NIH NATIONAL CANCER INSTITUTE

Depression (PDQ®)–Health Professional Version

Go to Patient Version

Overview

Depression is a comorbid disabling syndrome that affects approximately 15% to 25% of cancer patients.[1-4] Depression is believed to affect men and women with cancer equally, and gender-related differences in prevalence and severity have not been adequately evaluated.[5] Individuals and families who face a diagnosis of cancer will 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 are observed (affect, sleep disturbance, thought patterns). These are specified in the categorization of psychiatric/behavioral disorders in the *Diagnostic and Statistical Manual of Mental Disorders,* 4th and 5th editions.[6,7] However, there are a number of pathways that may result in the symptom clusters that lead to the consideration of depression, including disruption in serotonin/dopamine pathways, experience of loss or anticipated loss, direct side effects of chemotherapy medications, presence of tumors in the central nervous system, poorly managed pain, disruption of sleep due to medical treatments, and anemia. Assessment and management of these symptoms require understanding of the various pathways and the evidence-based treatment options.

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.[8] Other syndromes described include dysthymia and subsyndromal depression (also called minor depression or subclinical depression). Dysthymia is a chronic mood disorder in which a depressed mood is present on more days than not for at least 2 years. In contrast, subsyndromal depression is an acute mood disorder that is less severe (some, but not all, diagnostic symptoms present) than major depression.

Possible Medical Causes of Depressive Symptoms in People With Cancer

- Uncontrolled pain.[9][Level of evidence: II]
- Metabolic abnormalities:
    - Hypercalcemia.
    - Sodium/potassium imbalance.
    - Anemia.
    - Vitamin B12 or folate deficiency.

    - Fever.
- Endocrine abnormalities:
    - Hyperthyroidism or hypothyroidism.
    - Adrenal insufficiency.
- Medications:[10][Level of evidence: I][11-13];[14][Level of evidence: II]
    - Steroids.
    - Endogenous and exogenous cytokines, i.e., interferon-alfa and aldesleukin (interleukin-2 [IL-2]).[15]
    - Methyldopa.
    - Reserpine.
    - Barbiturates.
    - Propranolol.
    - Some antibiotics (e.g., amphotericin B).
    - Some chemotherapeutic agents (e.g., procarbazine, L-asparaginase).

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.[16] 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 serious depression or anxiety is not experienced by everyone who is diagnosed with cancer.

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 non-caregivers, while there was an increased incidence of Hospital Anxiety and Depression Scale–defined depression among women.[17]

There are many myths about cancer and how people cope with it, such as the following:

- All people with cancer are depressed.
- Depression in a person with cancer is normal.
- Treatments for depression are not helpful.
- Everyone with cancer faces suffering and a painful death.

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.[8] 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 is not simply sadness or a blue mood. Major depression affects approximately 25% of patients and has recognizable symptoms whose diagnosis and treatment are essential because they have an impact on quality of life.[19,20] 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.[21] 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% confidence interval, 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.[21]

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.[22] 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.[22]

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. Epidemiologic studies, however, suggest that at least one-half of all people diagnosed with cancer will successfully adapt.

Markers of successful adaptation to a diagnosis of cancer include the following:[23]

- Maintaining active involvement in daily life.
- Minimizing the disruptions to one's life roles (e.g., spouse, parent, employee) caused by the illness.
- Regulating the normal emotional reactions to the illness.
- Managing feelings of hopelessness, helplessness, worthlessness, and/or guilt.

Some studies suggest an association between maladaptive coping styles and higher levels of depression, anxiety, and fatigue symptoms.[24,25] 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.[25] 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.[24] 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 Caucasian women.[24]

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.[26]

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.[27] 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.[28] 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.[29] 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.[30]

Evidence-based recommendations have described various approaches to the problems of cancer-related fatigue, anorexia, depression, and dyspnea.[31] 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.[20,32,33] Anxiety and depression in early treatment are good predictors of these same problems at 6 months.[34] 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.[35]

The pathophysiology of cancer-related depression remains unclear and probably encompasses many mechanisms. A study of patients with advanced metastatic cancer showed that both plasma interleukin-6 (IL-6) concentrations and hypothalamic-pituitary-adrenal axis dysfunction were markedly higher in patients with

clinical depression.[36] A cut-off value of 10.6 pg/mL for IL-6 yielded a sensitivity of 79% and specificity of 87%, while a cut-off value of 33.5% for cortisol variations yielded a sensitivity of 81% and specificity of 88%. One limitation of this study was that neither pain levels nor fatigue levels were measured, which might independently affect these relationships.

Although the etiology of depression is largely unknown, many risk factors for depression (such as those listed below) are known.

- Cancer-related risk factors:
  - Depression at time of cancer diagnosis.[34,37]
  - Poorly controlled pain.[9]
  - Advanced stage of cancer.[9]
  - Increased physical impairment or discomfort.
  - Pancreatic cancer.[38]
  - Being unmarried and having head and neck cancer.[39]
  - Treatment with certain chemotherapeutic agents:
    - Corticosteroids.
    - Procarbazine.
    - L-Asparaginase.
    - Interferon-alfa.[14,40]
    - IL-2.[10,14,40]
    - Amphotericin-B.
- Non–cancer-related risk factors:
  - History of depression:
    - Two or more episodes in a lifetime.
    - First episode early or late in life.
  - Lack of family support.[34]
  - Additional concurrent life stressors.[41]
  - Family history of depression or suicide.
  - Previous suicide attempts.
  - History of alcoholism or drug abuse.
  - Concurrent illnesses that produce depressive symptoms (e.g., stroke or myocardial infarction).
  - Past treatment for psychological problems.[42]

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.

References

1. Henriksson MM, Isometsä ET, Hietanen PS, et al.: Mental disorders in cancer suicides. J Affect Disord 36 (1-2): 11-20, 1995. [PUBMED Abstract]
2. Bodurka-Bevers D, Basen-Engquist K, Carmack CL, et al.: Depression, anxiety, and quality of life in patients with epithelial ovarian cancer. Gynecol Oncol 78 (3 Pt 1): 302-8, 2000. [PUBMED Abstract]
3. Lloyd-Williams M, Friedman T: Depression in palliative care patients--a prospective study. Eur J Cancer Care (Engl) 10 (4): 270-4, 2001. [PUBMED Abstract]
4. Derogatis LR, Morrow GR, Fetting J, et al.: The prevalence of psychiatric disorders among cancer patients. JAMA 249 (6): 751-7, 1983. [PUBMED Abstract]
5. Miaskowski C: Gender differences in pain, fatigue, and depression in patients with cancer. J Natl Cancer Inst Monogr (32): 139-43, 2004. [PUBMED Abstract]
6. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. 4th rev. ed. Washington, DC: American Psychiatric Association, 2000.
7. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. Washington, DC: American Psychiatric Association, 2013.
8. Block SD: Assessing and managing depression in the terminally ill patient. ACP-ASIM End-of-Life Care Consensus Panel. American College of Physicians - American Society of Internal Medicine. Ann Intern Med 132 (3): 209-18, 2000. [PUBMED Abstract]
9. Ciaramella A, Poli P: Assessment of depression among cancer patients: the role of pain, cancer type and treatment. Psychooncology 10 (2): 156-65, 2001 Mar-Apr. [PUBMED Abstract]
10. Capuron L, Ravaud A, Dantzer R: Early depressive symptoms in cancer patients receiving interleukin 2 and/or interferon alfa-2b therapy. J Clin Oncol 18 (10): 2143-51, 2000. [PUBMED Abstract]
11. Cancer chemotherapy. Med Lett Drugs Ther 29 (736): 29-36, 1987. [PUBMED Abstract]
12. Drugs of choice for cancer chemotherapy. Med Lett Drugs Ther 33 (840): 21-8, 1991. [PUBMED Abstract]
13. Drugs that cause psychiatric symptoms. Med Lett Drugs Ther 31 (808): 113-8, 1989. [PUBMED Abstract]
14. Capuron L, Ravaud A, Neveu PJ, et al.: Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. Mol Psychiatry 7 (5): 468-73, 2002. [PUBMED Abstract]
15. Menzies H, Chochinov HM, Breitbart W: Cytokines, cancer and depression: connecting the dots. J Support Oncol 3 (1): 55-7, 2005 Jan-Feb. [PUBMED Abstract]
16. Watson M, St James-Roberts I, Ashley S, et al.: Factors associated with emotional and behavioural problems among school age children of breast cancer patients. Br J Cancer 94 (1): 43-50, 2006. [PUBMED Abstract]
17. Grov EK, Dahl AA, Moum T, et al.: Anxiety, depression, and quality of life in caregivers of patients with

cancer in late palliative phase. Ann Oncol 16 (7): 1185-91, 2005. [PUBMED Abstract]

18. Petersen RW, Quinlivan JA: Preventing anxiety and depression in gynaecological cancer: a randomised controlled trial. BJOG 109 (4): 386-94, 2002. [PUBMED Abstract]
19. Massie MJ, Holland JC: The cancer patient with pain: psychiatric complications and their management. Med Clin North Am 71 (2): 243-58, 1987. [PUBMED Abstract]
20. Lynch ME: The assessment and prevalence of affective disorders in advanced cancer. J Palliat Care 11 (1): 10-8, 1995 Spring. [PUBMED Abstract]
21. Wilson KG, Chochinov HM, Skirko MG, et al.: Depression and anxiety disorders in palliative cancer care. J Pain Symptom Manage 33 (2): 118-29, 2007. [PUBMED Abstract]
22. Chochinov HM, Kristjanson LJ, Hack TF, et al.: Burden to others and the terminally ill. J Pain Symptom Manage 34 (5): 463-71, 2007. [PUBMED Abstract]
23. Spencer SM, Carver CS, Price AA: Psychological and social factors in adaptation. In: Holland JC, Breitbart W, Jacobsen PB, et al., eds.: Psycho-oncology. New York, NY: Oxford University Press, 1998, pp 211-22.
24. Reddick BK, Nanda JP, Campbell L, et al.: Examining the influence of coping with pain on depression, anxiety, and fatigue among women with breast cancer. J Psychosoc Oncol 23 (2-3): 137-57, 2005. [PUBMED Abstract]
25. Beresford TP, Alfers J, Mangum L, et al.: Cancer survival probability as a function of ego defense (adaptive) mechanisms versus depressive symptoms. Psychosomatics 47 (3): 247-53, 2006 May-Jun. [PUBMED Abstract]
26. Nelson CJ, Rosenfeld B, Breitbart W, et al.: Spirituality, religion, and depression in the terminally ill. Psychosomatics 43 (3): 213-20, 2002 May-Jun. [PUBMED Abstract]
27. Edwards B, Clarke V: The psychological impact of a cancer diagnosis on families: the influence of family functioning and patients' illness characteristics on depression and anxiety. Psychooncology 13 (8): 562-76, 2004. [PUBMED Abstract]
28. Lewis FM, Fletcher KA, Cochrane BB, et al.: Predictors of depressed mood in spouses of women with breast cancer. J Clin Oncol 26 (8): 1289-95, 2008. [PUBMED Abstract]
29. Patrick DL, Ferketich SL, Frame PS, et al.: National Institutes of Health State-of-the-Science Conference Statement: Symptom Management in Cancer: Pain, Depression, and Fatigue, July 15-17, 2002. J Natl Cancer Inst 95 (15): 1110-7, 2003. [PUBMED Abstract]
30. Meyer TJ, Mark MM: Effects of psychosocial interventions with adult cancer patients: a meta-analysis of randomized experiments. Health Psychol 14 (2): 101-8, 1995. [PUBMED Abstract]
31. Dy SM, Lorenz KA, Naeim A, et al.: Evidence-based recommendations for cancer fatigue, anorexia, depression, and dyspnea. J Clin Oncol 26 (23): 3886-95, 2008. [PUBMED Abstract]
32. Massie MJ, Holland JC: Overview of normal reactions and prevalence of psychiatric disorders. In: Holland JC, Rowland JH, eds.: Handbook of Psychooncology: Psychological Care of the Patient With Cancer. New York, NY: Oxford University Press, 1989, pp 273-82.
33. Massie MJ, Shakin EJ: Management of depression and anxiety in cancer patients. In: Breitbart W, Holland JC, eds.: Psychiatric Aspects of Symptom Management in Cancer Patients. Washington, DC:

American Psychiatric Press, 1993, pp 470-91.

34. Nordin K, Glimelius B: Predicting delayed anxiety and depression in patients with gastrointestinal cancer. Br J Cancer 79 (3-4): 525-9, 1999. [PUBMED Abstract]
35. Goodwin JS, Zhang DD, Ostir GV: Effect of depression on diagnosis, treatment, and survival of older women with breast cancer. J Am Geriatr Soc 52 (1): 106-11, 2004. [PUBMED Abstract]
36. Jehn CF, Kuehnhardt D, Bartholomae A, et al.: Biomarkers of depression in cancer patients. Cancer 107 (11): 2723-9, 2006. [PUBMED Abstract]
37. Karnell LH, Funk GF, Christensen AJ, et al.: Persistent posttreatment depressive symptoms in patients with head and neck cancer. Head Neck 28 (5): 453-61, 2006. [PUBMED Abstract]
38. Green AI, Austin CP: Psychopathology of pancreatic cancer. A psychobiologic probe. Psychosomatics 34 (3): 208-21, 1993 May-Jun. [PUBMED Abstract]
39. Kugaya A, Akechi T, Okuyama T, et al.: Prevalence, predictive factors, and screening for psychologic distress in patients with newly diagnosed head and neck cancer. Cancer 88 (12): 2817-23, 2000. [PUBMED Abstract]
40. Capuron L, Ravaud A, Gualde N, et al.: Association between immune activation and early depressive symptoms in cancer patients treated with interleukin-2-based therapy. Psychoneuroendocrinology 26 (8): 797-808, 2001. [PUBMED Abstract]
41. Green BL, Krupnick JL, Rowland JH, et al.: Trauma history as a predictor of psychologic symptoms in women with breast cancer. J Clin Oncol 18 (5): 1084-93, 2000. [PUBMED Abstract]
42. Burgess CC, Ramirez AJ, Richards MA, et al.: Does the method of detection of breast cancer affect subsequent psychiatric morbidity? Eur J Cancer 38 (12): 1622-5, 2002. [PUBMED Abstract]

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 1):

- “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.

Limited data suggest that depressive symptomatology in cancer patients undergoing cytokine therapy with interferon-alfa and interleukin-2 may be mediated by changes in availability of neurotransmitter precursors.

[3] 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.

A prospective study of terminally ill Japanese patients who were assessed for psychiatric illness by structured clinical interview at the time of registration (baseline) and again at admission to a palliative care unit (follow-up) found that 5 (42%) of the 12 patients diagnosed with adjustment disorder at baseline progressed to major depression at follow-up. Only the Hospital Anxiety and Depression Scale was significantly predictive of psychiatric diagnoses at follow-up.[6] Heightened awareness of this facilitates early diagnosis and the use of appropriate interventions.[7] In the medically ill, early manifestations of delirium may be mistaken for anxiety or depression. These disorders should be considered among the differential diagnoses in individuals who present with depressive symptoms.

Screening and Assessment for Depression

Because of the common underrecognition and undertreatment of depression in people with cancer, screening tools can be used to prompt further assessment.[8] 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 persons 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?”[9] 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.[10]
- The Hospital Anxiety and Depression Scale.[11] The Hospital Anxiety and Depression Scale may have utility 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.[12-14]
- The Psychological Distress Inventory.[15]

- The Edinburgh Depression Scale.[16]
- The Brief Symptom Inventory.[17]
- The Zung Self-Rating Depression Scale.[18]
- The Distress Thermometer.[19]

One study of women with newly diagnosed breast cancer (n = 236) successfully utilized brief screening instruments such as the Distress Thermometer and the Patient Health Questionnaire to identify women requiring further assessment to detect clinically significant levels of distress and psychiatric symptoms.[20]

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.[21]

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 Hospital Anxiety and Depression Scale and is brief, potentially making it an effective tool for routine screening in oncology settings.[22] 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.[23]

It is important that screening instruments be validated in cancer populations and used in combination with structured diagnostic interviews.[24] 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 Hospital Anxiety and Depression Scale were reported (r = 0.87), no indication of cut-offs 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.[7,25]

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.[26] 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.[27] 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.[28]

Clinical interview

Table 1. 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 is your care totally under others' control?	Helplessness
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.[29]

Organic Mood Syndromes or Mood Syndromes Related to Another Medical Condition (MSRAMC), as they are referred to in the DSM, 5th edition (DSM-5),[30] 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.[31]

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.[32]

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.[33]

Suicidal ideation, when it occurs, is frightening for the individual, the health professional, and the family. 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. Refer to the Suicide Risk in Cancer Patients section of this summary for more information about suicide.

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.[34][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. 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. (Refer to the PDQ summary on Adjustment to Cancer: Anxiety and Distress for more information.)

References

1. Jacobsen PB, Donovan KA, Weitzner MA: Distinguishing fatigue and depression in patients with cancer. Semin Clin Neuropsychiatry 8 (4): 229-40, 2003. [PUBMED Abstract]
2. De Leeuw JR, De Graeff A, Ros WJ, et al.: Negative and positive influences of social support on depression in patients with head and neck cancer: a prospective study. Psychooncology 9 (1): 20-8, 2000 Jan-Feb. [PUBMED Abstract]
3. Capuron L, Ravaud A, Neveu PJ, et al.: Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. Mol Psychiatry 7 (5): 468-73, 2002. [PUBMED Abstract]
4. de Leeuw JR, de Graeff A, Ros WJ, et al.: Prediction of depression 6 months to 3 years after treatment of head and neck cancer. Head Neck 23 (10): 892-8, 2001. [PUBMED Abstract]
5. Paice JA: Managing psychological conditions in palliative care. Am J Nurs 102 (11): 36-42; quiz 43, 2002. [PUBMED Abstract]
6. Akechi T, Okuyama T, Sugawara Y, et al.: Major depression, adjustment disorders, and post-traumatic stress disorder in terminally ill cancer patients: associated and predictive factors. J Clin Oncol 22 (10): 1957-65, 2004. [PUBMED Abstract]
7. Passik SD, Kirsh KL, Theobald D, et al.: Use of a depression screening tool and a fluoxetine-based algorithm to improve the recognition and treatment of depression in cancer patients. A demonstration project. J Pain Symptom Manage 24 (3): 318-27, 2002. [PUBMED Abstract]
8. Passik SD, Dugan W, McDonald MV, et al.: Oncologists' recognition of depression in their patients with cancer. J Clin Oncol 16 (4): 1594-600, 1998. [PUBMED Abstract]
9. Chochinov HM, Wilson KG, Enns M, et al.: "Are you depressed?" Screening for depression in the terminally ill. Am J Psychiatry 154 (5): 674-6, 1997. [PUBMED Abstract]
10. Akizuki N, Akechi T, Nakanishi T, et al.: Development of a brief screening interview for adjustment disorders and major depression in patients with cancer. Cancer 97 (10): 2605-13, 2003. [PUBMED Abstract]
11. Zigmond AS, Snaith RP: The hospital anxiety and depression scale. Acta Psychiatr Scand 67 (6): 361-70, 1983. [PUBMED Abstract]
12. Love AW, Kissane DW, Bloch S, et al.: Diagnostic efficiency of the Hospital Anxiety and Depression Scale in women with early stage breast cancer. Aust N Z J Psychiatry 36 (2): 246-50, 2002. [PUBMED Abstract]
13. Lloyd-Williams M, Friedman T, Rudd N: An analysis of the validity of the Hospital Anxiety and Depression scale as a screening tool in patients with advanced metastatic cancer. J Pain Symptom Manage 22 (6):

990-6, 2001. [PUBMED Abstract]

14. Lloyd-Williams M, Spiller J, Ward J: Which depression screening tools should be used in palliative care? Palliat Med 17 (1): 40-3, 2003. [PUBMED Abstract]

15. Morasso G, Costantini M, Baracco G, et al.: Assessing psychological distress in cancer patients: validation of a self-administered questionnaire. Oncology 53 (4): 295-302, 1996 Jul-Aug. [PUBMED Abstract]

16. Lloyd-Williams M, Riddleston H: The stability of depression scores in patients who are receiving palliative care. J Pain Symptom Manage 24 (6): 593-7, 2002. [PUBMED Abstract]

17. Derogatis LR, Melisaratos N: The Brief Symptom Inventory: an introductory report. Psychol Med 13 (3): 595-605, 1983. [PUBMED Abstract]

18. Dugan W, McDonald MV, Passik SD, et al.: Use of the Zung Self-Rating Depression Scale in cancer patients: feasibility as a screening tool. Psychooncology 7 (6): 483-93, 1998 Nov-Dec. [PUBMED Abstract]

19. Roth AJ, Kornblith AB, Batel-Copel L, et al.: Rapid screening for psychologic distress in men with prostate carcinoma: a pilot study. Cancer 82 (10): 1904-8, 1998. [PUBMED Abstract]

20. Hegel MT, Moore CP, Collins ED, et al.: Distress, psychiatric syndromes, and impairment of function in women with newly diagnosed breast cancer. Cancer 107 (12): 2924-31, 2006. [PUBMED Abstract]

21. Hegel MT, Collins ED, Kearing S, et al.: Sensitivity and specificity of the Distress Thermometer for depression in newly diagnosed breast cancer patients. Psychooncology 17 (6): 556-60, 2008. [PUBMED Abstract]

22. Akizuki N, Yamawaki S, Akechi T, et al.: Development of an Impact Thermometer for use in combination with the Distress Thermometer as a brief screening tool for adjustment disorders and/or major depression in cancer patients. J Pain Symptom Manage 29 (1): 91-9, 2005. [PUBMED Abstract]

23. Meyer HA, Sinnott C, Seed PT: Depressive symptoms in advanced cancer. Part 1. Assessing depression: the Mood Evaluation Questionnaire. Palliat Med 17 (7): 596-603, 2003. [PUBMED Abstract]

24. Lynch ME: The assessment and prevalence of affective disorders in advanced cancer. J Palliat Care 11 (1): 10-8, 1995 Spring. [PUBMED Abstract]

25. Lees N, Lloyd-Williams M: Assessing depression in palliative care patients using the visual analogue scale: a pilot study. Eur J Cancer Care (Engl) 8 (4): 220-3, 1999. [PUBMED Abstract]

26. Patrick DL, Ferketich SL, Frame PS, et al.: National Institutes of Health State-of-the-Science Conference Statement: Symptom Management in Cancer: Pain, Depression, and Fatigue, July 15-17, 2002. J Natl Cancer Inst 95 (15): 1110-7, 2003. [PUBMED Abstract]

27. Andersen BL, DeRubeis RJ, Berman BS, et al.: Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. J Clin Oncol 32 (15): 1605-19, 2014. [PUBMED Abstract]

28. Wellisch DK, Lindberg NM: A psychological profile of depressed and nondepressed women at high risk for breast cancer. Psychosomatics 42 (4): 330-6, 2001 Jul-Aug. [PUBMED Abstract]

29. Roth AJ, Holland JC: Psychiatric complications in cancer patients. In: Brain MC, Carbone PP, eds.: Current Therapy in Hematology-Oncology. 5th ed. St. Louis, Mo: Mosby-Year Book, Inc., 1995, pp 609-18.

30. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. Washington, DC: American Psychiatric Association, 2013.
31. Breitbart W, Holland JC: Psychiatric complications of cancer. Current Therapy in Hematology-Oncology 3: 268-74, 1988.
32. Reuter K, Raugust S, Bengel J, et al.: Depressive symptom patterns and their consequences for diagnosis of affective disorders in cancer patients. Support Care Cancer 12 (12): 864-70, 2004. [PUBMED Abstract]
33. Detmar SB, Aaronson NK, Wever LD, et al.: How are you feeling? Who wants to know? Patients' and oncologists' preferences for discussing health-related quality-of-life issues. J Clin Oncol 18 (18): 3295-301, 2000. [PUBMED Abstract]
34. Nordin K, Wasteson E, Hoffman K, et al.: Discrepancies between attainment and importance of life values and anxiety and depression in gastrointestinal cancer patients and their spouses. Psychooncology 10 (6): 479-89, 2001 Nov-Dec. [PUBMED Abstract]

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:[3-5]

- 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 pharmacologic 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 be cooperative with medical treatment.

Pharmacologic 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]

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 (refer to Table 2).

Table 2. Antidepressant Medications[a] and Adjunctive Pharmacological Treatments

SSRIs	**• Most commonly used in patients with cancer because of better safety-tolerability profiles than other antidepressants.**
	• Most-common side effects: GI (e.g., nausea, diarrhea, constipation) and sexual dysfunction (e.g., delayed ejaculation, anorgasmia, decreased libido).
	• Risk of hyponatremia and bleeding.

	• Risk of serotonin syndrome and risk of serotonin discontinuation syndrome with abrupt discontinuation.		
Medication	***Starting Dose (mg/day)***	***Maintenance Dose (mg/day)***	***Comments***
– Citalopram	10–20	20–40	Minimal drug-drug interactions.
			Better safety-tolerability profile than other antidepressants.
			Potential for QTc prolongation (dose increase limited in patients with cardiac issues).
– Escitalopram	5–10	10–20	S-enantiomer of citalopram.
			Minimal drug-drug interactions.
			Better safety-tolerability profile than other antidepressants.
– Fluoxetine	10–20	20–60	Minimal risk of serotonin discontinuation syndrome due to long half-life.
			Significant inhibitor of CYP2D6.

– Fluvoxamine	25–50	100–300	Better anxiolytic properties than other SSRIs.
			Significant inhibitor of CYP1A2 and CYP3A4.
– Paroxetine	10–20	20–60	High risk of serotonin discontinuation syndrome.
			Modest anticholinergic properties.
			Significant inhibitor of CYP2D6.
– Sertraline	25–50	100–200	Higher risk of GI side effects.
			Dose-dependent inhibition of CYP2D6.
– Vilazodone	10	20–40	Risk of GI side effects.
			Possibly less risk of sexual dysfunction, but evidence inconclusive.
SNRIs[b]	**• Known for positive impact on certain comorbidities, specifically pain syndromes and hot flashes. Commonly used in depressed patients with these comorbidities.**		
	• Risk of hypertension and other cardiac issues. Baseline ECG recommended in some cases.		

	• Risk of headaches and excessive sweating.		
	• Risk of GI side effects, hyponatremia and bleeding.		
	• Risk of serotonin syndrome and risk of serotonin discontinuation syndrome with abrupt discontinuation.		
Medication	***Starting Dose (mg/day)***	***Maintenance Dose (mg/day)***	***Comments***
– Desvenlafaxine	50	50–100	Active metabolite of venlafaxine.
			Minimal drug-drug interactions.
			Positive impact on hot flashes.
– Duloxetine	30	30–60	First-line treatment in patients with comorbid neuropathic pain (in doses as high as 120 mg).
			Higher risk of GI side effects and hypertension.
			Risk of hepatotoxicity.
– Levomilnacipran	20	40–120	More-potent noradrenergic effects, activating effects.

			Useful for comorbid cognitive and pain symptoms.
			Increased risk of cardiovascular side effects, sweating, and urinary hesitancy.
– Venlafaxine (IR and XL)	37.5–75	150–225	First-line treatment in patients with comorbid hot flashes.
			Higher risk of serotonin discontinuation syndrome.
			Minimal drug-drug interactions.
NDRIs	**Baseline ECG recommended in some cases.**		
Medication	***Starting Dose (mg/day)***	***Maintenance Dose (mg/day)***	***Comments***
– Bupropion (IR, SR, and XL)	100–150 (SR and XL)	150–450	Stimulating effects and lack of sexual dysfunction.
			Dose-dependent seizure risk (rare), insomnia, headaches, and weight loss.
			SR and XL commonly used to avoid anxiogenic

			effects and higher seizure risk associated with IR.
Atypical antidepressants			
Medication	***Starting Dose (mg/day)***	***Maintenance Dose (mg/day)***	***Comments***
– Mirtazapine	7.5–15	30–45	Frequently used in cancer patients with comorbid insomnia and cachexia. Known for its antinausea effects.
			Decreased elimination in elderly.
			Sedation, weight gain, and dizziness.
			Risk of hepatotoxicity and neutropenia.
– Trazodone	25–50	50–200	Primarily used as adjunct to other antidepressants. Useful for comorbid insomnia and anxiety.
			Marked sedation and anxiolytic effects.
			Risk of orthostatic hypotension, dizziness, and priapism (rare).

TCAs			
TCAs	**• Not commonly used as first-line agents due to high risk of cardiotoxicity and neurotoxicity. Baseline ECG recommended to evaluate for preexisting cardiac conduction abnormalities.**		
	• Primarily used as adjunctive treatments at low dosages.		
	• Risk of weight gain and anticholinergic effects such as dry mouth, orthostatic hypotension, dizziness, and sedation.		
	• Useful in patients with comorbid insomnia and/or headaches.		
	• Certain TCAs have known therapeutic plasma concentrations.		
	• Risk of serotonin syndrome and risk of serotonin discontinuation syndrome with abrupt discontinuation.		
Medication (only most commonly used TCAs included below)	***Starting Dose (mg/day)***	***Maintenance Dose (mg/day)***	***Comments***
– Amitriptyline	10–25	150–300	Marked sedation and anticholinergic effects.
			Weight gain.
			Orthostatic hypotension.
			Dizziness.
– Clomipramine	25	100–250	More serotonergic effects, less sedation, and fewer anticholinergic effects

			than other TCAs.
– Desipramine	25–50	100–300	Mild sedation.
			Minimal anticholinergic effects.
– Doxepin	10–25	75–300	Marked sedation and anticholinergic effects.
			Weight gain.
			Orthostatic hypotension.
			Dizziness.
– Imipramine	25–50	75–300	Moderate sedation.
			Weight gain.
			Anticholinergic effects.
			Orthostatic hypotension.
			Dizziness.
– Nortriptyline	10–25	90–150	Mild sedation.
			Moderate anticholinergic effects.
MAOIs	**• Primarily used for treatment-refractory depression.**		

	• Involvement of psychiatric prescribers and pharmacy consultation strongly recommended because MAOIs carry serious risks of side effects, drug-drug interactions, and drug-food interactions.
	• Common side effects include orthostatic hypotension, dizziness, anticholinergic side effects, and headaches.
	• Serious risk of serotonin syndrome and hypertensive crisis.
	• Low-tyramine diet required.
	• Medications: phenelzine, selegiline, and tranylcypromine.
Psychostimulants as adjunctive treatments to antidepressants	• Used for stimulating/energy-enhancing effects, especially in patients with prominent fatigue symptoms.
	• Risk of anxiety, agitation, insomnia, anorexia, and psychosis.
	• Risk of hypertension and arrhythmia (baseline ECG recommended); can lower seizure threshold.
	• Risk of tolerance, abuse, and dependence liability.
	• Medications: dextroamphetamine and methylphenidate.
Other adjunctive treatments	• Antipsychotic medications.
	• Buspirone primarily used as adjunct to treat comorbid anxiety symptoms.

CYP = cytochrome P450 enzyme; ECG = electrocardiogram; GI = gastrointestinal; IR = immediate release; MAOI = monoamine oxidase inhibitor; NDRI = norepinephrine-dopamine reuptake

inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; SR = sustained release; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; XL = extended release.

[a]All antidepressants carry a boxed warning about the risk of suicidal thinking and behavior, risk of mania, and risk of drug-drug interaction when combined with MAOIs (refer to the MAOIs section of this summary for more information).

[b]Refer to the Serotonin-norepinephrine reuptake inhibitors (SNRIs) section of this summary for more information about side effects associated with SNRIs.

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.[7,12]

Selective serotonin reuptake inhibitors

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 and predilection to cause certain side effects (e.g., gastrointestinal [GI] side effects and sexual dysfunction). However, they differ in terms of severity of these side effects and can have additional effects related to their impact on other neurobiological systems (e.g., anticholinergic effects, sedation, or insomnia).

SSRIs generally undergo hepatic metabolism and 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 (refer to the Serotonin discontinuation syndrome section of this summary for more information). The shorter the half-life of the SSRI and its metabolites, the higher the risk of serotonin discontinuation syndrome.

Serotonin-norepinephrine reuptake inhibitors (SNRIs)

The mixed SNRIs increase levels of both 5-HT and norepinephrine (NE) in the synapse by blocking reuptake of these neurotransmitters by their respective transporters. SNRIs include older agents such as TCAs and newer agents such as venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran. 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.

The newer agents—venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran—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 differential 5-HT and NE effects may be associated with differential efficacy and side effect profiles in different patient populations (e.g., 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 and sexual side effects. Other side effects associated with SNRIs result from their anticholinergic and antihistamine properties. These are much more prominent with TCAs than with the newer agents and include sedation, dry mouth, constipation, dizziness (due to orthostatic hypotension), blurred vision, and urinary retention. SNRIs are also associated with increased risk of headaches and excessive sweating.

The precise underlying mechanisms of these side effects remain unknown. Certain SNRIs, primarily TCAs, have established efficacy in the treatment of headaches. Certain newer SNRIs, specifically venlafaxine and desvenlafaxine, are known to treat hot flashes associated with menopausal symptoms. Other side effects of SNRIs include dose-related diastolic hypertension and increased risk of cardiovascular side effects, primarily resulting from their noradrenergic effects.

TCAs are associated with significant cardiotoxicity and neurotoxicity, including risk of seizures. Use of TCAs requires extreme caution because overdoses of even small amounts of these medications can be fatal. These drugs are primarily used as adjuncts in the treatment of refractory depression and in the treatment of comorbidities such as headaches and neuropathy. The newer SNRIs are safer in overdoses and are used much more frequently as primary treatments, especially in the management of depression with comorbidities such as hot flashes and pain syndromes.

Serotonin discontinuation syndrome

A discontinuation syndrome has been associated with stoppage of serotonergic antidepressants, both SSRIs and SNRIs.[13] 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 [14] 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: immediate release (three times daily), sustained release (twice daily), and extended release (once daily). 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 history of seizures, head trauma, brain tumor, and eating disorders. **Bupropion should be avoided in patients with malignant diseases involving the brain and histories of cranial trauma or seizure disorder,**[15] **and it is contraindicated in persons with a history of bulimia.**[16][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.[7,12]

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 its minimal risk of drug-drug interactions, mild antiemetic effects, and 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 (refer to the Serotonin syndrome section of this summary for more information), primarily when taken in combination with other potent serotonergic medications; it is not associated with serotonin discontinuation syndrome.

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. Such classes include sympathomimetics, anesthetics, other noradrenergic agents, serotonergic agents, and 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. Avoidance of foods containing 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 due to lack of tyramine processing by the MAO enzymes.

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 is 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.[17] 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 depressed mood, apathy, decreased energy, poor concentration, and weakness.[18][Level of evidence: II] They 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, and even psychotic symptoms. They are also associated with adverse cardiovascular effects and increased risk of seizures. 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 non-cancer (general psychiatry) literature suggests a role for other medications and medication classes as adjuncts to antidepressants in treatment-refractory cases.[17] Such medications and medication classes include antipsychotic medications, thyroid hormone, lithium, buspirone, and certain combination strategies for different antidepressant classes. Some of these medications (e.g., antipsychotic medications and lithium) are associated with a significant burden of side effects. Referral 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.[19,20] 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.[20] 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.[20] 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 and 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.[12] 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 (refer to the Serotonin syndrome section of this summary for more information) and serotonin discontinuation syndrome (refer to the Serotonin discontinuation syndrome section of this summary for more information). Such factors include antidepressant-dependent factors and patient- or illness-related factors:[21,22]

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.[23] 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.[23]

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. (Refer to the Serotonin syndrome section of this summary for more information.) The risk of serotonin syndrome in these cases will also depend on the doses of both medications and the schedule of cross-taper.[23]

For the discontinuation of serotonergic antidepressants, it is strongly recommended that antidepressants be tapered gradually to minimize the risk of serotonin discontinuation syndrome. (Refer to the Serotonin discontinuation syndrome section of this summary for more information.)

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. (Refer to Table 3 for a list of antidepressants and the risk of serotonin discontinuation syndrome.)

Table 3. Antidepressants and Risk of Serotonin Discontinuation Syndrome

Agent	Risk[a]	Comment(s)
SSRI		
Citalopram	++	

Escitalopram	++	
Fluoxetine	+	Very long half-life; generally, no taper required
Fluvoxamine	++	
Paroxetine	+++	
Sertraline	++	
Vilazodone	++	
SNRI		
Desvenlafaxine	+	~2% risk; no taper required for most patients
Duloxetine	++	
Levomilnacipran	++	
Venlafaxine	+++	
TCA		
Clomipramine	++	Most serotonergic TCA
Other TCAs	+	
Other antidepressant		

Bupropion	+	Minimal to no risk
MAOI		
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.[24][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).[24] 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 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.[25] The new, carefully worded warning emphasizes 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 acknowledges 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.[26] 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.[27][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.[28]

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:[29][Level of evidence: II];[30-32][Level of evidence: I][33]

- 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, reinforce strongly that, though 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.[34,35][Level of evidence: II] Support group interventions have demonstrated significant effects on mood disturbance, use of positive coping strategies, improvement in quality of life, and positive immune responses.[36,37][Level of evidence: I][38] 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.[39] Reviews have also concluded that psychotherapy is an effective intervention for cancer patients experiencing depression.[40][Level of evidence: II][28] In studies designed to prevent the occurrence of depression (i.e., patients not selected because of their depressive symptoms), intervention effects are positive, though small to moderate effect sizes have been reported (effect size range, 0.19–0.54).[28] However, in those studies in which patients were intentionally selected because they exhibited depressive symptoms, intervention effects were strong (effect size, 0.94).[40] 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.[41][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 (a) better defining and formulating the nature of problems, (b) generating a wide range of alternative solutions, (c) systematically evaluating consequences of a solution while deciding on an optimal one, and (d) 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 or a wait-list control. Overall results showed both improved problem-solving abilities and clinically significant decreases in symptoms of depression.

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.

References

1. Whooley MA, Simon GE: Managing depression in medical outpatients. N Engl J Med 343 (26): 1942-50, 2000. [PUBMED Abstract]
2. Hart SL, Hoyt MA, Diefenbach M, et al.: Meta-analysis of efficacy of interventions for elevated depressive symptoms in adults diagnosed with cancer. J Natl Cancer Inst 104 (13): 990-1004, 2012. [PUBMED Abstract]
3. Derogatis LR, Morrow GR, Fetting J, et al.: The prevalence of psychiatric disorders among cancer patients. JAMA 249 (6): 751-7, 1983. [PUBMED Abstract]
4. Endicott J: Measurement of depression in patients with cancer. Cancer 53 (10 Suppl): 2243-9, 1984. [PUBMED Abstract]
5. Massie MJ, Holland JC: Consultation and liaison issues in cancer care. Psychiatr Med 5 (4): 343-59,

1987. [PUBMED Abstract]

6. Fisch M: Treatment of depression in cancer. J Natl Cancer Inst Monogr (32): 105-11, 2004. [PUBMED Abstract]
7. Laoutidis ZG, Mathiak K: Antidepressants in the treatment of depression/depressive symptoms in cancer patients: a systematic review and meta-analysis. BMC Psychiatry 13: 140, 2013. [PUBMED Abstract]
8. Stockler MR, O'Connell R, Nowak AK, et al.: Effect of sertraline on symptoms and survival in patients with advanced cancer, but without major depression: a placebo-controlled double-blind randomised trial. Lancet Oncol 8 (7): 603-12, 2007. [PUBMED Abstract]
9. Ashbury FD, Madlensky L, Raich P, et al.: Antidepressant prescribing in community cancer care. Support Care Cancer 11 (5): 278-85, 2003. [PUBMED Abstract]
10. Williams JW Jr, Mulrow CD, Chiquette E, et al.: A systematic review of newer pharmacotherapies for depression in adults: evidence report summary. Ann Intern Med 132 (9): 743-56, 2000. [PUBMED Abstract]
11. Fisch MJ, Callahan CM, Kesterson JG, et al.: The use of an electronic patient record system to identify advanced cancer patients and antidepressant drug use. J Palliat Med 2 (4): 403-9, 1999.
12. Gartlehner G, Hansen RA, Morgan LC, et al.: Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. Ann Intern Med 155 (11): 772-85, 2011. [PUBMED Abstract]
13. Haddad PM: Antidepressant discontinuation syndromes. Drug Saf 24 (3): 183-97, 2001. [PUBMED Abstract]
14. Iqbal MM, Basil MJ, Kaplan J, et al.: Overview of serotonin syndrome. Ann Clin Psychiatry 24 (4): 310-8, 2012. [PUBMED Abstract]
15. Physician's Desk Reference. 51st ed. Montvale, NJ: Medical Economics, 1997.
16. Horne RL, Ferguson JM, Pope HG Jr, et al.: Treatment of bulimia with bupropion: a multicenter controlled trial. J Clin Psychiatry 49 (7): 262-6, 1988. [PUBMED Abstract]
17. Epstein I, Szpindel I, Katzman MA: Pharmacological approaches to manage persistent symptoms of major depressive disorder: rationale and therapeutic strategies. Psychiatry Res 220 (Suppl 1): S15-33, 2014. [PUBMED Abstract]
18. Homsi J, Nelson KA, Sarhill N, et al.: A phase II study of methylphenidate for depression in advanced cancer. Am J Hosp Palliat Care 18 (6): 403-7, 2001 Nov-Dec. [PUBMED Abstract]
19. Gartlehner G, Thaler K, Hill S, et al.: How should primary care doctors select which antidepressants to administer? Curr Psychiatry Rep 14 (4): 360-9, 2012. [PUBMED Abstract]
20. Grassi L, Caruso R, Hammelef K, et al.: Efficacy and safety of pharmacotherapy in cancer-related psychiatric disorders across the trajectory of cancer care: a review. Int Rev Psychiatry 26 (1): 44-62, 2014. [PUBMED Abstract]
21. Wilson E, Lader M: A review of the management of antidepressant discontinuation symptoms. Ther Adv Psychopharmacol 5 (6): 357-68, 2015. [PUBMED Abstract]

22. Ogle NR, Akkerman SR: Guidance for the discontinuation or switching of antidepressant therapies in adults. J Pharm Pract 26 (4): 389-96, 2013. [PUBMED Abstract]

23. Keks N, Hope J, Keogh S: Switching and stopping antidepressants. Aust Prescr 39 (3): 76-83, 2016. [PUBMED Abstract]

24. Musselman DL, Lawson DH, Gumnick JF, et al.: Paroxetine for the prevention of depression induced by high-dose interferon alfa. N Engl J Med 344 (13): 961-6, 2001. [PUBMED Abstract]

25. U.S. Food and Drug Administration: Antidepressant Use in Children, Adolescents, and Adults. Rockville, Md: Food and Drug Administration, Center for Drug Evaluation and Research, 2007. Available online. Last accessed January 3, 2018.

26. Hammad TA, Laughren T, Racoosin J: Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 63 (3): 332-9, 2006. [PUBMED Abstract]

27. Bridge JA, Iyengar S, Salary CB, et al.: Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA 297 (15): 1683-96, 2007. [PUBMED Abstract]

28. Barsevick AM, Sweeney C, Haney E, et al.: A systematic qualitative analysis of psychoeducational interventions for depression in patients with cancer. Oncol Nurs Forum 29 (1): 73-84; quiz 85-7, 2002 Jan-Feb. [PUBMED Abstract]

29. Forester B, Kornfeld DS, Fleiss JL: Psychotherapy during radiotherapy: effects on emotional and physical distress. Am J Psychiatry 142 (1): 22-7, 1985. [PUBMED Abstract]

30. Holland JC, Morrow GR, Schmale A, et al.: A randomized clinical trial of alprazolam versus progressive muscle relaxation in cancer patients with anxiety and depressive symptoms. J Clin Oncol 9 (6): 1004-11, 1991. [PUBMED Abstract]

31. Greer S, Moorey S, Baruch JD, et al.: Adjuvant psychological therapy for patients with cancer: a prospective randomised trial. BMJ 304 (6828): 675-80, 1992. [PUBMED Abstract]

32. Worden JW, Weisman AD: Preventive psychosocial intervention with newly diagnosed cancer patients. Gen Hosp Psychiatry 6 (4): 243-9, 1984. [PUBMED Abstract]

33. Lovejoy NC, Matteis M: Cognitive-behavioral interventions to manage depression in patients with cancer: research and theoretical initiatives. Cancer Nurs 20 (3): 155-67, 1997. [PUBMED Abstract]

34. Cain EN, Kohorn EI, Quinlan DM, et al.: Psychosocial benefits of a cancer support group. Cancer 57 (1): 183-9, 1986. [PUBMED Abstract]

35. Montazeri A, Jarvandi S, Haghighat S, et al.: Anxiety and depression in breast cancer patients before and after participation in a cancer support group. Patient Educ Couns 45 (3): 195-8, 2001. [PUBMED Abstract]

36. Fawzy FI, Fawzy NW, Hyun CS, et al.: Malignant melanoma. Effects of an early structured psychiatric intervention, coping, and affective state on recurrence and survival 6 years later. Arch Gen Psychiatry 50 (9): 681-9, 1993. [PUBMED Abstract]

37. Spiegel D, Bloom JR, Yalom I: Group support for patients with metastatic cancer. A randomized outcome study. Arch Gen Psychiatry 38 (5): 527-33, 1981. [PUBMED Abstract]

38. Spiegel D, Glafkides MC: Effects of group confrontation with death and dying. Int J Group Psychother 33 (4): 433-47, 1983. [PUBMED Abstract]

39. Lambert MJ, Ogles BM: The efficacy and effectiveness of psychotherapy. In: Lambert MJ: Bergin and Garfield's Handbook of Psychotherapy and Behavior Change. 5th ed. New York: John Wiley & Sons Inc, 2004, pp 139-93.

40. Sheard T, Maguire P: The effect of psychological interventions on anxiety and depression in cancer patients: results of two meta-analyses. Br J Cancer 80 (11): 1770-80, 1999. [PUBMED Abstract]

41. Nezu AM, Nezu CM, Felgoise SH, et al.: Project Genesis: assessing the efficacy of problem-solving therapy for distressed adult cancer patients. J Consult Clin Psychol 71 (6): 1036-48, 2003. [PUBMED Abstract]

Suicide Risk in Cancer Patients

Demographics and Statistics

Epidemiological studies conducted across several countries indicate that cancer is a risk factor for suicide.[1-5] One retrospective cohort study (N = 3,594,750) found that patients with cancer had nearly twice the incidence of suicide as did the general population.[1] Increased rates of suicidal ideation, suicidal behaviors, and suicide attempts have been documented in patients with cancer compared with the general population.[5-7] 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.[3]

Certain clinical and sociodemographic risk factors for suicide have been identified in patients with cancer.[3,8] As in the general population, suicide risk is higher in male patients with cancer than in female patients.[3,9] Older age is another significant risk factor. One group of investigators found that suicide risk increased with age and that older men were 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 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 play an important role. Single, divorced, or widowed white men carry higher suicide risk than do other patient populations.[10]

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 3 to 5 months.[3,4,9] 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] Certain cancer types have been associated with higher suicide risk, including head and neck cancer, bladder cancer, pancreatic cancer, lung cancer, cancers of the upper digestive tract, brain cancer, and cervical cancer.[1,9,11] Other risk factors include nonlocalized disease and aggressive or advanced cancer with a survival rate of fewer than 5 years.[8] Certain comorbidities have been associated with higher suicide risk, including substance use; cancer-related pain; and comorbid psychiatric illness, specifically depression and anxiety.[12,13]

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.[14]

Risk factors for suicide in the cancer population are as follows:[15]

- Sociodemographic factors:
  - Male gender.
  - 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.

References

1. Misono S, Weiss NS, Fann JR, et al.: Incidence of suicide in persons with cancer. J Clin Oncol 26 (29): 4731-8, 2008. [PUBMED Abstract]

2. Schairer C, Brown LM, Chen BE, et al.: Suicide after breast cancer: an international population-based study of 723,810 women. J Natl Cancer Inst 98 (19): 1416-9, 2006. [PUBMED Abstract]
3. Hem E, Loge JH, Haldorsen T, et al.: Suicide risk in cancer patients from 1960 to 1999. J Clin Oncol 22 (20): 4209-16, 2004. [PUBMED Abstract]
4. Yousaf U, Christensen ML, Engholm G, et al.: Suicides among Danish cancer patients 1971-1999. Br J Cancer 92 (6): 995-1000, 2005. [PUBMED Abstract]
5. Björkenstam C, Edberg A, Ayoubi S, et al.: Are cancer patients at higher suicide risk than the general population? Scand J Public Health 33 (3): 208-14, 2005. [PUBMED Abstract]
6. Rasic DT, Belik SL, Bolton JM, et al.: Cancer, mental disorders, suicidal ideation and attempts in a large community sample. Psychooncology 17 (7): 660-7, 2008. [PUBMED Abstract]
7. Druss B, Pincus H: Suicidal ideation and suicide attempts in general medical illnesses. Arch Intern Med 160 (10): 1522-6, 2000. [PUBMED Abstract]
8. Kendal WS: Suicide and cancer: a gender-comparative study. Ann Oncol 18 (2): 381-7, 2007. [PUBMED Abstract]
9. Innos K, Rahu K, Rahu M, et al.: Suicides among cancer patients in Estonia: a population-based study. Eur J Cancer 39 (15): 2223-8, 2003. [PUBMED Abstract]
10. Llorente MD, Burke M, Gregory GR, et al.: Prostate cancer: a significant risk factor for late-life suicide. Am J Geriatr Psychiatry 13 (3): 195-201, 2005. [PUBMED Abstract]
11. Lu D, Fall K, Sparén P, et al.: Suicide and suicide attempt after a cancer diagnosis among young individuals. Ann Oncol 24 (12): 3112-7, 2013. [PUBMED Abstract]
12. Henriksson MM, Isometsä ET, Hietanen PS, et al.: Mental disorders in cancer suicides. J Affect Disord 36 (1-2): 11-20, 1995. [PUBMED Abstract]
13. Akechi T, Nakano T, Akizuki N, et al.: Clinical factors associated with suicidality in cancer patients. Jpn J Clin Oncol 32 (12): 506-11, 2002. [PUBMED Abstract]
14. Akechi T, Okamura H, Yamawaki S, et al.: Why do some cancer patients with depression desire an early death and others do not? Psychosomatics 42 (2): 141-5, 2001 Mar-Apr. [PUBMED Abstract]
15. Anguiano L, Mayer DK, Piven ML, et al.: A literature review of suicide in cancer patients. Cancer Nurs 35 (4): E14-26, 2012 Jul-Aug. [PUBMED Abstract]

Assessment and Management of Suicidal Patients

Assessment

Suicide assessment occurs frequently along the cancer continuum. Components of suicide assessment include evaluation of risk factors, patient's mental state, social context, and nonverbal signs of extreme distress or depression (such as poor eye contact, agitation, or excessive slowing).[1-3] 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 Beck Hopelessness Scale, the Suicide Intent Scale, and the Columbia-Suicide Severity Rating Scale are used to screen for suicide risk in the general population and in

patients with mental illness.[5] 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 (refer to the Requests for Hastened Death section in the PDQ summary on Last Days of Life for more information), and/or euthanasia are complex and poorly understood.[7,11] The desire for hastened death involves a hope for death to come quickly. Such a desire can be 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; [12] or a healthy process of closure, i.e., a manifestation of letting go.[13]

Patients who are found to be suicidal require careful further assessment (refer to Table 4). 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 a depressive illness, a desire for hastened death, or an expression of the desire to have ultimate control over intolerable symptoms.[7] 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. (Refer to the PDQ summary on Cancer Pain for more information.)

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 4. 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 abuse
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.

References

1. Spoletini I, Gianni W, Caltagirone C, et al.: Suicide and cancer: where do we go from here? Crit Rev Oncol Hematol 78 (3): 206-19, 2011. [PUBMED Abstract]
2. K Hughes M: Suicide Screening in the Oncology Population. J Adv Pract Oncol 7 (1): 101-104, 2016 Jan-Feb. [PUBMED Abstract]
3. Morriss R, Kapur N, Byng R: Assessing risk of suicide or self harm in adults. BMJ 347: f4572, 2013. [PUBMED Abstract]
4. Abbey JG, Rosenfeld B, Pessin H, et al.: Hopelessness at the end of life: the utility of the hopelessness scale with terminally ill cancer patients. Br J Health Psychol 11 (Pt 2): 173-83, 2006. [PUBMED Abstract]
5. Bolton JM, Gunnell D, Turecki G: Suicide risk assessment and intervention in people with mental illness.

BMJ 351: h4978, 2015. [PUBMED Abstract]

6. Fang CK, Chang MC, Chen PJ, et al.: A correlational study of suicidal ideation with psychological distress, depression, and demoralization in patients with cancer. Support Care Cancer 22 (12): 3165-74, 2014. [PUBMED Abstract]
7. Cooke L, Gotto J, Mayorga L, et al.: What do I say? Suicide assessment and management. Clin J Oncol Nurs 17 (1): E1-7, 2013. [PUBMED Abstract]
8. Clarke DM, Kissane DW: Demoralization: its phenomenology and importance. Aust N Z J Psychiatry 36 (6): 733-42, 2002. [PUBMED Abstract]
9. Kissane DW, Wein S, Love A, et al.: The Demoralization Scale: a report of its development and preliminary validation. J Palliat Care 20 (4): 269-76, 2004. [PUBMED Abstract]
10. Lee CY, Fang CK, Yang YC, et al.: Demoralization syndrome among cancer outpatients in Taiwan. Support Care Cancer 20 (10): 2259-67, 2012. [PUBMED Abstract]
11. Anguiano L, Mayer DK, Piven ML, et al.: A literature review of suicide in cancer patients. Cancer Nurs 35 (4): E14-26, 2012 Jul-Aug. [PUBMED Abstract]
12. Filiberti A, Ripamonti C, Totis A, et al.: Characteristics of terminal cancer patients who committed suicide during a home palliative care program. J Pain Symptom Manage 22 (1): 544-53, 2001. [PUBMED Abstract]
13. Nissim R, Gagliese L, Rodin G: The desire for hastened death in individuals with advanced cancer: a longitudinal qualitative study. Soc Sci Med 69 (2): 165-71, 2009. [PUBMED Abstract]
14. Breitbart W, Passik SD: Psychiatric aspects of palliative care. In: Doyle D, Hanks GW, MacDonald N, eds.: Oxford Text Book of Palliative Medicine. New York: Oxford University Press, 1993, pp 609-26.
15. Roth AJ, Holland JC: Psychiatric complications in cancer patients. In: Brain MC, Carbone PP, eds.: Current Therapy in Hematology-Oncology. 5th ed. St. Louis, Mo: Mosby-Year Book, Inc., 1995, pp 609-18.

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 insomnia, irritability, changes in eating habits, and 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]

Pharmacologic management

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]

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]

Refer to the subsection on Depression and Suicide in the PDQ summary on Pediatric Supportive Care for information on pediatric considerations for suicidality and cautions about the use of selective serotonin reuptake inhibitors.

References

1. Deuber CM: Depression in the school-aged child: implications for primary care. Nurse Pract 7 (8): 26-30, 68, 1982. [PUBMED Abstract]
2. Kazak AE: Psychological issues in childhood cancer survivors. J Assoc Pediatr Oncol Nurses 6 (1): 15-6, 1989. [PUBMED Abstract]
3. O'Malley JE, Koocher G, Foster D, et al.: Psychiatric sequelae of surviving childhood cancer. Am J Orthopsychiatry 49 (4): 608-16, 1979. [PUBMED Abstract]
4. Kaplan SL, Busner J, Weinhold C, et al.: Depressive symptoms in children and adolescents with cancer: a longitudinal study. J Am Acad Child Adolesc Psychiatry 26 (5): 782-7, 1987. [PUBMED Abstract]
5. Fritz GK, Williams JR, Amylon M: After treatment ends: psychosocial sequelae in pediatric cancer survivors. Am J Orthopsychiatry 58 (4): 552-61, 1988. [PUBMED Abstract]
6. Greenberg HS, Kazak AE, Meadows AT: Psychologic functioning in 8- to 16-year-old cancer survivors and their parents. J Pediatr 114 (3): 488-93, 1989. [PUBMED Abstract]
7. Rait DS, Jacobsen PB, Lederberg MS, et al.: Characteristics of psychiatric consultations in a pediatric cancer center. Am J Psychiatry 145 (3): 363-4, 1988. [PUBMED Abstract]
8. Tebbi CK, Bromberg C, Mallon JC: Self-reported depression in adolescent cancer patients. Am J Pediatr Hematol Oncol 10 (3): 185-90, 1988 Fall. [PUBMED Abstract]
9. Kashani J, Hakami N: Depression in children and adolescents with malignancy. Can J Psychiatry 27 (6): 474-7, 1982. [PUBMED Abstract]
10. Archenbach TM, ed.: Manual for the Child Behavior Checklist and Revised Child Behavior Profile. Burlington, Vt: T.M. Achenbach, 1983.
11. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. 4th rev. ed. Washington, DC: American Psychiatric Association, 2000.
12. Malmquist CP: Major depression in childhood: why don't we know more? Am J Orthopsychiatry 53 (2): 262-8, 1983.
13. Pfefferbaum-Levine B, Kumor K, Cangir A, et al.: Tricyclic antidepressants for children with cancer. Am J Psychiatry 140 (8): 1074-6, 1983. [PUBMED Abstract]
14. Coffey BJ: Review and update: benzodiazepines in childhood and adolescence. Psychiatr Ann 23 (6): 332-9, 1993.
15. Maisami M, Sohmer BH, Coyle JT: Combined use of tricyclic antidepressants and neuroleptics in the management of terminally ill children: a report on three cases. J Am Acad Child Psychiatry 24 (4): 487-9, 1985. [PUBMED Abstract]

Changes to This Summary (11/02/2017)

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.

Intervention

Added Switching or discontinuing antidepressants as a new subsection.

This summary is written and maintained by the PDQ Supportive and Palliative Care Editorial Board, which is editorially independent of NCI. The summary reflects an independent review of the literature and does not represent a policy statement of NCI or NIH. More information about summary policies and the role of the PDQ Editorial Boards in maintaining the PDQ summaries can be found on the About This PDQ Summary and PDQ® - NCI's Comprehensive Cancer Database pages.

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 population. It is intended as a resource to inform and assist clinicians who care for cancer 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:

- Joseph Bubalo, PharmD, BCPS, BCOP (Oregon Health and Science University Hospital)
- Jayesh Kamath, MD, PhD (University of Connecticut Health Center)

- Anne Kazak, PhD, ABPP (Alfred I. duPont Hospital for Children)
- Edward B. Perry, MD (VA Connecticut Healthcare System)
- Amy Wachholtz, PhD, MDiv, MS (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.

Permission to Use This Summary

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]

Disclaimer

The information in these summaries should not be used as a basis for insurance reimbursement determinations. More information on insurance coverage is available on Cancer.gov on the Managing Cancer Care page.

Contact Us

More information about contacting us or receiving help with the Cancer.gov website can be found on our Contact Us for Help page. Questions can also be submitted to Cancer.gov through the website’s Email Us.

Updated: November 2, 2017