 20 patients in the placebo group (relative risk [RR] = 0.24;

95% confidence interval [CI], 0.08–0.93). Moreover, there were significantly fewer treatment discontinuations in the paroxetine group (5% vs. 35%, RR = 0.14; 95% CI, 0.05–0.85).[28] Further study is required to confirm these findings and to determine whether prophylactic use of antidepressants has benefit in other treatment settings.

Suicide risk of antidepressant medications

Over the past few years, significant concerns have been raised about the risk of suicidal thinking and behavior with the use of antidepressants in children, adolescents, and young adults. In October 2004, the U.S. Food and Drug Administration (FDA) mandated pharmaceutical companies to add a boxed warning to the labeling of all antidepressants suggesting increased risk of suicidality in pediatric patients who were taking antidepressants. The FDA revised this boxed warning in May 2007 to include young adults younger than 25 years.[29] The carefully worded revision emphasized that the risk of suicidality is associated with both antidepressants and depression. In addition to raising concerns about increased suicidality in children, adolescents, and young adults, the warning acknowledged a significant protective effect of antidepressants in adults aged 65 years and older.

The meta-analysis that led to the initial boxed warning in pediatric patients concluded that the antidepressants are associated with a twofold increase in suicidal ideation and behavior compared with the placebo in children and adolescents.[30] A major meta-analysis published in the *Journal of the American Medical Association* re-analyzed the data from the child and adolescent studies (including seven studies not included in the initial meta-analysis), using a random-effects model.[31][Level of evidence: I] While this re-analysis found an overall increased risk of suicidal ideation/suicidal behavior consistent with the initial meta-analysis, the pooled risk

differences were found to be smaller and statistically insignificant.

Concerns have been raised that the unintended consequence of the warnings will be overly restricted use of antidepressants among those who benefit the most and, hence, an increase in suicidality that the warning seeks to prevent.

In summary, the risks-benefits-alternatives principle favors appropriate use of antidepressants with careful monitoring for suicidality. None of the studies that led to the boxed warning included or focused on patients being treated for cancer. Clinical experience and results of small clinical trials suggest that antidepressants can be safely administered to adult cancer patients, although there are no large controlled clinical trials to support this position. When antidepressants are prescribed for patients with cancer, implementation of a careful monitoring plan should be considered by individuals with expertise, and consultation referral made for patients who do not respond as anticipated or who present other concerns.

Psychotherapy

Overview

Traditionally, depressive symptomatology was managed with insight-oriented psychotherapy, which is quite useful for some people with cancer. For many other people, these symptoms are best managed with some combination of crisis intervention, brief supportive psychotherapy, and cognitive-behavioral techniques.

Psychotherapy for depression has been offered in a variety of forms. Most interventions have been time limited (range, 4–30 hours), have been offered in both individual and small-group formats, and have included a structured educational component about cancer or a specific relaxation component.[32]

Cognitive-behavioral psychotherapy has been one of the most prominent types of therapies studied. Cognitive-behavioral interventions focus on the following:

- Altering specific coping strategies aimed at improving overall adjustment.
- Specific thoughts and their relationship to emotions and behaviors.

Understanding and altering one's thoughts can change emotional reactions and accompanying behaviors. For example, frequent, intrusive, uncontrollable thoughts about loss, life changes, or death can cause poor concentration and precipitate feelings of sadness, guilt, and worthlessness. In turn, these feelings can result in increased sleep, withdrawal, and isolation. A cognitive-behavioral intervention focuses on the intrusive thoughts, often challenging their accuracy or rationality and noting specific patterns of cognitive distortions. Simultaneously, patients develop specific cognitive coping strategies that are designed to alter emotional reactions and accompanying behaviors. The result is improved coping, enhanced adjustment, and better overall quality of life.

Other goals of psychotherapy include:[33][Level of evidence: II]; [34-36][Level of evidence: I];[37]

- Enhancing coping skills.
- Directly reducing distress.
- Improving problem-solving skills.
- Mobilizing support.
- Reshaping negative or self-defeating thoughts.
- Developing a close personal bond with a knowledgeable, empathic health care provider.

Consultation with a cleric or a member of a pastoral care department may also help some individuals.

Specific goals of these therapies include the following:

- Assist people with cancer and their families by answering questions about the illness and its treatment, clarifying information, correcting misunderstandings, giving reassurance, and normalizing responses to the illness and its effect on patients' families. Explore the present situation with the patient and how it relates to his or her previous experiences with cancer.
- Assist with problem solving, bolster the patient's usual adaptive defenses, and help the patient and family develop further supportive and adaptive coping mechanisms. Identify maladaptive coping mechanisms and assist the family in developing alternative coping strategies. Explore areas of related stressors (e.g., family role and lifestyle changes), and encourage family members to support and share concerns with each other.
- When the focus of treatment changes from cure to palliation, strongly reinforce that, although curative treatment has ended, the team will aggressively treat symptoms as part of the palliation plan; the patient and family will not be abandoned; and staff members will work very hard to maintain comfort, control pain, and maintain the dignity of the patient and his or her family members.

Cancer support groups can be useful adjunctive therapies in the treatment of cancer patients.[38][Level of evidence: II] Support group interventions have demonstrated the following:[39]

- Significant effects on mood disturbance.
- Use of positive coping strategies.
- Improvement in quality of life.

- Positive immune responses.

Support groups can be found through the Cancer Support Community, the American Cancer Society, and many other community resources, including the social work departments of medical centers and hospitals.

Empirical studies of the efficacy of psychotherapy

Psychotherapy as a treatment for depression in the general adult mental health population has been extensively researched and found to be effective.[40] Reviews have also concluded that psychotherapy is an effective intervention for cancer patients experiencing depression.[41][Level of evidence: II];[32] In studies designed to prevent the occurrence of depression (i.e., patients not selected because of their depressive symptoms), intervention effects are positive, although small to moderate effect sizes have been reported (effect size range, 0.19–0.54).[32] However, in those studies in which patients were intentionally selected because they exhibited depressive symptoms, intervention effects were strong (effect size, 0.94).[41] An effect size of 0.94 indicates that the average patient in the treatment group was advantaged, compared with approximately 82% of patients in the control group.

One well-designed randomized clinical trial of a cognitive-behavioral intervention for depressed cancer patients investigated the effect of problem-solving training on symptoms of depression.[42][Level of evidence: I] The intervention consisted of 10 1.5-hour weekly individual psychotherapy sessions focused on training to become an effective problem solver. Problem-solving tasks were emphasized, including skills in the following aspects:

- Better defining and formulating the nature of problems.
- Generating a wide range of alternative solutions.

- Systematically evaluating consequences of a solution while deciding on an optimal one.
- Evaluating outcome after solution implementation.

Between-session homework with tasks relevant to each step was assigned, and patients were provided with a written manual and encouraged to refer to it as problems arose. One hundred thirty-two adult cancer patients were randomly assigned to the problem-solving treatment (PST), PST with a significant other, or a wait-list control. Overall results showed that PST (alone or with a significant other) improved problem-solving abilities and clinically significantly decreased symptoms of depression.[42]

A potential intervention to address depression in survivors is mindfulness meditation and survivorship education. In a randomized clinical trial of 247 younger breast cancer survivors, compared with a wait-list control group, both groups had decreased depression from preintervention to postintervention.[43][Level of evidence: I] Notably, the improvements were maintained 6 months postintervention. The mindfulness meditation group also showed improvements that were sustained over 6 months for fatigue, insomnia, and vasomotor symptoms (e.g., hot flashes and night sweats). These types of interventions may be beneficial for other cancer populations.

Physical Activity

Physical activity for the management of depressive symptoms in individuals who completed treatment for breast cancer was studied in the Physical Activity for Cancer Survivors (PACES) randomized clinical trial. The trial included 336 participants, 3 months to 10 years after treatment for breast cancer, who were assessed to be insufficiently physically active (i.e., <150 min/wk engagement in moderate-to-vigorous physical activity).[44][Level of evidence: I] Using the block randomization method, participants were assigned into one of 16 cohorts, whose

interventions ranged from receiving physical activity educational materials only (all participants) to the full cadre of PACES intervention components: educational materials, active living every day (ALED; 12 biweekly educational sessions), facility access (i.e., 6-month local fitness facility membership), Fitbit wearable device, and supervised exercise. A linear mixed-effects model using the self-rate Quick Inventory of Depression Symptomology as the outcome measure was used in the analyses. Depressive symptoms improved over time for all participants. The greatest improvement was for the ALED intervention component. This study provides some evidence that engagement in physical activity, especially through a supportive educational program such as ALED, may benefit individuals with depressive symptoms who have completed treatment for breast cancer.

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Suicide Risk in Cancer Patients

Demographics and Statistics

Epidemiological studies conducted across several countries indicate that cancer is a risk factor for suicide.[1-3][Level of evidence: III] One retrospective cohort study (N = 3,594,750) found that patients with cancer had nearly twice the incidence of suicide as the general population.[1] Another study (N = 6,754,704) found suicide rates three times higher than in the general population, and up to ten times higher in people with cancers with poorer prognosis, e.g., pancreatic cancer.[4] Increased rates of suicidal ideation, suicidal behaviors, and suicide attempts have been documented in patients with cancer compared with the general population.[3][Level of evidence: III]; [5,6] The actual incidence of suicide in cancer patients is probably underestimated because there may be reluctance to report death by suicide in these circumstances and because of methodological issues related to the validity of suicide statistics. [7]

It is important to distinguish among suicidal ideation, attempted suicide, and actual suicide in assessing patients at greatest risk. Suicidal ideation is loosely defined as having thoughts, ideas, contemplation, wishes, and preoccupation with death and suicide. Some patients may have passive suicidal ideation, which is a general wish to end one's life without an actual plan. A suicidal attempt is a planned and initiated suicide that does not result in death. An actual suicide is death through self-inflicted injury.[8]

Certain clinical and sociodemographic risk factors for suicide have been identified in patients with cancer.[3][Level of evidence: III];[9]

Gender

As in the general population, suicide risk is higher in male patients with cancer than in female patients.[3][Level of

evidence: III] In adolescents and young adults (AYAs), however, suicide risk is higher in female patients, according to a study using Surveillance, Epidemiology, and End Results (SEER) Program data.[10][Level of evidence: III] Risk of suicide was measured by calculating the standardized mortality ratio (SMR) and odds ratio (OR). Specifically, the SMR is a percentage of the number of deaths (by suicide in this analysis) among the expected age- and sex-specific rates of death in a standard population. The OR was calculated for demographic and clinical factors associated with actual suicides in the AYAs. Of note, actual suicides were greater among male AYAs, consistent with the adult population.

Age and marital status

Older age is another significant risk factor for suicide in patients with cancer. One group of investigators found that suicide risk increased with age, with older men at the highest risk.[1] This study found that the age-adjusted suicide rate was 52.4 per 100,000 person-years among patients aged 80 to 84 years, compared with 22.0 per 100,000 person-years for the same age group in the general population. Notably, the suicide rate for men with cancer in this age group was substantially higher (100.3 per 100,000 person-years) than the suicide rate for women. Race and marital status also played an important role. Single, divorced, or widowed White men had a higher suicide risk than other patient populations.[11]

Social and structural health determinants

Suicide risk also differs by social and structural health determinants. An investigation of more than 5.3 million individuals with cancer across 635 counties included in the SEER 18 database found that among the 6,357 of these individuals who died of suicide, the SMR of suicide among those in the lowest-income counties, compared with those in the highest-income counties, was significantly higher (SMR, 1.94; 95%

confidence interval [CI], 1.76–2.13 vs. SMR, 1.30; 95% CI, 1.26–1.34).[12][Level of evidence: III] Similarly, compared with individuals with cancer in urban counties (SMR, 1.35; 95% CI, 1.32–1.39), those in rural counties had a higher SMR of 1.81 (95% CI, 1.70–1.92). In addition, the suicide rates among individuals with cancer were higher in counties that had lower educational levels, greater unemployment rates, and a higher percentage of Black residents.

Time since diagnosis

Another consistent risk factor is related to the time since diagnosis. Studies have consistently found higher risk of suicide in the first year after diagnosis, especially in the first 6 months.[3][Level of evidence: III];[4,13,14] Generally, this risk declines over time. However, for certain cancer types, there is evidence of increased long-term suicide risk many years after the diagnosis.[2]

Poorer prognosis, nonlocalized disease, and aggressive or advanced cancer with a survival rate of fewer than 5 years have been found to be closely associated with higher suicide risk early after cancer diagnosis, with an even greater risk in populations with higher baseline risk factors (male, White race, aged 60 years and older).[4,9]

Cancer types

Certain cancer types have been associated with higher suicide risk, including the following:[1,14-17][Level of evidence: III]

- Pancreatic cancer.
- Head and neck cancer.
- Bladder cancer.
- Lung cancer.
- Cancers of the upper digestive tract.

- Brain cancer.
- Cervical cancer.

In addition, veteran survivors with head and neck cancer are at a particularly high risk for suicide. In a study of 7,803 U.S. veteran survivors of head and neck cancer (98.4% male; mean age, 65 years), the rate of suicidal self-directed violence was 922.7 per 100,000.[16][Level of evidence: III] The rate of death by suicide was 653.6 per 100,000. These rates far exceed those associated with male sex and older age.[1] Veterans treated for head and neck cancer should be screened for suicidal risk.

Comorbidities

Certain comorbidities have also been associated with higher suicide risk, including the following:[18,19]

- Substance use disorder.
- Cancer-related pain.
- Comorbid psychiatric illness, specifically depression and anxiety.

In a study of Japanese patients (n = 220) who had cancer and who were diagnosed with major depression after being referred for psychiatric consultation, approximately 50% reported suicidal ideation. In a retrospective analysis of predictors of suicidal ideation, researchers found that those with more symptoms of major depression and poorer physical functioning were significantly more likely to report suicidal ideation.[20]

Summary of Risk Factors

Risk factors for suicide in the cancer population are as follows:[21]

- Sociodemographic factors:

- Male sex.
- Older age.
- Single, divorced, or widowed status.

- Medical factors:
  - Advanced-stage, nonlocalized, or aggressive disease.
  - Poor prognosis (survival rate <5 years).
  - Recent cancer diagnosis (highest risk within 3–5 months after diagnosis).
  - Cancer site such as prostate, lung, head and neck, and pancreas.
  - Physical symptoms such as uncontrollable pain.
  - Decreased function and performance status.
  - Inadequately controlled pain.

- Psychiatric and psychosocial factors:
  - Comorbid depression or anxiety.
  - Feelings of hopelessness.
  - Demoralization.
  - Aggression; lack of therapeutic alliance with treatment team.
  - Preexisting psychopathology.
  - Comorbid substance use.
  - History of suicide attempts.
  - Family history of suicides.
  - Poor social support.
  - Loss of independence and feeling of being a burden; associated guilt.

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Assessment and Management of Suicidal Patients

Assessment

Suicide assessment occurs frequently along the cancer continuum. Components of suicide assessment include the following:[1-3]

- Evaluation of risk factors.
- Patient's mental state.
- Social context.
- Nonverbal signs of extreme distress or depression (such as poor eye contact, agitation, or excessive slowing of speech and movement).

Hopelessness is a powerful predictor of suicidal ideation and completed suicides in the general population and in cancer patients.[4] Certain suicide screening tools such as the following are used to screen for suicide risk in the general population and in patients with mental illness:[5]

- The Beck Hopelessness Scale.
- The Suicide Intent Scale.
- The Columbia-Suicide Severity Rating Scale.

However, these tools are not validated for cancer patients.[2]

Other complicating factors in suicide assessment include the demoralization syndrome and desire for hastened death.[6,7] The concept of demoralization syndrome involves persistent inability to cope with feelings of hopelessness, helplessness, and loss of meaning of life.[8] Demoralization syndrome can be assessed using the Demoralization Scale.[9] Evidence suggests that demoralization syndrome can be present with or without depression symptomatology in cancer patients.[10] A study conducted in Taiwanese patients (n = 200) found that demoralization was more predictive of suicidal ideation than was depression symptomatology.[6] The study found that the loss of meaning was a critical factor in the effect of demoralization on suicidal ideation.

The relationships between suicidal ideation and the desire for hastened death, requests for physician-assisted suicide and/or euthanasia are complex and poorly understood.[7,11] For more information, see the Requests for Hastened Death section in Last Days of Life. The desire for hastened death involves a hope for death to come quickly. Such a desire can be:[12,13]

- Psychopathological, as an expression of despair with an exit plan (idea of suicide).
- A socially driven desire to not be a burden to family or friends.
- A healthy process of closure, i.e., a manifestation of letting go.

Patients who are found to be suicidal require careful further assessment (see Table 5). The risk of suicide increases if the patient reports ideation (i.e., thoughts of suicide) plus a plan (i.e., description of the means). Risk continues to increase to the extent that the plan is lethal.[3] Lethality is determined by an

assessment of how likely death would follow, if the reported plan were carried out.

Factors to consider in assessing lethality include:

- Availability of the means.
- Reversibility of the means. (Once begun, can it be stopped?)
- Proximity of help.

For the cancer patient reporting suicidal ideation, it is essential to determine whether the underlying cause is the following:[7]

- A depressive illness.
- A desire for hastened death.
- An expression of the desire to have ultimate control over intolerable symptoms.

Prompt identification and treatment of major depression is essential in lowering the risk of suicide in cancer patients. Risk factors, particularly hopelessness (which is an even stronger predictive factor for suicidal ideation and completed suicides than is depression), requires careful assessment.[4] The assessment of hopelessness is not straightforward in the patient with advanced disease with no hope of cure. It is important to assess the underlying reasons for hopelessness, which may be related to poor symptom management, fears of painful death, or feelings of abandonment.[14]

Establishing rapport is of prime importance in working with suicidal cancer patients as it serves as the foundation for other interventions. The clinician must believe that talking about suicide will not cause the patient to attempt suicide. On the contrary, talking about suicide legitimizes this concern and permits patients to describe their feelings and fears, providing a sense of control.[2,7] A supportive therapeutic relationship is

maintained, which conveys the attitude that much can be done to alleviate emotional and physical pain. For more information, see Cancer Pain.

A crisis intervention–oriented psychotherapeutic approach that mobilizes as much of a patient's support system as possible is initiated.[2] Contributing symptoms (e.g., pain) are aggressively controlled and depression, psychosis, agitation, and underlying causes of delirium are treated.[2,7] These problems are most frequently managed in the medical hospital or at home. Although uncommon, psychiatric hospitalization can be helpful when there is a clear indication and the patient is medically stable.[2]

Table 5. Suggested Questions for the Assessment of Suicidal Symptoms in People With Cancer[a]

Questions	Assessment
Most people with cancer have passing thoughts about suicide such as, "I might do something if it gets bad enough."	Acknowledge normality by opening with a statement recognizing that a discussion does not enhance risk
Have you ever had thoughts like that? Any thoughts of not wanting to live or wishing your illness might hasten your death?	Level of risk
Do you have thoughts of suicide? Have you thought about how you would do it? Do you intend to harm yourself?	Level of risk

Have you ever been depressed or made a suicide attempt?	History
Have you ever been treated for other psychiatric problems, or have you been psychiatrically hospitalized before getting diagnosed with cancer?	History
Have you had a problem with alcohol or drugs?	Substance dependence
Have you lost anyone close to you recently? (Family, friends, others with cancer.)	Bereavement

[a]Adapted from Roth et al.[15]

Management

In clinical practice, the goal of management of suicidal patients is to attempt to prevent suicide that is driven by desperation due to poorly controlled symptoms. Prolonged suffering due to poorly controlled symptoms can lead to such desperation. Thus, effective symptom management is critical to decrease psychological distress in suicidal cancer patients.[2,7] Patients close to the end of life may be unable to maintain a wakeful state without high levels of emotional or physical pain. This frequently leads to suicidal thoughts or requests for aid in dying. Such patients may require sedation to ease their distress.

At times, it may be important to limit access to potentially lethal medications for patients considered at risk of suicide. When potentially lethal medications are limited, it is important to weigh the impact on symptom management against the impact on suicide risk because poorly controlled symptoms may contribute to risk. Furthermore, suicidal patients will often have other means available to complete suicide attempts and these

must also be evaluated. Strategies to lessen suicidal risk include frequent contact to reassess suicidal risk and symptom control, as well as regular delivery of limited quantities of medications facilitating rapid dose titration for effective management of poorly controlled symptoms when necessary. For patients receiving parenteral or intrathecal opioids, programmable pumps with limited access to programming and locked, inaccessible cartridges may provide an element of safety.

Strategies to lessen suicide risk in cancer patients include the following:

- Make a referral to a psychologist or other mental health professional.
- Use medications that work rapidly to alleviate distress (e.g., a benzodiazepine for anxiety or a stimulant for fatigue) while waiting for the clinical effects from antidepressant therapy.
- Pay scrupulous attention to symptom management.
- Limit access as appropriate to quantities of medications that are lethal in overdose and ensure that the family has a home-use naloxone kit in states/locations where available.
- Maintain frequent contact with and closely observe the patient.
- Avoid having the patient spend long periods of time alone.
- Mobilize support for the patient.
- Carefully assess the patient's psychological responses at each crisis point over the course of the disease.

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Considerations for Pediatric Depression

Information concerning the incidence of depression in healthy children is limited. One study of children seen in a general practice showed that 38% had problems that required major intervention by a psychiatrist. Another study of children aged 7 to 12 years showed a 1.9% incidence of depression. If applied to the general population of the United States, these results show that 40,000 12-year-olds are depressed. Teachers have estimated that as many as 10% to 15% of their students are depressed. The Joint Commission on Mental Health of Children states that 1.4 million children younger than 18 years need immediate help for disorders such as depression; only one-third of these children receive help for their disorder.[1]

Most children cope with the emotional upheaval related to cancer and demonstrate not only evidence of adaptation but

positive psychosocial growth and development. A minority of children, however, develops the following psychological problems:[2]

- Depression.
- Anxiety.
- Sleep disturbances.
- Difficulties in interpersonal relationships.
- Noncompliance with treatment.

These children require referral to and intervention by a mental health specialist.

In one of the first studies of depression in childhood cancer, 114 children and adolescents were studied, and 59% were found to have mild psychiatric problems.[3] A study of 17 adolescent and 21 pediatric oncology patients, all of whom were administered a self-report psychosocial life events inventory, showed that the adolescent samples had a mean level of depressive symptoms similar to that of the general population. The pediatric oncology sample demonstrated significantly lower depressive symptoms than the general population.[4][Level of evidence: II] Forty-one adolescent survivors of childhood cancer were assessed using questionnaires and interviews to determine the psychosocial status of the survivors; most survivors were functioning well, and depression was rare.[5]

A study of long-term cancer survivors and their mothers, comparing the survivors with a group of 92 healthy children, showed that most former patients were functioning within normal limits. Not surprisingly, children with severe late effects had more depressive symptoms.[6][Level of evidence: II] One researcher looked at the characteristics of psychiatric consultations in a pediatric cancer center and found that adjustment disorder was the chief psychosocial diagnosis. This

finding is similar to results obtained from studies of adult cancer patients. This study also found that anxiety reactions were more common in the younger pediatric patients, and depressive disorders were more common in older patients.[7] In a study conducted in 1988 with a sample of 30 adolescent cancer patients, the rate of major depression was not higher than the rate for the population at large.[8][Level of evidence: II] One review reported a 17% incidence of depression using the criteria of the *Diagnostic and Statistical Manual of Mental Disorders,* 3rd edition.[9]

Most cancer survivors demonstrate general resiliency and successful psychological adjustment to the disease and its treatment. Despite evidence for successful adaptation, most studies document psychological difficulties in a significant subset of cancer survivors.

Assessment and Diagnosis of Pediatric Depression

Assessment

The term *depression* refers to a symptom, a syndrome, a set of psychological responses, or an illness.[1] Duration and intensity of the behavioral manifestation (e.g., sadness) differentiates the symptoms from the disorder. For example, a sad affect can be a child's response to trauma and is usually of short duration; however, a depressive illness is characterized by long duration, and is associated with the following:

- Insomnia.
- Irritability.
- Changes in eating habits.
- Severe impairment of the child's scholastic and social adjustment.

Depression should be considered whenever any behavior problem persists. Depression does not refer to transitory moments of sadness, but rather to a disorder that affects development and interferes with realization of the child's innate potential.[1]

Some manifestations of depression in a school-aged child include the following:[1]

- Anorexia.
- Lethargy.
- Sad affect.
- Aggression.
- Weeping.
- Hyperactivity.
- Somatization.
- Fear of death.
- Frustration.
- Feelings of sadness or hopelessness.
- Self-criticism.
- Frequent daydreaming.
- Low self-esteem.
- School refusal.
- Learning problems.
- Slow movements.
- Vacillating hostility toward parents and teachers.
- Loss of interest in previously pleasurable activities.

Differentiating these symptoms from behavioral responses to normal developmental stages is important.

Assessment of depression includes determination of the child's: [10]

- Family situation.
- Level of emotional maturity.
- Ability to cope with illness and treatment.
- Age.
- State of development.
- Previous experience with illness.
- Personal ego strength.

A comprehensive assessment for childhood depression is the basis for accurate diagnosis and treatment. Evaluation of the child and family situation focuses on the pediatric health history, behaviors observed by the practitioner or reported by others (e.g., parents and teachers), interviews with the child, and judicial use of tests such as the Beck Depression Inventory or the Child Behavior Checklist.[10]

Diagnosis

In discussing the diagnosis of childhood depression, experts stress the importance of understanding childhood depression as an entity distinct from depression in adults because developmental issues in childhood are distinctly different from those of adulthood.[11]

A model of childhood affective disorders uses the following explicit criteria:[12]

- Dysphoric mood (children younger than 6 years must also have a sad facial expression).
- At least 4 of the following signs or symptoms present every day for a period of at least 2 weeks:

- Appetite disturbance.
- Insomnia or hypersomnia.
- Psychomotor agitation or retardation.
- Loss of interest or pleasure in usual activities (children younger than 6 years must also have signs of apathy).
- Fatigue or loss of energy.
- Feelings of worthlessness, self-reproach, or excessive, inappropriate guilt.
- Diminished ability to think or concentrate.
- Recurrent thoughts of death or suicide.

Management of Pediatric Depression

Treatment regimens implemented for childhood depression reflect theoretical models, etiology, and manifestations of the disorder.[1] Individual and group psychotherapy are commonly utilized as the primary treatment modality and are directed at helping the child to master his or her difficulties and to enable the child to develop in an optimal manner. Play therapy may be used as a means of exploring a younger child's view of himself or herself, the disease, and its treatment. The child needs to be helped from the beginning to explore and understand, at a level appropriate for his or her developmental age, the diagnosis of cancer and the treatments involved.[1]

As is the case with depression in adult cancer patients, there are few, if any, revealing trials of antidepressants in children with cancer. One author described rapid clinical response to low doses (<2 mg/kg/d) of imipramine or amitriptyline for eight depressed children with cancer.[13][Level of evidence: III] Another author described the use of benzodiazepines such as lorazepam, diazepam, alprazolam, and clonazepam for the treatment of anxiety disorders. Trials of benzodiazepines are short term. These drugs are tapered slowly when they are

discontinued.[14]

Pharmacological management

The combined use of tricyclic antidepressants and neuroleptics in the management of three children with severe symptoms of depression and anxiety has been reported. The children studied were in the terminal phases of their disease and were treated with a combination of low-dose amitriptyline and haloperidol. Levels of anxiety and depression were decreased, and this intervention allowed the patients and their families to deal with issues involved in death and dying.[15][Level of evidence: III]

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Latest Updates to This Summary (07/25/2024)

The PDQ cancer information summaries are reviewed regularly

and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

Suicide Risk in Cancer Patients

Updated Harmer et al. as reference 8.

Added text about a study that found suicide rates in people with cancer were three times higher than in the general population, and up to ten times higher in people with cancers with poorer prognosis, e.g., pancreatic cancer (cited Kinslow et al. as reference 4).

Added text to state that poorer prognosis, nonlocalized disease, and aggressive or advanced cancer with a survival rate of fewer than 5 years have been found to be closely associated with higher suicide risk early after cancer diagnosis, with an even greater risk in populations with higher baseline risk factors (male, White race, aged 60 years and older).

This section was reformatted.

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About This PDQ Summary

Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about cancer-related depression and suicide risk in both the adult and the pediatric populations. It is intended as a resource to inform and assist clinicians in the care of their patients. It does not provide formal guidelines or recommendations for making health care decisions.

Reviewers and Updates

This summary is reviewed regularly and updated as necessary by the PDQ Supportive and Palliative Care Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

Board members review recently published articles each month to determine whether an article should:

- be discussed at a meeting,
- be cited with text, or
- replace or update an existing article that is already cited.

Changes to the summaries are made through a consensus process in which Board members evaluate the strength of the evidence in the published articles and determine how the article should be included in the summary.

The lead reviewers for Depression are:

- Marilyn J. Hammer, PhD, DC, RN, FAAN (Dana-Farber Cancer Institute)
- Natalie Jacobowski, MD (Nationwide Children's Hospital)

- Jayesh Kamath, MD, PhD (University of Connecticut Health Center)
- Amy Wachholtz, PhD, MDiv, MS, ABPP (University of Colorado)

Any comments or questions about the summary content should be submitted to Cancer.gov through the NCI website's Email Us. Do not contact the individual Board Members with questions or comments about the summaries. Board members will not respond to individual inquiries.

Levels of Evidence

Some of the reference citations in this summary are accompanied by a level-of-evidence designation. These designations are intended to help readers assess the strength of the evidence supporting the use of specific interventions or approaches. The PDQ Supportive and Palliative Care Editorial Board uses a formal evidence ranking system in developing its level-of-evidence designations.

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The preferred citation for this PDQ summary is:

PDQ® Supportive and Palliative Care Editorial Board. PDQ Depression. Bethesda, MD: National Cancer Institute. Updated <MM/DD/YYYY>. Available at: https://www.cancer.gov/about-cancer/coping/feelings/depression-hp-pdq. Accessed

<MM/DD/YYYY>. [PMID: 26389407]

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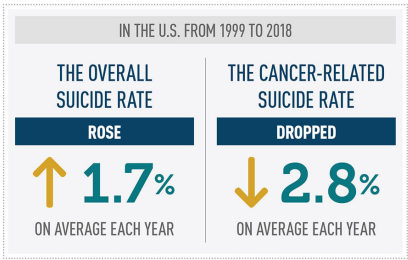
Updated: July 25, 2024

Rate of Suicides Related to Cancer Is Declining

February 17, 2021, by Sharon Reynolds

Over the last 2 decades, the suicide rate in the United States has been on a grim, steady march upwards. But a new study highlights an encouraging exception: between 1999 and 2018, the rate of suicide related to cancer decreased.



Credit: National Cancer Institute

This drop was greatest among people considered to be at higher suicide risk in general, including men and older adults.

The findings were published January 19 in *JNCI: Journal of the National Cancer Institute*.

People with cancer and those who have completed treatment can face a range of daunting challenges, said Emily Tonorezos, M.D., M.P.H., of NCI's Office of Cancer Survivorship, who was not involved with the study. These can include pain from the cancer, disabling side effects of treatment, and financial distress.

"But we know that there have been tremendous advances in palliative and supportive care, in hospice, in providing mental health care, and in making it easier for survivors to access those types of resources," Dr. Tonorezos said.

Supportive care is care given to improve the quality of life of patients who have a serious or life-threatening disease. Its goal

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is to prevent or treat as early as possible the symptoms of a disease, side effects caused by treatment of a disease, and related psychological, social, and spiritual issues.

The new study could not directly link improvements in supportive care to the reduced cancer-related suicide rate, "but this reduction represents something really positive for cancer survivors," Dr. Tonorezos said.

Better mental health care, palliative care, hospice care, and symptom management for cancer patients and survivors all have the potential to reduce the risk of suicide, explained Xuesong Han, Ph.D., of the American Cancer Society, who led the research. "That's what motivated us to examine the trends in cancer-related suicide," she said.

> If you are in crisis, call the toll-free National Suicide Prevention Lifeline at 1-800-273-TALK (8255). The service is available 24 hours a day, 7 days a week, to anyone. All calls are confidential. You can also contact the Crisis Text Line, a texting service for emotional crisis support. To speak with a trained listener, text HELLO to 741741. It is free, available 24/7, and confidential.

Improvements across Populations

Dr. Han and her colleagues used death certificate data collected by the Centers for Disease Control and Prevention between 1999 and 2018. Among deaths recorded as suicides, a subset were coded as cancer-related suicides. These could have been among either people undergoing cancer treatment or those who had completed treatment, Dr. Han explained.

As seen in previous studies, the overall suicide rate across the United States rose during those 2 decades, by an average of 1.7% a year. But over the same period, cancer-related suicides

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dipped, by about 2.8% each year. In addition to the large declines among people aged 65 and over and men, substantial drops in such suicides were seen among people in the southern and northeastern United States, in urban areas, and among people with prostate or lung cancers.

However, prostate and lung cancer, as well as colorectal cancer, were still the most common cancers among people who died by suicide. As well as being some of the most common cancer types, "symptoms of these cancers tend to be harsh, and can have a large impact on [that person's] quality of life," said Dr. Han.

These three cancer types can also overlap with other risk factors for suicide, she added. For example, gender: Men are at higher risk of suicide overall, and prostate cancer occurs exclusively in men. Men make up a greater proportion of lung cancer patients as well. And people with some pre-existing mental health conditions that increase suicide risk, including depression, are more likely to smoke—the leading cause of lung cancer, she explained.

More Room for Improvement

The sobering flip side of the encouraging decreases seen in the study is that "rates of suicide among cancer patients continue to be higher than [among] the general population, highlighting cancer patients as an at-risk group," wrote a team led by Tessa Flores, M.D., of Roswell Park Comprehensive Cancer Center, in an accompanying editorial.

"Cancer patients experience depression at higher rates than the general population and report high levels of sleep disturbance, post-traumatic stress, anxiety, fear, and worry," they wrote. These conditions "can get carried" forward beyond the completion of treatment, they explained.

Despite improvements in supportive care, people living with cancer can still be negatively affected by broader trends in

health care. For example, efforts to contain the opioid epidemic may be playing a role in declining access to pain medication for patients with cancer. Although doctors are usually very willing to prescribe opioids to help treat cancer-related pain, Dr. Tonorezos noted, cancer patients can be affected by opioid restrictions.

"For example, they may not be able to use a local pharmacy because the pharmacy doesn't stock the drugs or at the quantities that they need," she said.

The cost of cancer care can also put immense stress on patients and their families. "It can be catastrophic to go through cancer treatment from a financial perspective," Dr. Tonorezos continued. This burden now even has its own name: financial toxicity.

"It's not just medical expenses," she said. Costs of caregiving, transportation, supplies, childcare, and more can add up, she explained. Financial hardship from cancer treatment has been shown to impact people under the age of 65 in particular.

Support for People with Cancer

NCI provides information on managing costs and medical information and organizations that offer support services. Patients and their families can also contact NCI's Cancer Information Service to ask for help finding referrals and resources.

Reaching More People in Need

The need to comprehensively screen for depression in people with cancer has come into greater focus in recent years. For example, in 2015 the Commission on Cancer, a consortium of cancer-related professional organizations, began directing accredited cancer centers to screen patients for depression and distress.

But screening for depression in cancer patients and survivors

can be easier said than done, said Gurvaneet Randhawa, M.D., of NCI's Healthcare Delivery Research Program, who was not involved with the study. “Everyone wants to get it done. But despite all the good intentions, despite all the alignment of policies and guidelines and evidence, we still have bottlenecks that hinder the diagnosis and treatment of depression in cancer patients,” Dr. Randhawa said.

The bottlenecks can include lack of coordination between oncologists, mental health professionals, and other members of the cancer care team, a shortage of mental health professionals, and lack of follow-up with patients who report depression, he explained.

“The challenge in depression screening is not that we don't have good instruments to screen and diagnose depression, or that we don't have good treatments for depression. The challenge is doing [all this] systematically,” he said.

NCI is currently funding research teams who are developing information technology solutions to better integrate screening and treatment for depression into oncology practices.

“If we manage depression better, we should hopefully see an even bigger impact on suicide,” said Dr. Randhawa.

More research is also needed to better target cancer survivors at particularly high risk for suicide. For example, Dr. Han and her colleagues explained, people treated for cancer during childhood are at increased risk of suicide through adulthood. This group is also at risk for other adverse mental health outcomes and may need close mental health follow-up over their lifetime.

And although advances in supportive care, as well as improvements in how long people are living after cancer treatment, have likely fueled the drop in cancer-related suicides, researchers would like to know more about which services provide the greatest reduction in risk and where people are

falling through the cracks.

Dr. Han and her team are currently following a large group of patients during and after cancer treatment to look at these questions. Such research is needed "to understand where more improvements are needed, and [how to] ensure equitable access to these services as well," she concluded.

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